Journal of Clinical Immunology (2022) 42 (Suppl 1):S1–S115
https://doi.org/10.1007/s10875-022-01216-6

ABSTRACTS

Selected Abstracts from the 13th Annual Meeting of the Clinical Immunology Society: 2022 Annual Meeting: Immune Deficiency and Dysregulation North American Conference

Published online: 30 March 2022

Charlotte, North Carolina, March 31-April 3

Sponsorship: Publication of this supplement was funded by the Clinical Immunology Society. All content was reviewed and approved by the Program Committee, which held full responsibility for the abstract selections.

All contributors have provided original material as submitted for publication in the Journal of Clinical Immunology.

Oral Presentations

(1) The effects of Microbiome and Immunoglobulin Therapy on Immune Dysregulation in Common Variable Immunodeficiency

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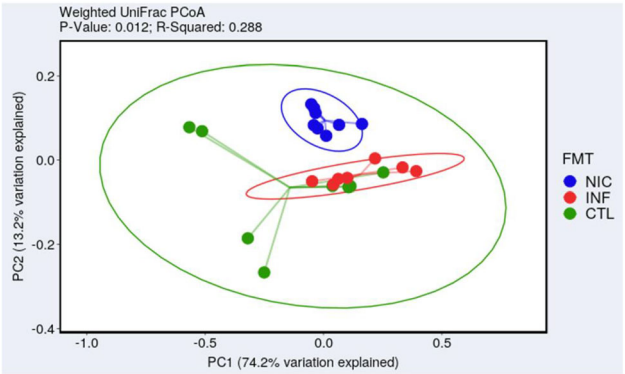
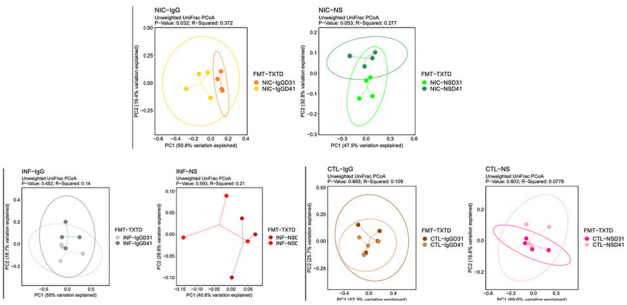
We seek to identify the role of the microbiome in immune dysregulation in Common Variable Immunodeficiency (CVID). CVID patients have two distinct phenotypes: patients who develop infections-only (INF), and patients who develop autoimmune and inflammatory complications (noninfectious complications (NIC)). Compared to INF-CVID, NIC-CVID patients have higher morbidity and mortality rates. Studies showed associations between NIC-CVID and gut microbiome aberrations, including imbalanced microbial composition, leaky gut, and systemic inflammation. To investigate the role of dysbiosis in the immune responses in CVID, we performed fecal microbiota transplant (FMT) from CVID patients to C57Bl/6J Germ-Free (GF) mice. GF-mice received FMT from NIC-CVID, INF-CVID, or a healthy control (CTL). Thirty days later, gut microbial alpha and beta diversity were significantly different between NIC, INF, and CTL-FMT recipients. Furthermore, FMT recipients from all CVID donors (NIC and INF) had significantly higher serum IgG2b and IgG2c, indicating inflammation. We next treated 50% of the mice in each group with normal saline (NS) and 50% with a single dose of intraperitoneal human IgG (h-IgG). Compared to NS, h-IgG resulted in a significant change in gut microbiome beta diversity in NIC-FMT but not in INF or CTL-FMT recipients. In addition, IgG-treated NIC-FMT recipients had a decrease in the relative abundance of Eggerthella, Bifidobacterium, and Ruminococcaceae genera. Dysregulation of the same genera has been described in CVID patients.
Thus, we provide a proof of concept that FMT from CVID patients to GF-mice recapitulates the microbiome alteration seen in CVID patients. Our data are from a single donor per group; however, confirmatory experiments using additional donor samples are underway. Our work will help provide new insight into immune dysregulation in CVID. It will also help identify the anti-commensal effects of IgG therapy. Our ultimate goal is to develop therapeutics to modulate the gut microbiome and treat and prevent NIC development in CVID.



There is a significant difference in alpha and beta gut microbiome diversity between NIC, INF, and CTL FMT recipients: Beta diversity between GF mice 30 days following FMT. Principal-coordinate analysis plots of Unifraction distances of fecal microbiota generated from 16S rRNA gene sequence analysis. Axis labels indicate the percentage of variance explained by the respective principal coordinate axis. PC1, principal coordinate 1; PC2, principal coordinate 2. Feces were freshly collected from GF (C57Bl/6J) mice (n=8/group, all males, ages 8-12 weeks), mice housed at the Gnotobiotics Core, BCM). Blue: NIC. Red: INF. Green: CTL.



Human IgG significantly changes the gut microbiome beta diversity of NIC-FMT recipient GF mice. Germ-Free mice received h-IgG 500 mg/kg

or NS 50µl, intraperitoneally (n=4/group). D30 and D40 represent days 30 & 40 post-FMT, respectively. Principal coordinate analysis plots of unweighted distances of fecal microbiota generated by the 16S rRNA gene sequence analysis. Axis labels indicate the percentage of variance explained by the respective principal coordinate axis. PC1, principal coordinate 1; PC2, principal coordinate 2

Keywords: Common Variable Immunodeficiency, Microbiome, Germ free mice, Immune Dysregulation, Immunoglobulin therapy

Disclosures: Joud Hajjar has relevant financial relationships with proprietary interests with The Texas Medical center Digestive Diseases Center (Research Grant includes principal investigator, collaborator or consultant and pending grants as well as grants already received), Jeffrey Modell Foundation (Research Grant includes principal investigator, collaborator or consultant and pending grants as well as grants already received), Immune Deficiency Foundation (Research Grant includes principal investigator, collaborator or consultant and pending grants as well as grants already received) Baxalta (Research Grant includes principal investigator, collaborator or consultant and pending grants as well as grants already received), Chao Physician-Scientist Foundation (Research Grant includes principal investigator, collaborator or consultant and pending grants as well as grants already received), Takeda (Consultant/Advisory Board Member), Pharming (Consultant/Advisory Board Member), Horizon: Consultant/Advisory Board Member, and Alfaisal University (ad hoc consultancy/speaker). Alton Swennes acts as a consultant for AbbVie, Merck, and OraSure Technologies. All other authors had no financial relationships to disclose.

(2) Proteomic profiling reveals restricted heavy chain subfamily expression of vaccine-elicited SARS-CoV-2 spike-specific antibodies in patients with primary antibody deficiencies

Alexander Troelnikov*[1], Jing Jing Wang[2], Bridie Armour[2], Trishni Putty[1], Tim Chataway[2], Anthony Smith[3], Tiffany Hughes[3], Jovanka King[4], Tom Gordon[3]
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Introduction: Predisposition to severe infection and impaired vaccination responses define Common Variable Immunodeficiency (CVID), although COVID-19 and other polypeptide vaccine responses appear to be only modestly reduced in some patients. However, the breadth and clonal composition of vaccination-elicited antibodies in CVID has not been evaluated. Through mass spectrometry-(MS) based proteomic profiling of antibodies we aimed to evaluate the molecular composition of circulating spike-specific antibodies following Pfizer mRNA vaccination in patients with CVID.
Methods: Spike-specific antibodies were purified from plasma samples using Spike S1 subunit-coupled magnetic beads and enzymatically digested to generate peptides for MS sequencing. Immunoglobulin heavy chain subfamilies were analysed using combined de novo amino acid sequencing and database matching.
Results: Three female patients with CVID (median age 41 years), receiving immunoglobulin therapy, fulfilling ESID criteria for CVID have been evaluated, along with 5 female controls (median age 39 years). Spike specific IgG levels were lower at 1 and 3 weeks after first dose vaccination but reached similar level as healthy controls at 4 weeks, following first dose (Figure 1A). When tested at 4 weeks, RBD mutant variant responses were similar to healthy controls. However, MS sequencing demonstrated a restriction of immunoglobulin heavy chain subfamily usage to 2-4 sub families in all CVID, in contrast to the broader (5 or more) subfamilies found in health controls (Figure 1B) at week 4 timepoint. Immunoglobulin products tested in parallel showed no significant anti-spike reactivity.
Discussion: Our interim results indicate a restricted repertoire of COVID-19 vaccine elicited antibodies in CVID, despite a mostly comparable magnitude IgG response to healthy, age matched peers. This finding suggests an impairment in B cell diversification and maturation as a pathomechanism of CVID, aligning with contemporary disease models. For the first time in CVID, clonal restriction can be demonstrated with secreted antibody repertoire. Further studies are underway to evaluate the level of somatic hypermutation of responding antibodies, and the immunophenotype and B cell receptor sequence of circulating spike specific B cells. Proteomic profiling of COVID-19 vaccination induced antibodies offers a new approach for exploratory and diagnostic evaluation of the humoral immune response in CVID.

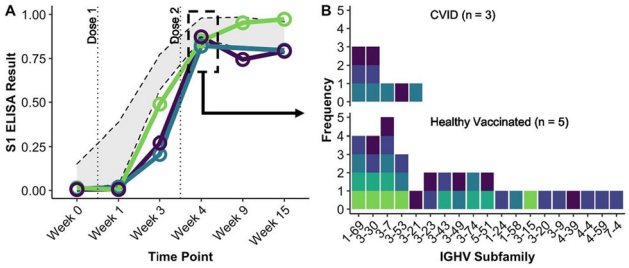

Figure 1: [A] SARS CoV 2 S1 Subunit IgG ELISA Results for CVID patients in comparison to healthy controls (displayed as grey range). [B] Ig heavy chain (IGHV) subfamily usage determined by proteomic sequencing of affinity purified anti S1 IgG from week 4 samples.

Keywords: Immunodeficiency, COVID, Proteomic, CVID, Antibody, Sequencing, Vaccination

Disclosures: All authors indicated they had no financial relationships to disclose.

(3) Epigenetic quantification of the Treg specific FOXP3 regulatory region (TSDR) can assist with variant classification and denote disease severity in IPEX syndrome

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IPEX syndrome is a life-limiting monogenic disorder that begins in infancy and typically manifests with severe multiple autoimmunity. Recently, atypical and late onset presentations have been reported. FOXP3 is the master transcription factor of regulatory T-cells (Tregs); pathogenic variants in FOXP3 cause IPEX primarily through disruption of Treg development and/or function. Assigning pathogenicity to FOXP3 variants is challenging due to the low rate of de novo variation, the heterogeneous phenotype, and inconsistent immunological abnormalities.
The Treg cell-specific demethylated region (TSDR) of FOXP3 was previously shown to be overrepresented in its unmethylated state in IPEX patients' whole blood DNA. Here, we aimed to assess TSDR analysis for characterization of disease severity and interpretation of novel FOXP3 variants in IPEX.

We quantified and compared methylation at the FOXP3-TSDR as a proportion of total CD4 (FOXP3/CD4) by methylation specific qPCR in individuals with atypical (n=9) and typical (n=6) IPEX. We show that TSDR/CD4 demethylation is consistently elevated in all IPEX patients and nominally higher among the typical and severe cases as compared to the atypical cases. We then extended the analysis to a large paediatric cohort of confirmed IPEX (n=46), FOXP3 variants of uncertain significance (VUS, n=17), IPEX-like monogenic autoimmunity (n=16), polygenic multi-autoimmunity (n=13) and unaffected controls (n=26).

FOXP3/CD4 was a good discriminator of individuals with IPEX vs. controls (ROC-AUC 0.85, mean 18.0% vs. 8.5%, p < 0.0001). Individuals with overlapping IPEX-like phenotypes due to other monogenic autoimmunity had similar FOXP3/CD4 to controls (mean 9.6%, p=0.9) as did those with polygenic multi-autoimmunity (10.1%, p=0.7) (Fig 1.). Individuals with diabetes and a novel FOXP3 VUS also had similar FOXP3/CD4 to controls (mean 10.1%, p=0.8). These individuals also had higher polygenic risk for type 1 diabetes, later onset of diabetes and no additional features of IPEX, consistent with the variants being benign.

Our data show that FOXP3/CD4 epigenetic analysis could be useful for both disease stratification and classification of novel FOXP3 variants in IPEX syndrome, facilitating early diagnosis, complementary to gene sequencing. Critically, this cost-effective method does not rely on fresh samples and utilises existing samples taken for genetic testing (e.g. dried blood or isolated genomic DNA).

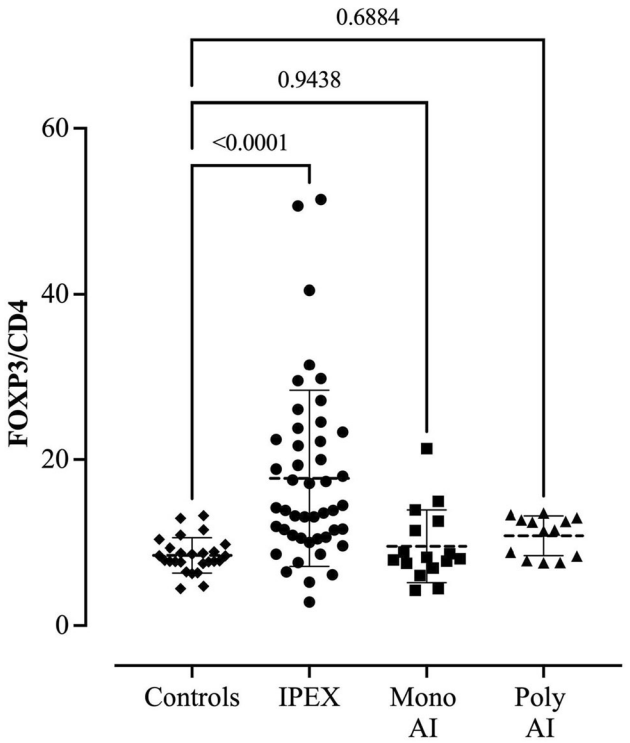

Figure 1: Plot to show FOXP3/CD4 values in controls (n=26, mean 8.5%, SD 2.1) compared with patients with IPEX (n=46, mean 18.0%, SD 10.6, p<0.0001), patients with overlapping IPEX-like phenotypes due to other monogenic autoimmunity (AI) (n=16, mean 9.6%, SD 4.3, p=0.9) and patients with polygenic multi-AI (n=13, mean 10.1%, SD 2.4, p=0.7). Horizontal lines represent the mean and standard deviation.

Keywords: IPEX, Epigenetics, FOXP3, Tregs, Diagnosis, Monogenic Autoimmunity

Disclosures: Steffi Walter is employed by Epimune GmbH. All other authors had no financial relationships to disclose.

(4) Gene Expression Profiling and Signaling Pathway Analysis of Tolerance in an IL-7R- SCID Patient Following Bilateral Orthotopic Lung Transplant and Bone Marrow Transplant from the Same Cadaveric Donor

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Rationale: Primary immunodeficiency (PID) patients may develop pulmonary complications, and most are ineligible for either Bilateral Orthotopic Lung Transplant (BOLT) or Bone Marrow Transplant (BMT) due to futility. A prospective trial in PID with pulmonary failure (NCT01852370) tests our hypothesis that persistent engraftment of cadaveric lung donor vertebral body (VB) marrow could restore immunity and may also induce tolerance.

Methods: A 14-year-old female (IL-7R- SCID) underwent BMT 4-months after BOLT from a 1/8 HLA-allele matched donor. Marrow suspension from VB was CD3+/CD19+depleted (CliniMACS®) and cryopreserved.

Mechanistic studies: we have previously shown reduced proliferative, cytotoxic and cytokine responses 2yrs post-BMT (1yr off ISD). Peripheral regulatory mechanism(s) were examined by depletion of Tregs, blocking the IL-10R or adding low dose of IL-2 to break anergy. T-cell receptor (TCR)B repertoire of alloreactive T-cell clones were assessed for deletion using ImmunoSEQ™ (Adaptive Biotechnology®). Gene expression profiling and signaling pathway analysis on alloreactive or tolerant T-cells were performed using RNA-sequencing and software of CLC Genomic Workbench®v21, GSEA®v4.1.0 and IPA®.

Results: She was initially engrafted with 100% donor cells. Declining donor chimerism (CD33+ myeloid or CD3+T-cell was 60-70% and ~27%, respectively) prompted DLI ~10-weeks post-BMT. Myeloid chimerism settled between 7-14% during years 2-5 while T-cells remained >90% donor. T/B cells, TCR/BCR repertoires, and sjTREC exceeded pre-BMT values by 3-6m. She was weaned off ISD by 1yr post-BMT and serial lung biopsies detected no rejection. Circulating donor T-cells 2yrs post-BMT were hyporesponsive to host DCs while vigorously responded to 3rd party APCs. Treg depletion or IL10R blocking did not lead to rebound alloreactivity. TCRβ ImmunoSEQ® revealed the gradual disappearance of host-reactive clones and remained undetectable even following exogenous IL2 testing anergy.

Unlike T-cells from the graft, tolerant T-cells in circulation presented distinct patterns of gene expressions, with downregulation of allograft rejection (GSEA-Hallmark) and T-helper response, co-stimulation, cell proliferation pathway paired with upregulation of co-inhibition and PTEN pathway (Fig1).

Conclusions: We demonstrate successful engraftment, immune competence, and acquisition of long-term tolerance from deceased organ donor VB marrow for the first time. Tolerance was characterized by clonal deletion of alloreactive T-cells, along with altered signaling pathways in tolerant T-cells.

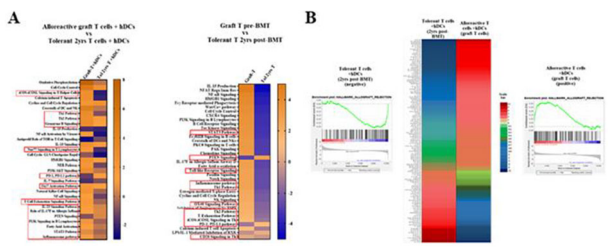

Figure 1. Comparison of signal pathway profiles between alloreactive T cells and tolerant T cells: A) (IPA software analysis) Several signal pathways related to immune responses were upregulated (■) in alloreactive T cells, whereas those pathways were downregulated (■) in tolerant T cells 2yrs post-BMT (1yr ISD withdrawal) after *in vitro* stimulating with (left) or without (right) host DC stimulation. The color scale bar is shown in right side of heatmap. **B) (GSEA software analysis): Allograft rejection pathway** was downregulated in tolerant T-cells 2yrs post-BMT, whereas the pathway was upregulated in graft alloreactive T-cells pre-BMT. Both T cells were stimulated *in vitro* with host-DCs. Enrichment plot for tolerant T-cells (left) and for alloreactive T-cells (right) were presented. The heatmap (center) of the pathway illustrates the genes up- or down-regulated in each sample. The color scale bar is shown on the right side of the heatmap.

Keywords: Organ transplant and bone marrow transplantation, Immune tolerance, gene expression and signal pathway

Disclosures: All authors indicated they had no financial relationships to disclose.

(5) A surface homophilic receptor LY9 governs IFN-γ and IL-17/22 immunity to protect humans from tuberculosis and candidiasis

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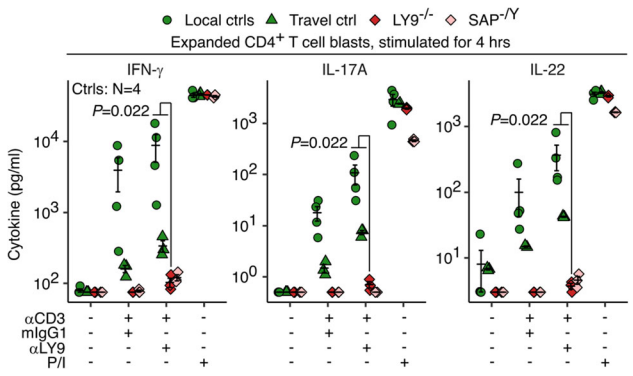
Inborn errors of interferon-gamma (IFN-γ) immunity and their autoimmune phenocopies underlie mycobacterial diseases, whereas inborn errors of interleukin 17 (IL-17) and IL-22 immunity and their autoimmune phenocopies underlie chronic mucocutaneous candidiasis (CMC) in humans and mice. We studied three unrelated patients with tuberculosis (TB), one of whom also presented CMC, due to inherited complete deficiency of a homophilic surface receptor LY9. We showed impaired IFN-γ production and T-bet expression in LY9-deficient CD4+ αβ T lymphocytes upon crosslinking the T-cell receptor (TCR) and LY9, which was rescued by complementing LY9. We also showed impaired IFN-γ production and T-bet expression in LY9-deficient CD4+ αβ T lymphocytes upon immunological synapse-mediated activation and mycobacterial infection in vitro. We also showed that LY9-deficient T lymphocytes produced abnormally small amounts of IL-17A, IL-17F, and IL-22 upon synapse-mediated activation and stimulation with Candida antigens. Conversely, LY9 complementation rescued the production of IL-17A and IL-22 and the expression of RORγT in T lymphocytes. Mechanistically, we found that T lymphocytes deficient in SLAM-associated protein (SAP) showed defective cytokine production upon LY9 crosslinking like LY9-deficient T lymphocytes. Thus, a surface homophilic receptor LY9 on T lymphocytes governs their production of IFN-γ, IL-17, and IL-22 through a SAP-dependent mechanism, thereby protecting humans from TB and CMC.



Cytokine production by expanded CD4+ T cell blasts stimulated with magnetic beads conjugated with anti-CD3 and anti-LY9 monoclonal antibodies or isotype control.

Keywords: Inborn errors of immunity, Tuberculosis, Chronic mucocutaneous candidiasis, T lymphocytes, IFN-γ, IL-17, IL-22

Disclosures: All authors indicated they had no financial relationships to disclose.

(6) Phase 3 Placebo-Controlled, Randomized Clinical Trial Outcomes of PI3K Delta Inhibitor Leniolisib in Patients with Activated PI3K Delta Syndrome (APDS/PASLI)

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Phosphoinositide 3-kinase delta (PI3Kδ) is encoded by PIK3CD and PIK3R1, and pathogenic genetic variants causing kinase hyperactivity can result in a primary immune regulatory disorder known as activated PI3Kδ syndrome (APDS1/2) or PASLI (Lucas CL, et al. Nat Immunol. 2014;15(1):88-97). Patients with APDS present with dysregulated T and B cells leading to lymphoproliferation and immunodeficiency manifesting as recurrent sinopulmonary and persistent herpesvirus infections, autoimmunity, enteropathy, and increased risk of lymphomagenesis. Current treatments are largely symptomatic and/or immunomodulatory. We previously reported use of molecularly targeted inhibition of hyperactive PI3Kδ signaling with leniolisib (CDZ173) in 6 patients with APDS in a 12-week, open-label, multi-center, within-subject dose-escalation Phase 2/3 clinical trial (Rao VK, et al. Blood. 2017;130(21):2307-2316). Leniolisib was found to be well-tolerated, and reduced PI3Kδ/AKT pathway hyperactivity, normalized immune cell phenotypes, and improved cytopenias and lymphoproliferation. An interim analysis of the open-label extension study reported continued consistency in effect, with half of patients stopping IRT (Rao VK, et al. Blood. 2018;132(suppl1):3706).

Here we report initial outcomes from Part 2 of the clinical trial (NCT02435173), a randomized 2:1; placebo-controlled; subject-, investigator-, and sponsor-blinded; fixed dose study. 31 patients were enrolled across the United States, Europe, and Russia. Patient demographics are shown in Table 1. The median age was 21.0 years (range, 12-55 years); 61.3% of patients were < 22 years old. The study population was 48.4% male, and skewed towards APDS1 (80.6%). 48.4% of patients had a known/probable family history of APDS. Lymphadenopathy and chronic infection were nearly universal (93.5% and 90.3%, respectively). 54.8% of patients had gastrointestinal symptoms including colitis, EoE, and GERD. Short stature was observed in 2 patients with APDS1 and 4 patients with APDS2. 74.2% of patients were on IRT at the time of the study. 19.4% had anxiety. Co-primary outcomes were change at 12 weeks from baseline in log10 transformed sum of product of diameters in the index lesions (lymph nodes) and change from baseline in percentage of naïve B cells out of total B cells.

Note: Outcome data is under analysis. Unblinded results from this investigational study will be presented at the CIS meeting in March 2022.

Table 1: APDS patient demographics

Patient	Age at onset/ enrollment (years)	Sex	Variant	Chronic infections	Lympho-proliferation	Cytopenias	Pulmonary	GI
1001005	0.5/29	F	*PIK3CD*	Pneumonia, URI	LAD, HSM	Lymphopenia	Bronchiectasis, restrictive lung disease	Colitis, EoE
1001006	1.5/16	F	*PIK3CD*	Recurrent URI	LAD, HSM	Iron deficiency anemia	Not reported	EoE
1001008	0.5/15	F	*PIK3CD*	Sinus, URI, pneumonia	Mild LAD	Iron deficiency anemia	Mild bronchiectasis	EoE
1001009	0.5/12	F	*PIK3R1*	Pneumonia, URI	LAD, HSM, profound oral lympho-proliferation	Microcytic anemia, lymphopenia	Bronchiectasis, GLILD, PE	Not reported
1001010	0.5/22	M	*PIK3R1*	Mycoplasma orale, disseminated, norovirus, pneumonia, sinusitis	LAD, HSM	Iron deficiency anemia, lymphopenia	Bronchiectasis	EoE, colitis
1001011	1/30	F	*PIK3CD*	EBV viremia, sinus	LAD, HSM	Lymphopenia	Bronchiectasis, ILD	Celiac disease
1001012	1/17	M	*PIK3CD*	EBV viremia, sinus, pneumonia	LAD, HSM	Iron deficiency anemia	Bronchiectasis, ILD	Colitis
1001013	1/13	M	*PIK3CD*	EBV viremia, sinus infections, cellulitis	LAD, SM	Iron deficiency anemia	Not reported	GERD
1001014	5/44	F	*PIK3CD*	EBV, HSV, HPV, MRSA, pseudomonas, pneumonia, sinusitis, candidiasis	LAD	Lymphopenia	Nodular lung infiltration, restrictive lung disease, bronchiectasis, L/U/L lung excision, PE	GERD
1001015	1/16	M	*PIK3CD*	Pneumonia, sinusitis, mastoiditis	LAD, SM	Thrombo-cytopenia	Bronchiectasis	Hyperplastic lymphoid tissue mass resection
1001016	6/17	F	*PIK3CD*	EBV viremia, URI, pneumonia, cellulitis,	LAD, HSM	Iron deficiency anemia, AI thrombo-cytopenia, neutropenia	Bronchiectasis, ILD	Not reported
1001017	2/29	F	*PIK3CD*	HSV, pneumonia, cellulitis	LAD, SM	Iron deficiency anemia, neutropenia	Bronchiectasis	Not reported
1001018	0.5/18	M	*PIK3CD*	CMV, EBV, *C difficile*, URI, pneumonia	LAD, HSM	AIHA, thrombo-cytopenia	Bronchiectasis	Lymphoid hyperplasia of gut, duodenal varix, colitis, non-infective hepatitis with ascites
1001020	1.5/18	M	*PIK3R1*	EBV viremia, URI, pneumonia, adenovirus, pseudomonas sepsis, lymphadenitis	LAD	Lymphopenia	Bronchiectasis	Not reported
1001022	1/21	M	*PIK3R1*	URI, cellulitis	LAD	Iron deficiency anemia, neutropenia, lymphopenia	Not reported	EoE, colitis, lymphoid hyperplasia of gut, rectal prolapse
1001023	14/48	F	*PIK3CD*	Pneumonia	LAD	Not reported	ILD, bronchiectasis	GERD
2002003	0.5/32	F	*PIK3CD*	None	LAD, SM	Lymphopenia	Bronchiectasis, asthma	None
3001002	1/23	F	*PIK3CD*	Upper and lower respiratory infections, episodic EBV viremia	LAD, SM, lymphoid hyperplasia in respiratory tract, adenoids, tonsils, cervical lymph nodes	Not reported	Bronchiectasis, atelectasis	Not reported
3001004	2/16	F	*PIK3CD*	Upper and lower respiratory infection, pneumonias	Not reported	Not reported	Bronchiectasis, fibrosis, lobe resection	Abdominal discomfort
3001005	1/31	F	*PIK3CD*	Upper and lower respiratory infections, recurrent labial HSV	LAD, SM, adenoids	Not reported	Bronchiectasis	Not reported
4001001	0.5/29	M	*PIK3CD*	Pneumonia, URI	LAD, SM	None	None	None
4001002	4/20	M	*PIK3CD*	Pneumonia, URI	LAD, SM	None	None	None
4001003	12/12	M	*PIK3CD*	None	LAD, SM	None	None	Blastocistis hominis infection
4002001	1/22	M	*PIK3CD*	Pneumonia, URI	LAD, HSM	Lymphopenia	Recurrent infections	Colitis, EoE
5001002	1.5/16	F	*PIK3CD*	Upper and lower respiratory tract infections (otitis, sinusitis, pneumonia)	LAD, hepato-megaly	None	None	None
6001001	0.5/44	F	*PIK3CD*	Upper and lower respiratory tract infections, pneumonia, multi-resistant pseudomonas infection and colonization, on long term O_2 therapy	LAD, HSM	None	Widespread bronchiectasis	Not reported
7001001	0.1/22	F	*PIK3CD*	Pneumonia, URI	LAD, HSM, hyperplasia of the lymphoid pharyngeal ring	Lymphopenia, anemia, thrombo-cytopenia	Deforming bronchitis, pneumofibrosis (bronchiectasis)	Anal fissure
8001002	0.25/12	M	*PIK3CD*	URI, otitis, purulent lymphadenitis, pneumonia	LAD	Neutropenia	ILD	Gastritis, colitis
8001003	11/14	M	*PIK3CD*	URI, purulent lymphadenitis, bronchitis	LAD	None	None	None
1101003	3/55	M	*PIK3R1*	Chronic otitis and sinusitis	None	None	None	None
1101002	2/28	M	*PIK3R1*	None	LAD	None	None	None
Averages	**Enrollment: 23.9**	**Male: 51.6%**	***PIK3CD*: 80.6%**	**90.3%**	**93.5%**	**61.3%**	**Bronchiectasis: 61.3%**	**54.8%**

AI, autoimmune; AIHA, autoimmune hemolytic anemia; ANCA, antineutrophil cytoplasmic antibody; CMV, cytomegalovirus; EBV, Epstein-Barr virus; EoE, eosinophilic esophagitis; F, female; GERD, gastroesophageal reflux disease; GLILD, granulomatous and lymphocytic interstitial lung disease; HSM, hepatosplenomegaly; HSV, herpes simplex virus; ILD, interstitial lung disease; LAD, lymphadenopathy; L/U/L, left upper lobe; M, male; PE, pulmonary embolism; RBBB, right bundle branch block; SM, splenomegaly; URI, upper respiratory tract infection.

Table 1: APDS patient demographics.

Keywords: activated PI3K delta syndrome, leniolisib, precision medicine, PI3K, PIK3CD, PIK3R1

Disclosures: Jason Bradt is employed by Pharming Healthcare Inc. Anna Shcherbina: has received speaker/honoraria from Novartis, Octapharma, and Sobi. Elaine Kulm has received a research grant from the National Cancer Institute (Research Grant includes principal investigator, collaborator or consultant and pending grants as well as grants already received, Funded by the NCI Contract No. 75N91019D00024, Task Order No. 75N91019F00131). Klaus Kucher is an employee and shareholder of Novartis Pharma AG. Kath Radford is employed by Novartis Pharma. All other authors indicated they had no financial relationships to disclose.

(7) Perturbation of adaptive immune responses to SARS-CoV-2 infection

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T cells have a crucial role in the induction of effector and memory responses to SARS-CoV-2 infections in immunocompetent and immunocompromised individuals. We performed high- throughput-sequencing of the T cell receptor beta (TRB) repertoire in over 1,000 peripheral blood samples derived from 739 adult patients infected by SARS-CoV-2 (548 critical, 182 severe, 195 moderate, 94 mild), 45 of which with hematological malignancy, and 146 uninfected controls from Italy. We also studied dynamics of TRB repertoire pre and post SARS-COV2 m-RNA vaccination in 21 patients with inborn error of immunity (IEI) and 10 healthcare workers (protocol NCT04582903). By matching our data to SARS-CoV-2-specific clonotype sequences previously identified using in vitro stimulation assays with SARS-CoV-2 peptides, we measured the breadth and depth of SARS-CoV-2 specific TRB repertoire, along with TRBV and TRBJ gene usage. We integrated these results with human leukocyte antigen (HLA) typing data obtained from whole genome sequencing (WGS) to characterize potential HLA restriction patterns associated with severity and to finely map epitope recognition.
SARS-CoV-2 specific clonotypes were present, but at low frequency, in uninfected individuals, likely reflecting previous exposure to seasonal

coronaviruses. We found that patients with older age, critical disease and hematologic malignancies have a reduced number of unique SARS-CoV-2-specific clonotypes, but a higher maximum productive frequency and clonality compared to immunocompetent infected individuals, consistent with a restricted repertoire in the former groups. This decrease in the diversity is not unique to the SARS-CoV-2 specific clonotypes, but is also observed across the entire TRB repertoire. We also identified differential TRBV and TRBJ gene usage patterns associated with age and severity. Furthermore, SARS-CoV-2-specific clonotype depths per antigen (class I and class II) in each age-severity group was different in infected patients versus controls and in subjects with heme malignancies compared to the infected subjects without heme malignancies. Analysis of the data from IEI patients and their post-vaccination response is currently ongoing.
This study suggest that the impaired adaptive immune responses may contribute to worse clinical outcomes in COVID-19 patients with critical disease and hematological malignancies. These findings have important implications in identifying optimal immunization and treatment strategies against COVID-19.

Keywords: COVID-19, T cell receptor repertoire, IEI, HTS, COVID-19 m-RNA vaccine

Disclosures: Ian Kaplan is employed by ADAPTIVE biotechnologies. Thomas M Snyder is an employee and shareholder of Adaptive biotechnologies. All other authors indicated they had no financial relationships to disclose.

(8) IDENTIFICATION OF GERMLINE MONOALLELIC MUTATIONS IN IKZF2 IN PATIENTS WITH IMMUNE DYSREGULATION

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Helios, encoded by IKZF2, is a member of the Ikaros family of transcription factors with pivotal roles in T-follicular helper, NK- and T-regulatory cell physiology. Somatic IKZF2 mutations are frequently found in lymphoid malignancies. Although germline mutations in IKZF1 and IKZF3, encoding Ikaros and Aiolos, have recently been identified in patients with phenotypically similar immunodeficiency syndromes, the effect of germline mutations in IKZF2 on human hematopoiesis and immunity remains enigmatic.
We performed whole exome sequencing in five patients with immune dysregulation and their family members. We then applied Co-immunoprecipitation, electrophoretic mobility shift assay and immunofluorescence microscopy techniques to assess dimerization and DNA binding capabilities of the mutations. Proteomic analysis by proximity-dependent Biotin Identification (BioID) was used to assess affinity of mutant Helios to its interaction partners, while single-cell RNA sequencing was applied to peripheral blood mononuclear cells (PBMCs) of one patient to study the transcriptional effect of the truncating IKZF2 mutation.
We identified germline IKZF2 mutations (one nonsense (p.R291X)- and 4 distinct missense variants) in six patients with systemic lupus erythematosus, immune thrombocytopenia or EBV-associated hemophagocytic lymphohistiocytosis. Patients were affected by disease at a mean age of 15yrs (2-25yrs) and exhibited hypogammaglobulinemia, decreased number of T-follicular helper and NK-cells. Single-cell RNA sequencing of PBMCs from the patient carrying the R291X variant revealed upregulation of pro-inflammatory genes associated with T-cell receptor activation and T-cell exhaustion. EMSA and immunofluorescence microscopy of

pericentromeric heterochromatin regions revealed the inability of HeliosR291X to homodimerize and bind target DNA as dimers. Additionally, co-immunoprecipitation experiments showed that HeliosR291X was neither able to homodimerize nor to form heterodimers with Ikaros and Aiolos. Moreover, BioID analysis revealed aberrant interaction of 3/5 Helios mutants with core components of the Nucleosome Remodeling histone Deacetylase (NuRD) complex conveying HELIOS-mediated epigenetic and transcriptional dysregulation.
Thus, germline heterozygous mutations in IKZF2 cause a novel syndrome associating immunodeficiency and profound immunedysregulation and disrupt interaction with the NuRD complex.

Keywords: Immune dysregulation, Inborn errors of immunity, Ikaros family of transcription factors, Transcriptional regulation, Systemic lupus erythematosus, Hemophagocytic lymphohistiocytosis

Disclosures: All authors indicated they had no financial relationships to disclose.

(9) Who's your data? Primary immune deficiency differential diagnosis prediction via machine learning and data mining of the USIDNET registry.

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Introduction: More than 450 primary immune deficiency (PID) diseases, and 7,000 rare diseases together afflict 1 in every 17 humans. Computational aids might facilitate the diagnostic task by extracting rules from large datasets and making predictions when faced with new problem cases.
Objective: In a data mining study, we aimed to predict PID diagnoses with a supervised machine-learning algorithm based on classification tree boosting.
Methods: Through a data query at the USIDNET registry we obtained a database of 2,396 patients with common diagnoses of PID, including their clinical and laboratory features. Twelve diagnoses and 286 features were included in the model. We used XGBoost with parallel tree boosting for supervised classification, and SHAP for variable importance interpretation, Python v3.7. The database was split into training and testing subsets, and after gradient descent boosting, the model measures prediction accuracy and individual feature importance. To correct for imbalanced classification, we used Class Weighting Hyperparameter, scale_pos_weight.
Results: The twelve diagnoses were CVID (1,098 patients), DiGeorge syndrome, Chronic granulomatous disease, Congenital agammaglobulinemia, ID not otherwise classified, Specific antibody deficiency, Complement deficiency, Hyper-IgM, Leukocyte adhesion deficiency, NEMO-ID, Severe combined immune deficiency, and Wiskott-Aldrich syndrome. For CVID, the model found an accuracy on the train sample of 0.80, with an area under the ROC curve (AUC) of 0.80, and a Gini coefficient of 0.60. In the test subset, accuracy was 0.76, AUC 0.75, and Gini 0.51. Positive feature value to predict CVID was highest for upper respiratory infections, asthma, autoimmunity and hypogammaglobulinemia. Features with highest negative predictive value were high IgE, growth delay, abscess, lymphopenia, and congenital heart disease. For the rest of the diagnoses, accuracy stayed between 0.75 and 0.99, AUC 0.46-0.87, Gini 0.07-0.75, and LogLoss 0.09-8.55. See tables and figures.

Discussion: Clinicians should remember to consider negative predictive features together with the positives. We are calling this a proof-of-concept to continue with our explorations. Good performance is encouraging, and feature importance might aid feature selection for future endeavors. In the meantime, we can learn from the rules derived by the model and build a user-friendly decision tree to generate differential diagnoses.

PIDD	n	Accuracy	AUC	Gini	LogLoss
CVID	1098	0.75	0.75	0.49	8.55
DGS	406	0.897	0.87	0.75	3.55
SCID	202	0.85	0.73	0.47	5.14
CGD	154	0.92	0.83	0.66	2.68
AGAMMA	135	0.88	0.76	0.52	3.84
CORE (ID)	132	0.88	0.72	0.44	4.18
SPAD	117	0.84	0.74	0.49	5.57
WAS	63	0.76	0.74	0.48	8.31
HIGM	46	0.93	0.65	0.30	2.59
NEMO-ID	25	0.97	0.62	0.23	1.01
COMPDEF	12	0.92	0.46	-0.07	2.64
LAD	6	0.997	0.66	0.33	0.09

Table 1. Number of patients and measures of prediction performance for 12 PID diagnoses.

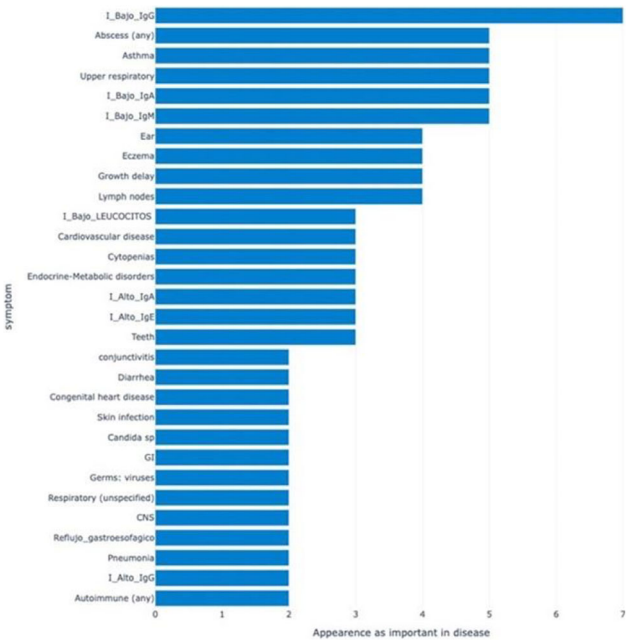

Figure 1. Most valuable features by frequency of appearance in twelve predictive models.

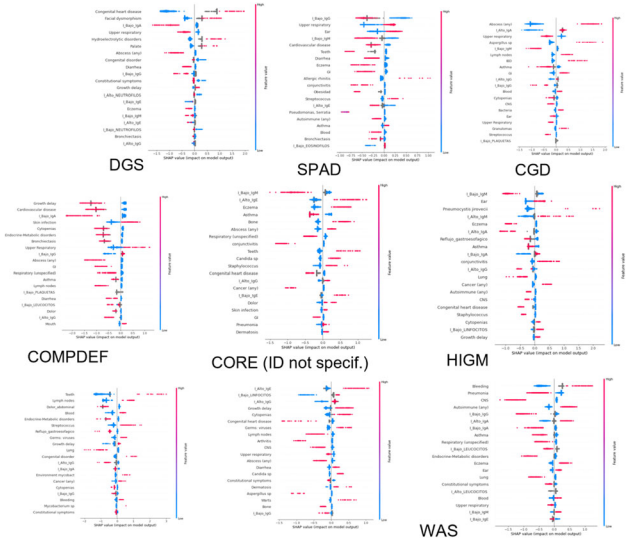

Figure 2. SHAP values by order of importance for positive (right) and negative (left) predictions in 9 models.

Keywords: inborn errors of immunity, data mining, extreme gradient boosting, Rare diseases, machine learning, diagnosis prediction, primary immune deficiencies, registry, classification

Disclosures: All authors indicated they had no financial relationships to disclose.

(10) Reduced mTORC1 signal in patients with dominant negative STAT3 mutations.

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Dominant-negative (DN) mutations in STAT3 (signal transducer and activator of transcription 3), underlie a syndrome of elevated serum IgE, eczematous dermatitis, recurrent skin and lung infections, and connective tissue abnormalities. Patients with mutations in the CARD11-MALT1-BCL10 (CBM) complex also develop elevated atopy and infection, and are known to have impaired mTORC1 signaling, which may explain their atopic phenotype. We therefore sought to determine if impaired mTORC1 signaling might also mechanistically underlie phenotypes in STAT3DN.
Here, we show that in mouse or human T-cells, chemical inhibition or dominant negative mutations in STAT3 result in reduced TCR-induced mTORC1 signaling. Exogenous glutamine could at least partially restore mTORC1 signaling in vitro. In vivo, treatment of mice with DN STAT3 mutations reduced total serum IgE levels. In addition, in vitro glutamine in human T-cells and in vivo oral supplementation in STAT3DN mice corrected their abnormal balance of tolerogenic foxp3+ rorgt+ tbet- Tregs cells vs. pathogenic foxp3+ rorgt- tbet+ pathogenic Tregs. Our data suggest that STAT3 promotes normal TCR-mediated mTORC1 signaling, and a normal tolerogenic Treg transcription factor signature, and that exogenous glutamine can reverse some of the phenotypic consequences of impaired STAT3 function.

Keywords: mTORC1, STAT3, IGE, Glutamine, Foxp3+

Disclosures: All authors indicated they had no financial relationships to disclose.

(11) The contribution of mosaic variants to molecular diagnosis in subjects with immune disorders.

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Background: The rate of molecular diagnosis within immunology ranges between 15%-79%, indicating that 21%-85% of cases remain "unsolved". Recent reports identified mosaic variants in UBA1 and TLR8, illustrating the role of mosaic variants in immune conditions. Here, we evaluate the contribution of mosaic variants to molecular diagnosis in a cohort of 3,395 subjects referred to the National Institute of Allergy and Infectious Diseases (NIAID) Centralized Sequencing Program (CSP).
Methods: We performed exome and/or genome sequencing on 3,395 study participants. We analyzed the data, confirmed our findings, and return the results to the referring teams and participants. Additionally, for 2,841 participants with exome data, we called variants with variant allele fractions (VAF) between 0.05 and 0.31 using LoFreq2, an algorithm that can detect variants with low VAF that may be missed by our standard GATK pipeline.
Results: Using our standard GATK approach, we detected numerous mosaic variants, including 28 variants in 28 individuals that were determined to be an underlying molecular diagnosis. Specifically, we detected mosaic KIT variants in 8 individuals, NLRP3 variants in 3 individuals, and TLR8 variants in 2 individuals. We also detected mosaic variants in NF1, TRPM4, ITGB2, NOD2, KRAS, IKBKG, IRF8, SAMD9L, JAK2, CXCR4, IKBKB, STAG3, and ATM, respectively, in 13 individuals. Additionally, we detected a mosaic variant in 2 sets of parents: STAT1 and CYBB which were inherited by their affected children.
Using LoFreq2, detected 167,703 mosaic variants in our exome cohort at a frequency of < 0.001 in gnomAD, including 25/28 variants from our standard GATK approach. Focusing on variants with CADD score >22 in genes implicated in inborn errors of immunity, we identified 265 variants in 115 genes. The top hits included POLR3C (n=17), LRBA (n=13), TNFRSF11A (n=13) and TET2 (n=11).
Discussion: Our analysis showed an important role of mosaic variants in immune disorders. Additional evaluation and confirmation are needed to determine whether variants called by LoFreq2 represent technical artifacts or whether they indeed underlie disease. Our data illustrate that alterations in the current exome/genome analysis pipelines would allow for the discovery of mosaic variants and a fuller understanding of their contribution to diseases.

Keywords: mosaic variants, molecular diagnosis, exome sequencing, genome sequencing

Disclosures: All authors indicated they had no financial relationships to disclose.

Friday Posters

(12) Heterozygous TNFRSF13B missense mutation in a 22q11.2 deletion syndrome patient with hypogammaglobulinemia and autoimmunity

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22q11.2 deletion syndrome has classically been associated with variable T-cell defects due to thymic hypoplasia or aplasia. Abnormalities in humoral immunity have also been reported and range from hypogammaglobulinemia to poor vaccine-specific antibody responses. Additionally, autoimmunity occurs at rates higher than the general population with idiopathic thrombocytopenic purpura, autoimmune hemolytic anemia, and thyroid disease being the most common.
Here we present the case of a 22-year-old patient with 22q11.2 deletion syndrome detected by FISH with a history of significant autoimmunity and hypogammaglobulinemia. The patient was first diagnosed with Evan's syndrome at one year of age. Despite treatment with chronic prednisone, monthly IVIG, rituximab, and splenectomy at age 12, the patient continued to require hospitalization multiple times a year for refractory anemia or thrombocytopenia. At age 14, the patient developed elevated liver function tests and positive anti-smooth muscle antibody titer (1:160). Liver biopsy was consistent with type 1 autoimmune hepatitis. His autoimmune hepatitis was difficult to treat though eventually responded to high-dose steroids in addition to mycophenolate and tacrolimus. The patient currently remains on monthly IVIG, tacrolimus, mycophenolate, and low-dose prednisone for management of his autoimmune conditions. His immune phenotype, while confounded by his chronic immunosuppression, is notable for T cell lymphopenia (CD4 238/cmm, CD8 172/cmm, naïve CD4 2/cmm, & naïve CD8 T cells 38/cmm), hypogammaglobulinemia (IgA < 8 mg/dL, IgM 272 mg/dL, IgG 1,160 mg/dL on IVIG), and low CD19+ B lymphocytes (47/cmm) with low switched memory B cells (1.1%). The patient's refractory autoimmune disease and hypogammaglobulinemia prompted whole exome sequencing and identified a heterozygous missense variant in TNFRSF13B (NM_012452.2:c.310T>C (p.Cys104Arg)), classified as pathogenic.
Both heterozygous and homozygous individuals with this TNFRSF13B variant have been reported amongst patients with common variable immunodeficiency (CVID). Additionally, CVID patients carrying TNFRSF13B variants have been observed to develop higher rates of autoimmunity and splenomegaly. Our patient is the second reported case of a heterozygous p.104C>R TNFRSF13B variant found in an individual with 22q11.2 deletion syndrome. This case highlights the importance of genetic testing to evaluate alternate inborn errors of immunity in 22q11.2 deletion patients who present with refractory autoimmunity or severe immunodeficiency.

Keywords: 22q11.2 deletion syndrome, TNFRSF13B, CVID

Disclosures: All authors indicated they had no financial relationships to disclose.

(13) COVID Antibody Response after Vaccination in Immunodeficient Patients

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Goal: To quantify antibody response in immunodeficient patients after receiving the COVID vaccine.
Methods: Data on adult immunodeficient patients within the Yale New Health Care system was collected from the electronic medical record. Pertinent variables were abstracted, including medications (i.e. immunosuppressants/immunomodulatory therapy), antibody levels post vaccination, and baseline flow cytometry. Data was analyzed using a conservative, albeit arbitrary, cutoff of 1000 and 8 as a positive antibody response (PAR) for the SARS-CoV-2 Total Ig Spike-RBD assay at Yale and Quest labs, respectively. These thresholds were chosen after reviewing current literature, although limited, on antibody neutralization thresholds in relation to anti-RBD antibody levels.
Results: 56 patients were analyzed thus far. 46% were over the age of 65. Immunodeficiencies included common variable immunodeficiency (CVID) (30%), hypogammaglobinemia (41%), other immunodeficiencies such as primary antibody deficiency, IgG 2 subclass deficiency (26%). 41% received Pfizer, 46% Moderna, and 5% Johnson&Johnson. 38% of all patients with immunodeficiencies had a PAR. 29% of the patients with CVID while 52% of the patients with hypogammaglobinemia demonstrated a PAR. 14% were on immunosuppressants/modulators and of those, 38% demonstrated a PAR. 59% had less than 20% CD27 switched memory B cells as baseline; of those patients, 20% had a PAR. 34% were on IVIG, of whom 47% had a PAR. Antibody response status was compared against age, CD27, CD3, CD4, CD8, CD45RA, CD45RO, CD19, NK cell values using a Mann-Whitney T-Test. Within the hypogammaglobulinemia subset, significant findings with respect to CD4/CD8 ratios and NK numbers was found; CD4/CD8, mean (Responders n=12) 4.776 +/- 3.551 vs (nonresp n=10) 2.195 +/- 1.135, p=0.0445. NK cells, mean (Responders n=12) 220.0 +/- 106.0 vs (nonresp n=10) 112.1 +/- 76.68, p=0.0112.
Conclusions: Investigation of the antibody response to COVID-19 vaccination with respect to the innate, humoral, and cellular immune system is needed, particularly in patients with immunodeficiencies. Our study found that higher NK cell numbers were significantly associated with a higher antibody response to COVID vaccination in patients with hypogammaglobinemia.

Keywords: COVID, Vaccine Response, Immunodeficiency, CVID, antibody titers

Disclosures: All authors indicated they had no financial relationships to disclose.

(14) First description of PAX1 as a dominant-negative cause of T lymphopenia

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Introduction: Paired box gene 1 (PAX1), a member of the PAX family of transcription factors, is critical in pattern formation during embryogenesis. In humans, it is expressed in the pharyngeal pouches that later give rise to important immunologic organs including the thymus and tonsils. PAX1 deficiency is associated with otofaciocervical syndrome type 2 (OTFCS2) with a variable phenotype including immunodeficiency with severe combined immunodeficiency (T-B+NK+ SCID). This syndrome has historically had an autosomal recessive mode of inheritance. Herein, we describe a newborn patient with T-cell lymphopenia found to have a heterozygous dominant-negative PAX1 variant with hypomorphic loss-of-function.
Case Report: We describe a 13-month-old male born to non-consanguineous parents who presented with an abnormal newborn screen for SCID (TRECs 10 copies/μL). Immunophenotyping showed a T-low/B+/NK+ profile with robust naïve percentages and proliferation to mitogens. Genetic testing revealed a rare heterozygous missense variant (NM_001257096.2, c.338G>A, p.Arg113His; 1 het in gnomAD) located within the DNA binding site. We performed a dual luciferase reporter assay to examine the transactivation of a regulatory sequence in the Nkx3-2 promoter region using wild type and variant PAX1 separately and together. The results showed decreased luciferase expression when the variant was alone; and when combined with wild type, the variant exerted a clear dominant-negative effect.
Discussion: We believe this is the first description of a heterozygous dominant-negative variant in PAX1 resulting in newborn T-cell lymphopenia. Dominant-negative PAX1 variants may underlie otherwise unexplained T-cell lymphopenia.

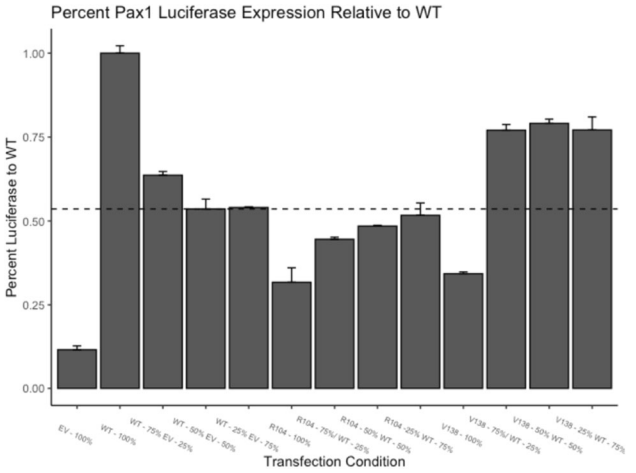

Figure 1. PAX1R104H exhibits dominant-negative loss of function activity

Keywords: PAX1, Thymus, T-cell lymphopenia, Immunodeficiency

Disclosures: All authors indicated they had no financial relationships to disclose.

(15) A novel mutation in NFκB1 presenting as post-operative inflammation and poor wound healing treated with anti-IL-1 therapy.

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The canonical NFκB pathway activates transcription factors critical in cell proliferation, inflammation, and immune response. Other NFκB1 variants were previously identified in patients presenting with immunodeficiency and immune dysregulation. NFκB1 patients with postsurgical complications developed deep necrotizing cellulitis with abscesses with fever and elevated inflammatory markers. We report a novel splice mutation in an individual with antibody deficiency, recurrent infections, hyperinflammatory response following surgery, and autoinflammatory processes.

A 7-year-old boy underwent multiple spinal surgeries for scoliosis with metal rod insertions. His initial repair was complicated by culture-negative sepsis and wound dehiscence concerning for osteomyelitis with negative wound cultures, requiring incision and drainage and hardware removal. Metal patch allergy testing was negative. He underwent a second scoliosis repair one year later. On postoperative day (POD) 1, the patient developed persistent fevers and increased wound drainage. Inflammatory markers increased with peak white blood cell count 58.8 x109/L, platelets 1,007 x 109/L and CRP 32.7 mg/dL by POD 12. Immunologic studies were significant for hypogammaglobulinemia (IgG 389 mg/dL), non-protective diphtheria and pneumococcal antibody titers, normal recent thymic emigrants, and decreased toll-like receptor cytokine responses. Genetic sequencing via a targeted primary immunodeficiency panel detected a likely pathogenic heterozygous variant of NFκB1, c.928-1G>A at an intronic, splice acceptor region. The patient was treated for hypogammaglobulinemia and presumed infection with immune globulin and antibiotics; he also required 14 washouts from POD 12 to 68, surgical rod exchange of the right rod, and removal of the left on POD 15. Blood and wound cultures remained negative. Given the likely NFkB1 pathogenic variant, sterile pyuria and hyperinflammatory state, anakinra (IL-1 inhibitor) was initiated on POD 25, with defervescence, normalized inflammatory markers, and fewer surgical site abscess formation. Anakinra was discontinued on POD 68 with no symptom recurrence. He will require future surgeries for rod extensions with plan to re-initiate anakinra preoperatively.

Genetic testing for NFκB1 variant should be considered in patients with hyper-inflamed responses to surgeries. While anti-IL-1 immunomodulators have been used in patients with chronic inflammatory conditions, this is a novel use in a patient with a splice-site NFkB1 mutation and hyperinflammatory response to spinal surgery.

Keywords: NFκB1, novel, culture-negative sepsis, postoperative inflammation, anakinra

Disclosures: All authors indicated they had no financial relationships to disclose.

(16) Advocacy and Understanding of SCID Founder Variants among Patients and Carriers in the U.S.-Based Irish Traveller Population

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The Irish Travellers are an ethnically distinct, endogamous, minority community originating from Ireland, with immigration to the U.S. resulting in a current subpopulation estimated in the 10,000s. Knowledge of rare genetic disorders, including an increased predisposition to severe combined immunodeficiency (SCID) and the value of carrier testing, is limited among some members of this population. Before newborn screening for SCID (NBS-SCID), affected individuals within this medically underserved community were recognized by onset of "the rash", a distinct feature of Omenn Syndrome (OS), a more serious and difficult to treat form of SCID. Hereby we describe SCID founder genes with clinical phenotypes and an advocacy and education program for carrier state among at-risk relatives, especially expecting parents in the U.S.-based Irish Traveller population.

A multi-institutional collaboration developed an outreach project for SCID patients and their relatives in the U.S.-based Irish Traveller community. SCID patients were identified through NBS-SCID and pedigree interviews with kindred Traveller members scattered in pockets across the U.S. Genetic testing was offered for SCID variants (Invitae) prioritizing members of child-bearing age. Educational sessions were designed to disseminate information on SCID and implications of carrier status.

Our team identified 14 SCID patients within the U.S. Irish Traveller population between 2003-2021, including four cases diagnosed via NBS-SCID. 10 of 14 patients were sequenced and harbored combinations

of pathogenic founder variants of two recombinase activating gene 1 (RAG1; p.Arg897*and p.Ser259Alafs*5) and one non-homologous end-joining 1 gene (NHEJ1; p.Gln224Argfs*27). At least 12 of 14 patients developed OS during the pre-transplant process. Of the 147 kindred identified, 33 at-risk members were screened for carrier state. Outreach and education were provided to those with pathogenic variants, with individualized counseling for two families with expectant mothers.
In contrast with the predominance of ADA SCID variant (Gly216Arg) within Ireland-based Travellers, U.S.-based Travellers additionally harbor an accumulation of two RAG1 and novel NHEJ1 variants. OS occurred in conjunction with any of the founder variants. Early diagnosis and treatment of affected members enabled by educational sessions and carrier screening within this high-risk population is vital to increase preparedness and avoid progression of SCID to OS.

Keywords: SCID, RAG-1 deficiency, NHEJ-1 deficiency, Founder variants, Irish Travellers, Omenn syndrome, Health disparities, Advocacy, Heterozygous carrier

Disclosures: Jennifer Heimall has relevant financial relationships with proprietary interests with ADMA (Advisory Board) , CIRM (Consultant, Other Financial or Material Support, Data Safety Monitoring Board) , CSL Behring (Advisory Board, Research Grant includes principal investigator, collaborator or consultant and pending grants as well as grants already received, Speaker/Honorariaincludes speakers bureau, symposia, and expert witness), Horizon (Advisory Board), Regeneron (Contracted Research), and UpToDate (Other Financial or Material Support, Section Author). Jolan Walter has relevant financial relationships with proprietary interests with Octapharma (Research Grant includes principal investigator, collaborator or consultant and pending grants as well as grants already received), Pharming (Consultant), Takeda (Consultant, Research Grant includes principal investigator, collaborator or consultant and pending grants as well as grants already received), X4 Pharmaceuticals (Consultant). All authors indicated they had no financial relationships to disclose.

(17) Farber Disease Revealed after Reevaluation of Refractory Inflammatory Disease

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Farber disease is a rare lysosomal storage disorder characterized by subcutaneous nodules, joint disease, and hoarse voice. It is autosomal recessive secondary to biallelic pathogenic variants in ASAH1 leading to deficient acid ceramidase activity. Subsequent formation of lipogranulomas leads to variable symptoms and severity depending on their location; inflammatory features are believed secondary to leukocyte dysregulation. We describe a patient with Farber disease with confounding ocular findings.
A 14-year-old neurotypical female first presented at age 1.5 years with subcutaneous nodules of the extremities and ears and erosive polyarthritis leading to contractures. Eye examination revealed bilateral keratitis; she was later noted to have bilateral corneal central fibrotic scars and visible corneal clouding of uncertain origin. Histopathology of the skin nodules suggested palisading histiocytes and fibrosis. Given the presence of nodules, arthritis and the question of eye inflammation, targeted sequencing of NOD2/CARD15 was performed and showed several variants. She was started on infliximab and corticosteroids. Due to poor growth, she underwent endoscopy, and histopathology showed vacuolated histiocytes of unclear significance in the large and small intestine, without definitive granulomas. She continued to develop nodules, and though she denied joint pain, active synovitis was revealed by MRI. Labwork demonstrated intermittent, mild ESR elevation (max 29 mm/hr) but consistently unremarkable blood counts and CRP. She additionally failed methotrexate, etanercept, adalimumab, and canakinumab. She was recently started on tofacitinib and receives regular intralesional triamcinolone injections with mild improvement in the nodules.
Due to her unusual clinical course, the underlying etiology for her condition was reevaluated using a commercially available gene panel which resulted with one pathogenic c.886C>T (p.Arg296*) and one likely pathogenic c.785+2T>C (splice donor) variant in ASAH1; her NOD2 variants are re-classified as benign. Familial testing confirmed the ASAH1 variants are in trans, and are also carried by her similarly affected brother. Enzymatic testing detected 3.2% of normal leukocyte acid ceramidase activity, confirming the diagnosis of Farber disease. Alternative treatment options (bone marrow transplant) are being explored. This case highlights both the dangers of diagnostic momentum and the often underappreciated overlap between metabolic and inflammatory disorders.

Keywords: Farber disease, lysosomal storage disorders, metabolic mimics

Disclosures: Burrage Lindsay has relevant financial relationships with proprietary interests Baylor Genetics (Employment, Other Financial or Material Support, Department of Molecular and Human Genetics receives revenue from clinical genetic testing completed at Baylor Genetics Laboratories). All other authors indicated they had no financial relationships to disclose.

(18) Ectonucleotidase expression on regulatory T cells in chronic granulomatous disease

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Ectonucleotidases (including CD39 and CD73) are involved in two-pronged anti-inflammatory action metabolizing proinflammatory adenosine triphosphate to anti-inflammatory adenosine. Both CD39 and CD73 are expressed on regulatory T-cells (Tregs) and dampen inflammatory responses, including anti-tutor response. Ectonucleotidase inhibitors hold promise as targeted anticancer therapy. However, administration of CD39/CD73 inhibitors may lead to long-term hyperinflammatory complications in patients with cancer. Besides, CD39/CD73 expressed on Tregs may play an important role in dampening autoimmunity/autoinflammation in various autoimmune/autoinflammatory disorders inuding those associated with inborn errors of immunity. We analyzed the expression of CD39 and CD73 on Tregs in patients with chronic granulomatous disease (CGD), a primary immunodeficiency characterised by prominent inflammatory manifestations. Aberrant CD39/CD73 expression or function may be one of the central mechanisms underlying the hyperinflammatory manifestations associated with both primary and secondary immunodeficiency (resulting, for example, from immune checkpoint blockade), and various autoimmune diseases.
Methods: We included 11 patients with CGD, 11 carriers (of CGD), and 11 controls. CD39 and CD73 expression on circulating Tregs was

analyzed using flow cytometry. Naïve (NTregs) and effector Tregs (ETregs) were defined as CD4+CD25+CD127–CD45RA+ and CD4+ CD25+CD127–CD45RA– lymphocytes, respectively.
Results: CD39–CD73+ Tregs were lower in cases as compared to controls. Reduced expression of CD39 was noted on CD39+CD73+ Tregs in patients with CGD. The absolute count of CD39+CD73+ NTregs and expression of CD39 on CD39+CD73+ NTregs was lower in carriers as compared to controls. Expression of CD73 on CD39+CD73+ ETregs was lower in cases as compared to carriers.
Conclusions: Aberrant expression of ectonucleotidases in Tregs may predispose patients and carriers of CGD to develop hyperinflammatory and autoimmune manifestations. Similarly long-term autoimmune/inflammatory predilection may result from CD39/CD73 inhibition in patients with cancer and other autoimmune diseases.

Keywords: Chronic granulomatous disease, Ectonucleotidases, T regulatory cells, CD73, CD39, inflammation, flow cytometry

Disclosures: Vignesh Pandiarajan has relevant financial relationships with proprietary interests with Indian Council of Medical Research (Research Grant includes principal investigator, collaborator or consultant and pending grants as well as grants already received),and Jeffrey Modell Foundation (Research Grant includes principal investigator, collaborator or consultant and pending grants as well as grants already received). All authors indicated they had no financial relationships to disclose.

(19) A novel variant causing RelA Haploinsufficiency

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RELA is a transcription factor of the canonical NFkB signaling pathway, essential for immune regulation and self-tolerance. RelA haploinsufficiency has clinical feature of recurrent fever, chronic mucocutaneous ulceration and inflammatory bowel disease with variable penetrance and expressivity. Here we present a patient with a pathogenic variant in RELA with a phenotype of autoimmunity and immune dysregulation.
A 13-year-old girl with no significant past medical history presented with one week of fever, lymphadenopathy and an exudative sore throat. Imaging was consistent with a peritonsillar abscess and antibiotics were initiated. The patient developed hypotension, thrombocytopenia (10k/uL) and neutropenia (0.3k/uL) managed with fluid resuscitation and platelet transfusions without improvement. Imaging of the neck, chest, abdomen and pelvis showed diffuse lymphadenopathy in the bilateral supraclavicular, axillary, retroperitoneal and mesenteric lymph nodes, in addition to bowel wall thickening in the terminal ileum and colon. A peripheral lymph node and bone marrow biopsy were negative for malignancy, infection or evidence of bone marrow failure. Due to persistent thrombocytopenia she was given intravenous immunoglobulin (IVIG) with temporary improvement in the platelet count and resolution of her neutropenia. Second line management of her thrombocytopenia included pulsed steroids and romiplostim with sustained improvement. On further evaluation she reports recurring episodes of severe abdominal pain and oral ulcerations. She also reports one episode of vaginal ulceration at age 10. Laboratory evaluation revealed for lack of autoantibodies, normal lymphocyte subsets and a lack of elevated TCRalphabeta+ double negative cells. Immunoglobulin level and protective antibody titers were within normal limits. A 407-gene primary immunodeficiency panel revealed a novel pathogenic variant in exon 8 of the RELA gene (c.853G>T (p.Glu285*)), leading to a premature translation stop signal, expected to result in an absent or disrupted protein. Maternal variant genetic testing was negative and paternal testing is needed.
This is the second described patient with an acute presentation of lymphoproliferation and autoimmune cytopenia due to RelA haploinsufficiency. Both patients have premature translation stop signals in exon 8, however the symptoms of both autoimmune cytopenias and chronic mucocutaneous ulceration are unique to this patient. Functional validation showing a defect in the IkB pathway is underway.

Keywords: RELA, autoimmune cytopenia, NFkB, chronic ulceration, immune dysregulation, lymphoproliferation

Disclosures: All authors indicated they had no financial relationships to disclose.

(20) Evolving cutaneous Rhizopus cellulitis in a CGD patient presenting with a contact rash

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Introduction: Chronic granulomatous disease (CGD) is caused by defects in nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and increases infection risk to catalase positive organisms. Aspergillus sp. is the most common fungal infection in CGD and accounts for approximately 20% of deaths(1); however, other rare fungi can also lead to severe infection. In a review of 68 CGD patients with non-aspergillus fungal infections, Rhizopus was the second most reported with 9 cases and infected the lung, liver, spleen and/or brain. There has been one report of Rhizopus skin infection in CGD patient(2). Here we present the second reported case of Rhizopus induced cellulitis in a CGD patient.
Case: A 20-month-old male with history of CGD and atopic dermatitis developed mild erythema with small white papules at the site of peripheral intravenous tape on his right upper extremity. This was initially treated with triamcinolone 0.025%. Over the following week the rash become more violaceous and indurated with papular lesions. He was then started on treatment dosing Bactrim for a presumed bacterial cellulitis. The infection was unresponsive and the patient developed swelling that extended to the wrist and elbow. He had remained afebrile. He was subsequently admitted for further work up and treatment. Initial labs revealed a CRP 1.1 mg/dL, ESR 56 mm/hr, WBC 16.9x10E3/uL, and platelets 445x10E3/uL. A biopsy of the affected tissue showed central ulceration with multifocal abscess formation with abundant eosinophils and poorly formed granulomas with giant cell formation. PAS and GMS staining revealed multifocal non-septate, wide, branching fungal hyphae that was identified as Rhizopus sp. The patient was started on posaconazole and micafungin and transitioned to micafungin alone after sensitivities resulted. He underwent complete excision of the infected arm tissue with final surgical resection margins negative for fungal organisms. He continues to do well and uses his right arm without limitation.
Discussion: Cutaneous manifestation in CGD patients encompass infectious and inflammatory conditions. In CGD patients presenting with abnormal skin findings, it is important to consider fungal organisms and pursue rapid identification of the cause.
1. Doi:10.3390/jof2020015
2. Doi: 10.1097/INF.0b013e3181dc8352

Keywords: CGD, Rhizopus, Cellulitis, Fungal, Cutaneous

Disclosures: All authors indicated they had no financial relationships to disclose.

(21) Fatal hemophagocytic lymphohistiocytosis revealing an hepatosplenic T cell lymphoma with somatic STAT5b gain-of-function mutation

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Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening syndrome of excessive immune activation. Secondary HLH develops as a complication of infection, rheumatologic conditions, or malignancy. Hepatosplenic T cell lymphoma (HSTCL) is a rare neoplasm of mature gamma/delta T cells with an aggressive clinical course. HSTCL involves the liver and the spleen, with little or no lymph node involvement. The bone marrow biopsy may be normal, creating a significant diagnostic challenge. Only a few cases of HSCTL-driven HLH are described in children.

We report herein the history of a 17-year-old boy who was admitted to our hospital with prolonged fever, asthenia and hepatosplenomegaly while fulfilling 6 of the 8 HLH criteria. PET scan showed a diffuse hypermetabolic spleen without associated hypermetabolic lymph node or liver. Functional and genetic tests excluded a primary HLH. Liver and bone marrow biopsies did not show evidence of malignant cells. The patient was treated for HLH of unknown origin with high-dose steroids, later combined with anakinra then etoposide. Clinical improvement only started by the addition of high-dose ruxolitinib, allowing progressive tapering of steroids. Six months after the initiation of therapy, a further clinical deterioration led to a new oncological screening. Suspicious cells were found on a new bone marrow aspiration, but the diagnosis of gamma/delta HSTCL was only made by splenectomy. The HSTCL was associated with the classical isochromosome 7q and trisomy 8 and a somatic N642H gain-of-function mutation in STAT5B. The patient failed to achieve complete remission despite intensive chemotherapy and underwent an allogeneic hematopoietic stem cell transplantation (HSCT) with a matched unrelated donor. Unfortunately, the HSTCL relapsed 7 months after HSCT with brain and bone marrow involvement.

This case illustrates the difficulty of diagnosing HSTCL, a rare etiology of HLH that should be evoked in the presence of unsolved HLH syndrome with prominent hepatosplenomegaly. In the present report, the use of ruxolitinib could also have participated in the delay in diagnosis since it targets the underlying altered pathway of this rare and aggressive tumor.

Keywords: Hemophagocytic lymphohistiocytosis, Hepatosplenic T cell lymphoma, STAT5b gain-of-function mutation, hematopoietic stem cell transplantation

Disclosures: Hélène Decaluwe has relevant financial relationships with proprietary interests with Eli Lilly Canada (Advisory Board). All other authors indicated they had no financial relationships to disclose.

(22) Hematopoietic cell transplantation and food allergy in patients with inborn errors of immunity: a twelve-year review

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Introduction: While the presence of food allergy (FA) has been investigated after allogeneic hematopoietic cell transplantation (HCT) in patients with hematologic malignancies, minimal data have been published on persistence of FA in post-HCT patients with inborn errors of immunity (IEI).

Methods: We reviewed records of patients with Wiskott-Aldrich syndrome (WAS) and Immunodysregulation, Polyendocrinopathy, Enteropathy, X-linked (IPEX), two IEI with a known risk for FA.

Results: We identified 14 patients with WAS or IPEX who underwent HCT at our institution over the past 12 years. Donors were either matched related or unrelated and none had known FA. Median age of HCT was 8 months (range 4-141). Median whole blood (WB) chimerism was 99% (range 79-100), myeloid 99% (76-100), T cell 99% (86-100), and B cell 100% (84-100). The most commonly allergenic foods were milk, egg, and peanut. Of the 11 WAS and 3 IPEX patients, 5 (35.7%) had FA pre-HCT. Of the 3 WAS patients with pre-HCT FA, 1 had completely resolved FA, 1 had partially resolved FA, and 1 had persistent FA post-HCT (this patient had CD3 chimerism < 90%). For the remaining 8 WAS patients without FA pre-HCT, 3 (37.5%) developed new FA with 2 completely resolved and 1 partially resolved. Of the 2 IPEX patients with pre-HCT FA, both resolved their food allergies post-HCT, while the third developed new FA (this patient had CD3 chimerism < 90%). For both IEIs transplanted, WB chimerism less than 100% showed a trend toward the development of new post-HCT FA compared to patients with 100% WB chimerism (3 of 5 versus 1 of 4).

Conclusions: This is the first study describing the persistence of FA post-HCT in patients with IEI and a predisposition to FA. HCT with 100% WB chimerism showed a trend toward lower risk of new FA, although more patients are needed to determine the variables impacting resolution of FA and development of new FA in patients with IEI who undergo HCT.

Table 1

* = a priori allergy by testing (no known reaction), ** = possible non-IgE mediated allergy when symptoms are noted, FA = food allergy, 6FED = 6 food elimination diet, EGID = eosinophilic gastrointestinal disorder

Pt	Dx	Age at HCT (months)	Chimerism (%)	Pre-HSCT FA	Post-HCT FA	FA resolved at last follow-up	Oral Food Challenge (Pass/Fail, time post-HCT)
1	WAS	5	WB 99 CD14/15 99 CD3 99 CD19 99	no	no	-	-
2	WAS	6	WB 100 CD14/15 100 CD3 100 CD19 100	no	no	-	-
3	WAS	10	WB 100 CD14/15 100 CD3 100 CD19 100	no	no	-	-
4	WAS	51	WB 99 CD14/15 100 CD3 97 CD19 99	no	no	-	-
5	WAS	141	WB 100 CD14/15 100 CD3 100 CD19 100	no	no	-	-
6	WAS	8	WB 95 CD14/15 99 CD3 90 CD19 100	Soy** (diarrhea)	Soy Wheat Lentil Chickpea Peanut Tree nuts Sesame*	no	Wheat F 23m Brazil nut P 33m
7	IPEX	4	WB 93 CD14/15 96 CD3 86 CD19 95	no	Egg	no	-
8	WAS	7	WB 99 CD14/15 99 CD3 99 CD19 100	no	Milk Egg Peanuts* Tree nuts* Sesame*	partially	Peanut P 9m Egg P 13m
9	WAS	8	WB 84 CD14/15 76 CD3 97 CD19 96	Milk** (bloody stools)	Peanut Tree nuts Egg Sesame* Sunflower seed*	partially	Milk, pecan, cashew, almond, egg, sesame, sunflower all resolved (home introduction)
10	WAS	11	WB 98 CD14/15 97 CD3 100 CD19 91	Peas Peanut Wheat	Peas Peanut Wheat Milk Tree nuts*	partially	Soy P 10m Milk P 22m Wheat F 63m
11	WAS	13	WB 100 CD14/15 100 CD3 100 CD19 100	no	Egg	yes	-
12	WAS	23	WB 99 CD14/15 99 CD3 99 CD19 100	no	Peanut Milk	yes	-
13	IPEX	5	WB 92 CD14/15 86 CD3 99 CD19 84	Milk (rash)**	Milk (rash)	yes	-
14	IPEX	91	WB 99 CD14/15 100 CD3 97 CD19 100	6FED for EGID** Sensitized to milk/egg/wheat	Milk Egg Wheat	yes	Egg P 23m Wheat P 24m Milk P 25m

Table 1 * = a priori allergy by testing (no known reaction), ** = possible non-IgE mediated allergy when symptoms are noted, FA = food allergy, 6FED = 6 food elimination diet, EGID = eosinophilic gastrointestinal disorder

Figure 2

CR = complete resolution, PR = partial resolution, NR = no resolution
If <100% WB chimerism, then 3 of 5 developed new food allergy. If 100% WB chimerism, then 1 of 4 developed new food allergy.

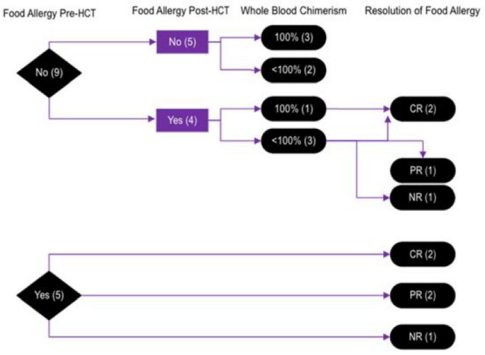

Figure 2 CR = complete resolution, PR = partial resolution, NR = no resolution If <100% WB chimerism, then 3 of 5 developed new food allergy. If 100% WB chimerism, then 1 of 4 developed new food allergy.

Keywords: hematopoietic cell transplantation (HCT), food allergy (FA), chimerism, Wiskott-Aldrich Syndrome (WAS), Immunodysregulation, Polyendocrinopathy, Enteropathy, X-linked (IPEX)

Disclosures: Jennifer Puck has relevant financial relationships with proprietary interests with Invitae (Employment, Ownership Interest includes stock, stock options, patent or other intellectual property) and UpToDate (Other Financial or Material Support, Royalties). Christopher Dvorak has relevant financial relationships with proprietary interests with Alexion Inc (Advisory Board, Consultant), Jazz Pharma (Consultant), and Omeros Corp (Consultant). All other authors indicated they had no financial relationships to disclose.

(23) Human Mast Cells Treated with Monoclonal Tumor Necrosis Factor-alpha Antibody Protect Neuronal Cells Against Hydrogen Peroxide-Induced Toxicity

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Introduction: Currently there is considerable evidence in the literature for the influence of inflammation and oxidative stress closely associated with activated mast cells on the development of neurodegenerative diseases. Trials of therapeutic strategies for such disorders have emerged in recent years using immunomodulatory agents that target mast cells or their secretome.
Aim: To investigate the protective effect of mast cells treated with TNF-α inhibitor against neurodegeneration.
Methods: An in vitro neurodegenerative model was generated by treating neuron-like human SH-SY5Y neuroblastoma cells with oxidant hydrogen peroxide (H2O2). Human bone marrow-derived mononuclear cells were differentiated into mature mast cells with Stem cell factor, IL-6, and IL-3 applications in 6-8 weeks' duration of culture. Mast cells were grouped as 1- non-activated, 2- activated with lipopolysaccharide (LPS), 3- LPS + Monoclonal TNF-α Antibody (10 μg/ml). After 24 hours' incubation, conditioned media (CM) of mast cell groups were collected and later be applied on with or without H2O2 -SH-SY5Y cells. Cell survival analysis of these cells were performed by MTT Assay. TNF-α concentrations in CM of mast cell groups were measured with ELISA.
Results: When SH-SY5Y cells were exposed to H2O2, a dose-dependent decrease in cell viability rates was observed. At the concentration of 500 μM, H2O2 decreased the rate of cell viability to 71±2% of the control, so this concentration was determined to be suitable for inducing neurotoxicity in subsequent experiments. Activated mast cell CM decreased viability rates of H2O2 treated-SH-SY5Y cells. Importantly, CM of monoclonal TNF-α Antibody treated 'activated mast cell' prevented the toxic effects of H2O2, and improved the cell viability rate up to 103±3%, providing a significant protective effect. The latter findings were supported by morphological assessments. Furthermore, CM of TNF-α antibody treated mast cell displayed lower TNF-α levels compared to control CM ($p < 0.05$).
Conclusion: Monoclonal TNF-α Antibody treated mast cell CM can effectively inhibit toxic effects of oxidant-H2O2. Mediatory effect of this agent on inflammation and oxidative stress seem to be important factors that account for the increased cell survival rates related to it. Our study indicates a promising pharmacotherapeutic role for TNF inhibitors against neurodegeneration.

Keywords: Monoclonal TNF-alpha Antibody, Human Bone-Marrow Derived Mast cells, SH-SY5Y cells, Neurodegeneration, Neuroinflammation, Tumor Necrosis Factor-alpha, Hydrogen Peroxide

Disclosure: All authors indicated they had no financial relationships to disclose.

(24) A possible association between thyroid autoantibodies among TIDM patients and Parvovirus B19 infection

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In recent years, an overwhelming association between Pediatric Type 1 Diabetes Miletus (T1DM) and autoimmune diseases has been largely reported. The current study aimed to determine a possible association of autoimmune thyroiditis (AIT), celiac disease (CD) autoantibodies among pediatric T1DM cases positive for Parvovirus B19 infection in southwestern Saudi Arabia. The overall prevalence of B19 antibodies in the study group was 70(14%). The prevalence of autoantibodies against thyroid and CD among pediatric T1DM patients to be 44(25%) and 25(14.4%) respectively. Further determination of the prevalence of Parvovirus B19 IgG antibodies and thyroid antibodies among T1DM pediatric patients revealed that there was significant association between them with a $p < 0.0491$. Similarly, the autoantibodies against thyroid were more among the seropositive Parvovirus B19 children with T1DM. A positive association in prevalence of autoantibodies against thyroid disease with the increase in duration of diabetes was also noted. Hence, regular screening of T1DM patients for B19 antibodies and autoantibodies for thyroid and CD might be valuable.

Keywords: Parvovirus B19 antibody, thyroid autoantibodies, celiac autoantibodies, T1DM

Disclosures: All authors indicated they had no financial relationships to disclose.

(25) Characterization of Diverse Human FOXN1 Mutations Reveals Complete and Partial Loss-of-Function and Gain-of-Function Consequences

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Thymus hypoplasia occurs in many clinical conditions, including individuals with autosomal recessive and compound heterozygous mutations in FOXN1. FOXN1 is the master transcriptional regulator of thymus epithelial cell development, with mutations in the gene causing reduced to absent T cell development in the thymus. Targeted exome and whole genome sequencing applied to patients with low TRECs (measure of T cell output) at birth has uncovered over 40 distinct mutations in FOXN1. The consequences of these FOXN1 mutations on patients is varied and somewhat complicated by delayed T cell development in some heterozygous carriers that corrects over time. To better understand how the various FOXN1 mutations impact T cell development, we compared their function using luciferase reporter assays and nuclear localization experiments. For selected compound heterozygous FOXN1 mutations, mice were also developed to genocopy these mutations to monitor thymopoiesis. Our findings reveal that certain FOXN1 mutations result in a complete loss-of-function while others have a partial loss-of-function consequences. Surprisingly, some mutations in FOXN1 result in gain-of-functions. Comparative analyses of thymopoiesis in murine embryos versus adult mice genocopying compound heterozygous mutations in one patient reveal a transient thymus hypoplasia that corrects over time. These results are remarkably like that reported for many patients, wherein peripheral T cell numbers will improve over time contingent on the mutation. Taken together, our findings establish FOXN1 genotype-phenotype relationships and suggest rapid functional screening approaches can be used to define the impact of the mutations. Such findings will better inform clinicians regarding the potential impact of FOXN1 mutations among their patient cohorts.

Keywords: Thymus hypoplasia, FOXN1 transcription factor, Thymopoiesis, TRECs

Disclosures: M. Louise Markert has relevant financial relationships with proprietary interests with Enzyvant (Other Financial or Material Support, Royalties, and Enzyvant (Other Financial or Material Support, Portion of salary was paid by funding from Enzyvant). All other authors indicated they had no financial relationships to disclose.

(26) B-cell Lymphopenia due to Transplacental Ocrelizumab Exposure

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Transient peripheral B-cell lymphopenia is reported in infants born to mothers exposed to rituximab, an anti-CD20 monoclonal antibody. Lymphopenia in these infants typically resolves by 6 months of age. Ocrelizumab, another anti-CD20 monoclonal antibody, was approved by the FDA for the treatment of multiple sclerosis in 2017. The potential effects of ocrelizumab on infants exposed in utero are not well defined. There is one report of an infant with second trimester exposure to ocrelizumab and low B cells at birth CD19+ 217 cells/mcL (300-2000 cells/mcL), with negative infection history.

We report a case of a female infant with secondary B-cell lymphopenia due to transplacental exposure to ocrelizumab. The patient's mother received 2 ocrelizumab infusions 6 months apart, with the most recent infusion approximately 1 month prior to conception. The patient was born without complication at 40 weeks weighing 3230 grams. Routine maternal infection laboratory tests were negative, and the infant had normal TRECs on newborn screen. Hepatitis B vaccine was administered on day of life (DOL) 2 without incident. On DOL 3, the patient was noted to have B cell lymphopenia, CD19+ 178 cells/mcL (300-2000 cells/mcL). At age 2.5 weeks, CD19+ cells remained low, 204 cells/mcL (300-2000 cells/mcL). Total memory and class switched memory B cells were relatively decreased, while transitional B cells were relatively increased (Table 1). Total lymphocyte, T cell, and NK cell counts were normal. At age 2.5 months, CD19+ cell count normalized to 449 cells/mcL (300-2000 cells/mcL). The relative decrease in switched memory B cells and increase in transitional B cells were improved from prior. IgG and IgM were normal, and IgA was decreased 8 mg/dL (20-53 mg/dL). The patient has not had infections or required antibiotic treatment. She received 2-, 4-, and 6-month routine vaccinations including rotavirus without adverse effect. Growth and development have been normal. To our knowledge, this is the first report of an infant with transient B cell lymphopenia due to transplacental exposure to ocrelizumab administered prior to pregnancy. Additional studies are needed to understand the safety of ocrelizumab in infants born to mothers exposed to the drug before and during pregnancy.

	3 days old	18 days old	2.5 months old
WBC (7.2-18 K/UL)		7.5	5.7 L
ALC (3.4-7.6 K/UL)		3.9	3.3 L
CD19+ (300-2000 cells/mcL)	178 L	204 L	449
CD3+ (2500-5500 cells/mcL)		3207	2640
CD4+ (1600-4000 cells/mcL)		2239	1880
CD8+ (560-1700 cells/mcL)		909	670
CD16+56+ (170-1100 cells/mcL)		319	204
CD27+ (4.6-49.1%)		2 L	3.6 L
CD27+IgM-IgD- (1.9-30.4%)		0.3 L	0.7 L
CD38+IgM+ (7.6-48.6%)		83.6 H	59.6 H
IgG (218-610 mg/dL)		722 H	349
IgA (20-53 mg/dL)		<5 L	8 L
IgM (11-51 mg/dL)		33	31

Table 1

Keywords: Anti-CD20 antibody, Ocrelizumab, B-cell lymphopenia

Disclosures: All authors indicated they had no financial relationships to disclose.

(27) Dense Genotyping of Immunologic Loci Identifies CXCR4 as a Novel Susceptibility Locus for Systemic Juvenile Idiopathic Arthritis

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Systemic juvenile idiopathic arthritis (sJIA) is a rare inflammatory disease which causes spiking fever, skin rash, chronic arthritis, and inflammation of the heart and lungs. Most of the mortality is owed to macrophage activation syndrome, a cytokine storm syndrome in which imbalanced cross-talk between cytotoxic cells and macrophages leads to

hemophagocytosis and multiorgan failure. Despite recognition of excessive innate immune responses to endotoxin, specific host or environmental factors that underlie sJIA are largely unknown.
Genomic investigations are an important tool for identifying new disease associated genes and pathways, and recent genomic studies of sJIA by our group and others are yielding important new insights. To explore the genetic contribution to sJIA, we studied an international cohort of sJIA cases and matched controls with the Immunochip, a single nucleotide polymorphism (SNP) array that generates exceptionally dense genotyping at 186 immunogenetic loci.
Using a combination of SNP genotyping, SNP imputation, haplotype analysis and association testing by logistic regression, we identified a novel, highly-significant susceptibility locus on chromosome 2 that contained CXCR4, encoding C-X-C chemokine receptor type 4. The strongest risk factor was a 124kb 6-SNP haplotype that contained the entire CXCR4 gene (p=4.3E-10). Examination of the risk haplotype in public databases revealed it to be a super-enhancer that regulates CXCR4 in lymphocytes that engages in 3 distinct chromatin loops with the CXCR4 promoter in EBV-B cells. Analysis of paired genomic and RNA sequencing data in silico identified positive correlation between the sJIA risk haplotype and CXCR4 expression in Epstein-Barr Virus (EBV)-B cells (p=4.0E-4). Consistent with these observations, in silico studies of primary sJIA monocytes found increased CXCR4 expression in sJIA cases compared to healthy children, irrespective of disease activity. To evaluate the effect of the risk haplotype on chemotaxis in a cell-specific manner, we are assaying primary leukocytes from subjects with 0 or 2 copies of the risk haplotype using a flow cytometry-based trans-well migration assay. This study has identified CXCR4 as a novel risk locus in sJIA. CXCR4 is critically important in the development, maturation and migration of many leukocyte populations. It has also been linked to mechanisms of LPS sensing.

Keywords: Systemic juvenile idiopathic arthritis (sJIA), CXCR4 (C-X-C chemokine receptor type 4), autoinflammation, genomics, immunochip

Disclosures: All authors indicated they had no financial relationships to disclose.

(28) Activated PI3 Kinase Delta Syndrome Leading to Severe Intestinal Nodular Lymphoid Hyperplasia Treated with Sirolimus

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A 4-year-old boy presented to his pediatrician with constipation, hematochezia, and rectal prolapse. Upper and lower endoscopies revealed nodular appearing mucosa in the esophagus, stomach, and duodenum, and a significant number of polypoid lesions throughout the colon. Biopsy of the lesions showed marked lymphoid hyperplasia.
Further immunologic evaluation revealed a decreased total CD4+ T-cell count with a decrease in CD4+ naïve T-cells and an increase in CD4+ memory T-cells. An increase in total CD8+ T-cells with an expansion of effector memory CD8+ T-cells was also observed. There was a normal total B-cell count with a decrease in CD21 positive cells and an increase in CD21 negative cells. IgG and IgM were increased while IgA was normal. Whole exome sequencing revealed a heterozygous pathogenic mutation in phosphatidylinositol 3-Kinase catalytic delta (PIK3CD, p.E1021K, c.3061 G>A), confirming the diagnosis of activated PI3K-delta syndrome (APDS). This gain of function mutation of the catalytic domain of PI3K results in the activation of the PI3K/AKT/mTOR/S6 kinase pathway which can lead to lymphocyte proliferation, T-cell senescence, and immunodeficiency. APDS clinical manifestations include recurrent sinopulmonary infections, chronic viral infections, lymphadenopathy, and nodular lymphoid hyperplasia typically involving respiratory and gastrointestinal mucosa. Laboratory findings include a decrease in naïve T-cells and an increase in memory T-cells, as was the case in our patient.
Initial treatment in the patient included a trial of both oral and rectal corticosteroids. Hydroxychloroquine was later used in combination with oral budesonide in an attempt to further decrease the intestinal lymphoid hyperplasia. Despite initial improvement, the patient's intestinal lymphoid hyperplasia progressed to the point where he developed a bowel obstruction at the ileocecal valve, requiring a partial bowel resection. The patient was subsequently started on sirolimus (rapamycin), which inhibits mTOR, a downstream effector of PI3K, and has previously been shown to decrease lymphoproliferation and improve clinical symptoms. The patient in this case has had an excellent clinical response to sirolimus. Patients with gastrointestinal manifestations of APDS may benefit from targeted treatment with sirolimus, especially if there has been progression despite the use of other immunosuppressants.

Keywords: PI3K, PIK3CD, APDS, intestinal nodular lymphoid hyperplasia, sirolimus

Disclosures: All authors indicated they had no financial relationships to disclose.

(29) A Hypomorphic Founder RAG1 p.C176F Variant with Diverse Clinical Presentation and Immune Phenotypes in U.S. Mennonite Populations

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Background: Recombinase activating gene 1 (RAG1) is essential in creating the T and B cell repertoire for protective antibody and cellular responses to infections. Pathogenic variants in RAG1 genes have been linked to variable forms of immunodeficiency, where genotype and residual recombinase activity correlates well with clinical and immunological presentation. Although in selected cases, intrafamilial clinical and immune phenotype variability is noted with the same variant among U.S. Mennonite communities.
Methods: Peripheral blood samples from patients and healthy controls were assayed for herpesviruses (CMV, EBV, VZV) as markers of microbial load and B cell activating factor (BAFF). Immune phenotyping was conducted using flow cytometry.
Results: We identified 12 patients (9 alive, 1 deceased, 2 s/p hematopoietic stem cell transplant (HSCT); median age, 18.5 years) with the RAG1 p.C176F variant in U.S. Mennonite communities. The clinical phenotype ranged from good health to recurrent infections/autoimmunity. Three were identified with state newborn screening (NBS) via T-cell receptor excision circle (TREC) quantitation. All patients uniformly had low naïve T cell counts, more so in symptomatic cases. Low TCRV7.2+ T cell count was a hallmark. The immune phenotype, BAFF levels and viral load were compared in two adult patients. Both patients had a history of upper/lower

respiratory infections but one had greater disease severity with additional history of bronchiectasis, enteritis, oral candidiasis and autoimmune interstitial lung disease. The more severely affected patient had lower fraction of recent thymic immigrants and higher expansion of Tbet+CD21lo B cells and follicular helper T cells. Viral loads were negative in both patients, however BAFF levels were increased in the patient with severe disease in comparison to the one with mild disease and healthy controls.
Discussion: Investigation of patients with p.C176F founder variant provides an opportunity to understand genetic, developmental, and environmental modifiers or markers related to variable presentation of partial RAG deficiency. Our findings may inform optimal management following NBS in pre-symptomatic newborns.

Keywords: partial recombinase activating gene deficiency, newborn screening, severe combined immunodeficiency, immune phenotype, marginalized patient population

Disclosures: Jolan Walter has relevant financial relationships with proprietary interests with Octapharma (Research Grant includes principal investigator, collaborator or consultant and pending grants as well as grants already received), Pharming (Consultant), Takeda (Consultant, Research Grant includes principal investigator, collaborator or consultant and pending grants as well as grants already received), and X4 Pharmaceuticals (Consultant). All other authors indicated they had no financial relationships to disclose.

(30) Clinical Red Flags of Monogenic Allergic Diseases

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Introduction: Primary Immunodeficiency diseases (PIDs) are genetic disorders that affect the function and/or development of the immune system. Although PIDs have traditionally been identified on the basis of enhanced susceptibility to infections, the presence of immune dysregulation occurs frequently in these conditions, with allergic inflammation described in several PIDs. Thus, we have begun to appreciate that the presence of severe, early-onset allergic diseases can also serve as important signs of an underlying PID, and in some cases, severe allergic inflammation may be the sole or the earliest manifestations of a monogenic immune defect. As such, recently the term primary atopic disorders (PADs) was coined to describe this group of heritable monogenic allergic disorders. In light of this, it is important for clinicians to recognize that allergic diseases such as food allergy, atopic dermatitis, and allergic asthma are expressions of misdirected immunity, and in patients who present with severe, early-onset, and/or coexisting allergic conditions, these can be indications of an underlying PID. Clinically, distinguishing PADs from common polygenic allergic diseases may challenging due to both conditions sharing common clinical features and pathophysiological processes; nonetheless, the mechanisms leading up to the allergic immune response may differ between the two, necessitating different management strategies and therapeutic interventions. Identifying monogenic allergic disease through next-generation sequencing (NGS) can dramatically improve outcomes through the use of precision-based therapy that targets the patient's underlying molecular defect. It is therefore imperative that clinicians recognize PADs to provide informed therapeutic options and improve patient outcomes. Here, through a comprehensive literature review, we identify clinical features and warning signs that warrant assessment for PADs and discuss the benefits of timely diagnosis and management of these conditions.
Methods: We performed a thorough literature review on the 39 PADs causing genes that have been identified and described in the literature, in order to come up with a list of clinical warning signs that would warrant workup for PADs.
Results & Conclusion: PADs can present with accompanying clinical conditions such as elevated IgE and eosinophils, autoimmune disorders, malignancies, short stature, connective tissue abnormalities, and enhanced risk of infections.

Keywords: Inborn errors of immunity, allergy, genetics, primary atopic disorders, atopy, immunogenetics

Disclosures: All authors indicated they had no financial relationships to disclose.

(31) Autosomal recessive Chronic Granulomatous Disease with Disseminated BCG and Burkholderia cepacia lung abcess

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Chronic granulomatous disease (CGD) is an inborn error of immunity that affects the innate immune system. In this genetic disorder, phagocytes are abnormal and unable to kill certain types of bacteria and fungus. Patients affected with CGD will be susceptible to frequent and life-threatening bacterial, fungal and atypical infections. This case write-up will discuss an unfortunate girl diagnosed with chronic granulomatous disease.
NN is a 2 years old girl, born at term. Parents are consanguineous. She presented with history of recurrent pneumonia and persistent right upper lobe collapse with history of BCG lymphadenitis. She was noted to have persistent left axillary swelling and had 1 episode of Salmonella species bacteraemia. She had failure to thrive. Her baseline investigations were unremarkable. She was investigated for underlying Inborn Error of Immunity (IEI). Her lymphocytes enumeration test showed elevated Total T cells (4080X10^6L) and B cells (4147X10^6/L) but normal CD8 and NK cells count. Her immunoglobulin levels showed elevated IgG, IgA and IgM at 25.05 g/l, 2.98 g/L and 1.83 g/L respectively. Her complement level C3 was elevated at 1.48 and C4 were within normal range. Her DHR test results showed markedly reduced neutrophil oxidative burst assay compared to control sample (patient's results was 3.0 compared to 100 in control using PMA). Genetic panel sent showed mutation in NCF 2.
She was treated as disseminated BCG infection and was started on anti-BCG treatment. During the first 2 months of therapy, clinically she was improving with anti-BCG treatment. She was then readmitted to hospital as she developed persistent fever with respiratory distress and required mechanical ventilation. Serial Chest radiograph done revealed worsening consolidation and collapse over right lung. CECT thorax revealed right lung abscess. Surgical intervention was done to drain the abscess. Unfortunately, patient succumbed a few days after the operation. Pus culture grew Burkholderia cepacia. Further evaluation of parents and younger male sibling revealed carrier status of NCF2 mutation.

Keywords: Chronic granulomatous disease, NCF 2 mutation, Disseminated BCG, Burkholderia cepacian

Disclosures: All authors indicated they had no financial relationships to disclose.

(32) Chronic disseminated lymphadenopathy as first manifestation of Hyper IgM Syndrome due to mutation in PIK3R1 (APDS2 syndrome) in a Colombian girl

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The phosphoinositide-3-kinase regulatory subunit 1 gene encodes the α p85 subunit that regulates the activity of an enzyme called phosphatidylinositol 3-kinase (PI3K) that is related to cell survival and proliferation due to its close relationship with the protein Akt [1,3]. Mutations in PIK3R1 has been associated with hyperactivation of the PIK3 pathway resulting in recurrent respiratory infections, hypo- or agammaglobulinemia, hyper IgM syndrome, T- and B-cell lymphopenia, lymphadenopathy, and increased predisposition to lymphomas [2,4]. We present a case of a 10-year-old female born to healthy non-inbred parents in whom the clinical manifestations began at 3 years of age with recurrent upper respiratory tract infections and chronical lymphadenopathies that initially appeared in the cervical region and spread to the axillary and inguinal regions. Initially, infectious causes (EBV, CMV, T. gondii, HHS I and II) were ruled out. Extended studies for infectious causes were ordered with M. tuberculosis labs return negative for both culture in liquid and solid media, tuberculin test and PCR of the lymph node aspirate. A bone marrow study was performed and revealed lymphopenia, with negative smears for infectious etiologies and negative bone marrow cultures. Inborn error of immunity was suspected, but the patient lost follow-up. She returned at 9 years old with a significant increase in lymph nodes (cervical, mediastinal, and mesenteric lymph nodes), tuberculosis and malignancy were again ruled out. Immunological work-up showed diminished CD4 lymphocytes, inverted CD4:CD8 ratio, NK cell deficiency, low IgA (28mg/dL reference value 45-236mg/dL), normal IgG (839mg/dL reference value 608-1572mg/dL) and significant elevation of IgM (605mg/dL reference value 52-242mg/dL). Whole exome sequencing showed that the patient carried the pathogenic variant NM_181523.3 (PIK3R1): c.1425 + 1G> A. Based on this finding, the diagnosis of APDS2 was made and immunoglobulin replacement therapy plus sirolimus were recently indicated with adequate clinical response. This case highlights the importance of thinking about inborn errors of immunity in patients with chronic lymphadenopathy, even in tropical settings where infectious causes are the most frequent etiology.

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Keywords: Activated phosphoinositide 3-kinase delta syndrome type 2, PIK3R1, Hyper IgM Syndrome, Antibody deficiency

Disclosures: Oscar Correa-Jimene has relevant financial relationships with proprietary interests with Takeda (Employment). All other authors indicated they had no financial relationships to disclose.

(33) A novel variant in FAS leading to atypical granulomatous bone marrow disease with fever, pancytopenia and hepatosplenomegaly

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Autoimmune lymphoproliferative syndrome (ALPS) is classically characterized by immune cytopenias, lymphadenopathy/hepatosplenomegaly, and elevated double-negative T cells (DNTs). Germline or somatic mutations may be found in FAS, FASLG or CASP10. We present a patient with unusual bone marrow granulomatous disease and only marginally elevated DNTs, who was found by whole exome sequencing to have a novel heterozygous nonsense mutation in the FAS Death-domain, c.931C>T (p.Q311*), inherited from her father.

An 11-year old previously healthy girl presented with 3 weeks of fever, fatigue, sore throat, and pancytopenia. On exam, she had hepatosplenomegaly without lymphadenopathy. Labs showed low immature platelet fraction, low reticulocyte count, and Direct Coombs Test micropositive for C3. Infectious work up was negative. Rheumatologic work-up notable for elevated ACE and 1,25-Vitamin D, suggesting non-specific granulomatous disease. Bone marrow biopsy then showed disrupted trilineage hematopoiesis and a lymphohistiocytic infiltrate arranged in loose granulomas without evidence of malignancy (Figure 1). Flow cytometry analysis showed 6% B cells and 52% T cells (CD4:CD8=0.8). Family history was significant for father with autoimmune hemolytic anemia and paternal uncle and first cousin with immune cytopenias. The patient's further work-up revealed DNTs 1.7%, normal Vitamin B12, elevated sFASL, elevated IL-10 and other cytokines, normal IgG, elevated IgE, elevated naïve B cell % and decreased naïve T cell % (Table 1). MRI showed hepatosplenomegaly and celiac lymphadenopathy. Lymphadenopathy and hepatosplenomegaly are features of ALPS, but generally demonstrate increased uptake on FDG-PET, absent in this case. FDG-avid adenopathy in ALPS is also typically associated with lymphoproliferative disease, not evident in this case. Diffuse FDG uptake in the marrow, seen here, is not a commonly described imaging feature of ALPS, but could represent cellular marrow expansion as noted on biopsy (Figure 2). Given the plausible pathogenic FAS variant and overall clinical phenotype, treatment for ALPS was started with methylprednisolone and sirolimus.

In summary, we describe a patient with a novel pathogenic FAS variant with atypical bone marrow and PET findings, and initial laboratory features only partially consistent with ALPS. This case illustrates the importance of early genetic testing when suspecting immune dysregulation and expands the clinical phenotype of FAS-associated disease.

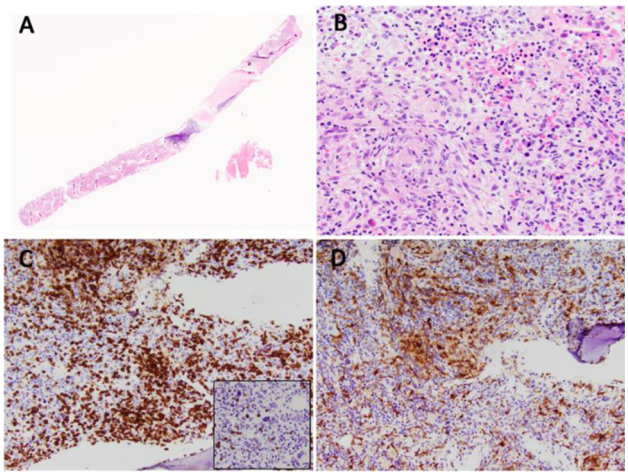

Figure 1. Histologic Images. (A) Biopsy demonstrates an appropriately cellular (95%) marrow (HE, 12.5x magnification). (B) A lymphohistiocytic infiltrate occasionally arranged in loose granulomas is seen diffusely throughout the biopsy. Trilineage hematopoiesis is present but disrupted by the lymphohistiocytic infiltrate (HE, 400x magnification). (C/D) Immunohistochemical stains for CD3 (C) and CD68 (D), highlight abundant T-lymphocytes and histiocytes, respectively, while in contrast only rare B-lymphocytes are present (CD20; C-inset).

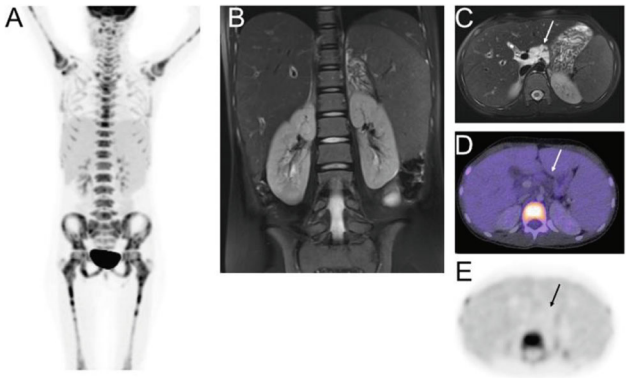

Figure 2. MRI & PET/CT images. (A) Coronal MIP from FDG-PET shows diffusely increased skeletal uptake, consistent with cellular marrow recovery from the severe pancytopenia and hemolytic anemia. (B,C) MRI showing hepatosplenomegaly and celiac lymphadenopathy with (D,E) no FDG uptake on associated FDG PET/CT.

Parameter	Value	Unit
WBC	2.41	K cells/ul
Hgb	9.6	K cells/ul
Platelet	41	K cells/ul
Immature Platelet Fraction	7.7	%
MPV	12.1	fL
MCV	83.5	fL
ANC	0.1	K cells/ul
ALC	2.43	K cells/ul
IgG	1302	mg/dL
IgA	287	mg/dL
IgM	339	mg/dL
IgE	2572	unit/mL
sIL2R	11352.8	pg/mL
IFN-gamma	16.6	pg/mL
IL-10	24.3	pg/mL
IL-13	8.3	pg/mL
IL-1beta	8.3	pg/mL
TNF-alpha	16.7	pg/mL
Total T cells (CD3+)	1826	cells/ul
CD4+ T cells (CD3+CD4+)	978	cells/ul
CD8+ T Cells (CD3+CD8+)	776	cells/ul
B cells (CD19+)	191	cells/ul
NK cellsCD3-/CD16+ or CD56+	67	cells/ul
Naïve CD4+ (CD45RA+CCR7+)	24.3	%
Naïve CD8+ (CD45RA+CCR7+)	17.5	%
DNT (CD3+CD4-CD8-TCRab+)	1.7	%
CD3+TCRgd+	3.5	%
Treg (CD4+CD25hiCD127lo)	5	%
Naïve B cell (IgD+CD27-)	87.3	%
ACE	190	unit/L
1,25-Dihydroxy Vitamin D	149	pg/mL
Vitamin B12	731	pg/mL
soluble Fas-Ligand	627	pg/mL

Table 1. Selected laboratory test results. Values below or above reference are indicated with blue and red respectively. Not shown: IL-2, IL-4, IL-5, IL-6, IL-8, IL-12, IL-17 were normal. 25-Hydroxy Vitamin D level was decreased. ANA, RF, and ANCAs were negative. Extensive infectious diseases testing was negative.

Keywords: ALPS, FAS, Granuloma, PET, Lymphoproliferative Disease, Evans Syndrome, Immune Cytopenias, Immune dysregulation, Genetic, Mutation

Disclosures: David Hoytema van Konijnenburg has relevant financial relationships with proprietary interests with Adivo Associates (Other Financial or Material Support, Ad Hoc Panel Expert) and Alcimed (Other Financial or Material Support, Ad Hoc Panel Expert). Holly Wobma has relevant financial relationships with proprietary interests with Immplacate Inc (Advisory Board, Intellectual Property / Patents, Ownership Interestincludes stock, stock options, patent or other intellectual property). Lauren Henderson has relevant financial relationships with proprietary interests with Adaptive Biotechnologies (Consultant), BMS (Research Grant includes principal investigator, collaborator or consultant and pending grants as well as grants already received), CARRA (Employment), Pfizer (Consultant), and Sobi (Consultant). All other authors indicated they had no financial relationships to disclose.

(34) ASCENIV™ Reduces Viral Infections and Associated Comorbidities in a Primary Immunodeficiency Patient

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Primary immunodeficiency (PI) patients are at risk for recurrent severe bacterial and viral respiratory infections despite immunoglobulin replacement therapy and prophylactic anti-infectives. These infections can progress to more severe presentations including pneumonia and acute hypoxemic respiratory failure.

We report on an 86-year-old male with late-onset combined immune deficiency (LOCID) due to hypogammaglobulinemia in combination with impaired cellular immunity. The patient's medical history was notable for uncontrolled recurrent bacterial and viral respiratory tract infections, bronchiectasis, and persistent asthma. Laboratory analysis at initial consultation revealed specific antibody deficiencies and impaired markers of cellular immunity. The patient had been experiencing frequent recurrent upper respiratory infections (URIs) that had resulted in bronchitis and, when untreated, progressed to pneumonia. Recurrent infections were of both bacterial and viral origin. The patient had required antibiotics, antivirals, and steroids at least every other month. He was started on subcutaneous immunoglobulin replacement therapy (SQIG) but infections were not fully controlled and recurrent viral URIs continued despite dose escalation and preventive antiviral therapy.

The patient's clinical status improved slightly on high dose SQIG with decreased incidence of bacterial infections but any clinical benefit of high dose SQIG against viral infection and associated comorbidities was short-lived. He was prescribed multiple courses of antivirals but was unable to continue use secondary to insurance overutilization and intolerability. The patient was started on ASCENIV™ (Immune Globulin Intravenous – slra, Human, ADMA Biologics, Boca Raton, FL), a commercially available immunoglobulin product that is standardized for neutralizing antibody titers against respiratory syncytial virus (RSV) and other respiratory viral pathogens. Following initiation, the patient demonstrated significant clinical improvement and continues to report that the persistent URIs have resolved with no further infections and that ASCENIV™ has

been well tolerated. The patient also reports that his asthma is much improved and he no longer requires systemic corticosteroids or inhalers. This product may provide a substantial benefit in immunodeficient patients who continue to experience breakthrough infections despite standard immunoglobulin replacement therapies or those high-risk patients that possess both humoral and cellular immunity defects.

Keywords: primary immunodeficiency, LOCID, recurrent infection, respiratory viral infection, immunoglobulin therapy, ASCENIV

Disclosures: Benjamin Greener has relevant financial relationships with proprietary interests with ADMA (Consultant, The editorial assistance of Benjamin Greener was supported by funding from ADMA Biologics).Gene Wetzstein has relevant financial relationships with proprietary interests with ADMA Biologics (Employment, Ownership Interest includes stock, stock options, patent or other intellectual property, Gene Wetzstein is Head of Scientific Engagement in Medical Affairs at ADMA Biologics). All other authors indicated they had no financial relationships to disclose.

(35) Compliance with follow-up and adherence to İmmunoglobulin Treatment in patients with primary immunodeficiency during The Pandemic

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Introduction: From the beginning of the SARS-CoV-2 pandemic, healthcare systems around the world have faced a huge challenge in managing patients with chronic diseases. Patients with primary immunodeficiencies (PID) were specifically vulnerable to inadequate medical care. The disease course varies from asymptomatic to mortal in patients with primary immunodeficiency.
Purpose: To evaluate the effects of the pandemic on follow-up and treatment adherence in patients with PID who received immunoglobulin replacement therapy.
Methods: We retrospectively evaluated the medical records of PID patients on Ig replacement treatment between March 2020 and September 2021. The differences in the frequency of regular admissions, the changes of treatment modality and vaccination records were analyzed.
Results: A total of 169 patients were included (93 males, 76 females). While one hundred twenty-four (73.4%) of the patients were treated withintravenous Ig (IVIg), forty-five (26.6) were on SCIg. While all of the patients who received subcutaneous treatment continued their treatment at home regularly, 80.4% of those who received IV treatment continued their treatment regularly (Table 1). They stated that the most common reason for giving up to go the hospital was the fear of contracting a covid infection. . It was observed that 17 (18.4%) of 92 patients aged ≥17 years and 15 (19.4%) of 77 patients aged ≤16 years did not have their mothers and/or fathers vaccinated. The main reasons for not vaccinating were distrust of vaccines, fear of side effects, and belief in the protection of Ig treatment.
Discussion: At the beginning of the pandemic, the European Society for Immunodeficiencies (ESID) recommended the continuation of Ig replacement treatment in PID patients. Treatment adherence was found to be higher in patients who use subcutaneous routes than in IV. In the pandemic period, Ig treatment modalities should be individualized according to patient characteristics and expectations.

Table 1. Characteristics of patients receiving Immunoglobulin (Ig) treatment	
The distrubution of gender	
Male: 93	
Female: 76	
The mean age of patients (mean±Std)	
IVIg: 18,5±19,1	
SC: 24,9±17,1	
Igadministration route n (%)	
Intravenous	124 (73.4%)
Subcutanous	45 (26,6%)
Changes in the practices of patients receiving IVIg during the pandemic period	
The place of IVIg application	
Hospital change	18 (10.7%)
Irregular administration	41 (24.2%)
IVIg brand changes	15 (8.9%)
Ig modality changes	26 (15.4%)

Keywords: Pandemic, intravenous immunoglobulin, subcutaneous immunoglobulin

Disclosures: All authors indicated they had no financial relationships to disclose.

(36) Autoimmunity in a large cohort of Primary Immune Deficiencies– Experience from a tertiary care center in South India

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Introduction: Autoimmune manifestations can be the first clinical presentation or sequel of PID. These include arthritis, colitis, autoimmune cytopenia etc. Availability of genetic analysis has increased our understanding of the complex relationship between primary immunodeficiency syndromes and autoimmune diseases.
Objective: To study the profile of autoimmune manifestations in patients with PIDs at a tertiary care centre in Bangalore, India.
Methods: A retrospective review of clinical records was performed and patients with PIDs were categorized according to the International Union of Immunological Societies (IUIS), Primary Immunodeficiency Diseases Committee Report on Inborn Errors of Immunity (2019). Patients with underlying PID who had autoimmune manifestations at presentation or during the course of their illness were included in the study. A detailed analysis was performed to understand the types of PIDs that predispose to autoimmunity.
Results: A total of 195 children with various PIDs were diagnosed during the study period (Feb 2017 to Aug 2021). The most common types of PIDs included Severe Combined Immune Deficiency (SCID) followed by combined immune deficiency (CID), phagocytic disorders, antibody deficiency diseases and diseases of immune dysregulation. Thirty two (16%) patients presented with or developed one or more autoimmune manifestations during the course of their illness. Male to female ratio in this subgroup was 3:1. Amongst them, autoimmunity was the key or only manifestation in 15 (46%) patients. The most common manifestation in our cohort was inflammatory colitis (37.5%) followed by autoimmune cytopenias (21.8%), arthritis (9.3%) and pyoderma gangrenosum (9.3%). Inflammatory Colitis was common among patients with phagocytic disorders (eg:chronic granulomatous disease), whereas, autoimmune cytopenia were more common in patients with immune dysregulation and Common Variable Immunodeficiency (CVID). Arthritis and skin manifestations predominated in patients with immunodeficiencies affecting cellular and humoral immunity and endocrine manifestations were more common in immune dysregulation syndromes. The frequency of autoimmunity was high among patients with CYBB, CYBA, LRBA, CTLA-4 haploinsufficiency, DOCK8, WAS and IL10RA deficiency. Details of the autoimmune manifestations in various PIDs have been tabulated (Table 1).
Conclusion: Autoimmunity being a frequent manifestation in patients with PIDs. We hope to increase awareness among general physicians, paediatricians, patients and care givers.

Autoimmune manifestations	No	PID	No
Colitis	13	CGD	5
		VEO-IBD	2
		HPS 7	1
		LRBA	2
		CHAI	3
Lupus	3	C1q deficiency	2
		CVID	1
Alopecia areata	1	CVID	1
Vitiligo	1	STAT1 GOF	1
ITP	2	CVID	1
		JAK1 GOF	1
Kawasaki disease	2	Cyclic neutropenia	1
		XLA	1
CNS vasculitis	1	DOCK8 deficiency	1
AIHA	5	DOCK8 deficiency	2
		CHAI	3
PG	3	Outulin deficiency	2
		LAD type 1	1
Arthritis	3	LRBA deficiency	2
		CVID	1
Type I DM	1	LRBA deficiency	1
Hypothyroidism	1	STAT1 GOF	1
Hepatitis	1	STAT3 GOF	1
D herpetiformis	1	WAS	1
Bullous pemphigoid	1	WAS	1
HLH	2	X-linked neutropenia	1
		CGD	1

Table I: Profile of autoimmune manifestations in patients with PID.

Keywords: Autoimmunity, Primary Immune deficiency diseases, colitis, autoimmune manifestat

Disclosures: All authors indicated they had no financial relationships to disclose.

(37) Congenital, Developmental and Inflammatory Findings in a Patient with a Newly Described RASopathy (RRAS2)

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Germline pathogenic variants in components of the RAS-MAPK pathway have been implicated in a spectrum of developmental disorders characterized by short stature, distinct dysmorphology, and congenital heart disease collectively known as "RASopathies." Patients with RASopathies appear at increased risk for also developing immune disorders, possibly secondary to aberrant thymic selection. Further, somatic variants in RAS proteins drive a rare syndrome of lymphoproliferation and autoimmune cytopenias. Recently, activating germline mutations in RRAS2 were described as a novel RASopathy. We report a patient with a de novo RRAS2 variant and immune dysregulation.

A 5-year-old female presented for genetic evaluation. Her medical history included complex congenital heart disease requiring multiple surgical interventions during infancy. Post-operatively, she developed a chylothorax, and while critically ill, a pulmonary embolism, middle cerebral artery stroke resulting in symptomatic seizures, and she was noted to have imaging changes concerning for chronic lung disease. At age 3, she experienced episodes of ketotic hypoglycemia of unknown etiology. Temporally, she developed persistent fevers, serositis, polyarthritis and rash, progressing to macrophage activation syndrome; she was diagnosed with systemic juvenile arthritis. Medical management of her inflammatory disease was complicated by elevated aminotransferases with concerns for hepatic fibrosis by biopsy. Immune modulation controlled her hyperinflammation, but she had persistent arthritis despite intraarticular and oral corticosteroids, meloxicam, hydroxychloroquine, leflunomide, and anakinra; she is now on tofacitinib. She had a non-traumatic fracture presumed secondary to chronic steroids. She has not had severe, unusual or recurrent infections despite thymectomy and transient chylothorax-related hypogammaglobulinemia. Physical exam was remarkable for dysmorphic features and arthritis. Exome sequencing revealed a likely pathogenic de novo 3-amino acid glycine duplication (p.Gly24_Gly26dup) in a critical region of RRAS2.

RASopathies are characterized by classic developmental and congenital findings and increased risk for immune dysregulation. Activating RRAS2 variants were recently reported in a small number of patients. As additional patients are reported, it will become clear if concurrent immune disease is also a feature of this new RASopathy. This case underscores the association of RAS-MAPK activation with immune dysregulation and highlights the importance of deep phenotyping in complex patients with rare and novel disorders.

Keywords: RASopathy, RRAS2, systemic juvenile arthritis

Disclosures: Burrage Lindsay has relevant financial relationships with proprietary interests with Baylor Genetics (Employment, Other Financial or Material Support, Department of Molecular and Human Genetics receives revenue from clinical genetic testing completed at Baylor Genetics Laboratories). Hsiao-Tuan Chao has relevant financial relationships with proprietary interests with Baylor (Employment, Other Financial or Material Support, Department of Molecular and Human Genetics receives revenue from clinical genetic testing completed at Baylor Genetics Laboratories). William Craigen has relevant financial relationships with proprietary interests with Baylor Genetics (Employment, Other Financial or Material Support, Department of Molecular and Human Genetics receives revenue from clinical genetic testing completed at Baylor Genetics Laboratories). Jill Rosenfeld has relevant financial relationships with proprietary interests with Baylor Genetics (Employment, Other Financial or Material Support, Department of Molecular and Human Genetics receives revenue from clinical genetic testing completed at Baylor Genetics Laboratories). All authors indicated they had no financial relationships to disclose.

(38) Clinical features and treatment of Peruvian children with inborn errors of immunity: A six-year experience

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Introduction: Inborn errors of immunity (IEI) are caused by genetic mutations that affect a wide range of immunological pathways and elements. They are considered rare diseases; however, prevalence and incidence are likely increasing due to improvement in diagnosis and laboratory resources, such as genome sequencing. Lack of timely recognition generates a significant disease burden in patients with these disorders, especially in countries with limited resources to perform appropriate diagnosis and management. Low level of knowledge and awareness about IEI in physicians are other factors involved in the diagnostic delay. Early recognition and diagnosis of IEI could reduce mortality and morbidity. Therefore, this study aimed to describe the clinical features and treatment of a cohort of Peruvian IEI patients from a pediatric center.
Methods: We retrospectively analyzed 81 IEI patients, followed from 2012 to 2018. Recollected data included demographics, clinical features, genetic analysis, and treatment.
Results: Forty-nine (60.5%) patients were male, the mean age was 9.4 ± 4.4 years, and the consanguinity rate was 7.4%. A family history of IEI was present in 9 patients. At the onset of symptoms and diagnosis, the median age was 0.8 (IQR: 0.2 - 7) and 3 (IQR: 1 - 6) years, respectively. The median delay in diagnosis was 1.5 (IQR: 0.3 - 3.6) years. The mortality rate was 14.8%, mainly in patients with Wiskott-Aldrich syndrome (3.7%). The most common IEI were predominantly antibody deficiencies (30.9%), combined immunodeficiencies with associated syndromic features (22.2%), and congenital defects of phagocytes (19.8%). Only 32 patients (39.5%) had a genetic diagnosis. The main clinical manifestations were pneumonia (64.2%), chronic diarrhea (58%), failure to thrive (45.7%), and skin infections (42%). Eight patients had multidrug-resistant tuberculosis (9.9%). Regarding treatment, 53 patients (65.4%) received immunoglobulin replacement therapy (IRT), while only five patients received hematopoietic stem cell transplantation.
Conclusion: Predominantly antibody deficiencies, pneumonia, and IRT were the main features. Only a few patients were genetically diagnosed and received hematopoietic stem cell transplantation. There are several challenges in diagnosing and treating IEI patients in our setting that could impact the patients' quality of life and prognosis.

PID categories	Number of cases (%)	Sex (M/F)	Consanguinity	Family history of PID	Mortality (%)
1. Immunodeficiencies affecting cellular and humoral immunity	6 (7.4)	6/0	0	0	2 (2.5)
Severe combined immunodeficiency	5 (6.2)	5/0	0	0	2 (2.5)
CD40L deficiency	1 (1.2)	1/0	0	0	0
2. Combined immunodeficiencies with associated or syndromic features	18 (22.2)	10/8	0	6	3 (3.7)
Wiskott-Aldrich syndrome	7 (8.6)	6/1	0	3	3 (3.7)
AD-HIES	5 (6.2)	2/3	0	0	0
Ataxia-telangiectasia	6 (7.2)	2/4	0	3	0
3. Predominantly antibody deficiencies	25 (30.9)	15/10	1	1	1 (1.2)
Common variable immunodeficiency	10 (12.3)	2/8	1	1	0
Agammaglobulinemia	14 (17.3)	13/1	0	0	1 (1.2)
Transient hypogammaglobulinemia of infancy	1 (1.2)	0/1	0	0	0
4. Diseases of immune dysregulation	7 (8.6)	4/3	3	2	0
Familial hemophagocytic lymphohistiocytosis	2 (2.5)	0/2	2	0	0
LRBA deficiency	3 (3.7)	2/1	1	1	0
Autoimmune lymphoproliferative syndrome	2 (2.5)	2/0	0	0	0
X-linked lymphoproliferative syndrome	1 (1.2)	1/0	0	1	0
5. Congenital defects of phagocyte number or function	16 (19.8)	11/5	1	0	3 (3.7)
Congenital neutropenia	9 (11.1)	6/3	1	0	1 (1.2)
Chronic granulomatous disease	6 (7.2)	5/1	0	0	2 (2.5)
Leucocyte adhesion deficiency	1 (1.2)	0/1	0	0	0
6. Defects in intrinsic and innate immunity	9 (11.1)	3/6	1	1	3 (3.7)
Mendelian susceptibility to mycobacterial disease	4 (4.9)	2/2	0	0	2 (2.5)
Chronic mucocutaneous candidiasis	5 (6.2)	1/4	1	1	1 (1.2)
Total	81	49/32	6	10	12

Table 1. Frequency and characteristics of IEI Peruvian patients

PID categories	IVIG n (%)	Prophylaxis		Hematopoietic stem cell transplant n (%)	Corticosteroids n (%)	G-CSF n (%)
		Antibiotics n (%)	Antifungal n (%)			
Immunodeficiencies affecting cellular and humoral immunity	6 (11.3)	4 (7.7)	0	0	4 (11.8)	0
Combined immunodeficiencies with associated or syndromic features	13 (24.5)	12 (33.1)	0	4 (80)	8 (23.5)	0
Predominantly antibody deficiencies	22 (41.5)	18 (34.6)	2 (25)	0	14 (41.2)	0
Diseases of immune dysregulation	5 (9.4)	7 (13.5)	0	1 (20)	2 (5.9)	1 (16.7)
Congenital defects of phagocyte number or function	4 (7.5)	10 (19.2)	1 (12.5)	0	5 (14.7)	5 (83.3)
Defects in intrinsic and innate immunity	3 (5.7)	1 (1.9)	5 (62.5)	0	1 (29.4)	0
Total	53 (100)	52 (100)	8 (100)	5 (100)	34 (100)	6 (100)

Table 2. Frequency and types of treatments in IEI Peruvian patients

Keywords: Inborn errors of immunity, Pediatrics, Peru, Clinical features, Treatment

Disclosures: All authors indicated they had no financial relationships to disclose.

(39) GATA2 Deficiency in a Teen: From Diagnosis to Phenotype Reversal

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Background: GATA2 is a zinc finger transcription factor critical to hematopoiesis. Pathogenic mutations in GATA2 cause a wide array of phenotypes. The constellation of nontuberculous mycobacterial infections, increased susceptibility to viral and fungal infections, profound monocytopenia and B and T cell lymphopenias are consistent with GATA2 deficiency. Depletion of various hematopoietic stem cell lines manifests as dysfunction in multiple pathways. Therefore, hematopoietic stem cell transplantation (HSCT) should be curative.
Case Presentation: A 16-year-old male presented with an 8-year history of recurrent, intractable warts on the lips, oral mucosa, tongue and soft palate. Biopsy showed Human Papilloma Virus (HPV) specifically in keeping with types 1 and 2. He had persistent leukopenia without significant infective symptomatology. Multiple specialty evaluations yielded no definitive diagnosis. Immune evaluation revealed monocytopenia and B, NK, and CD4+ T cell lymphopenia. Sequencing identified GATA2 c.1114G>A; p.Ala372Thr in the second zinc finger. Worsening warts were treated with subcutaneous interferon gamma without improvement.
Bone marrow biopsy revealed GATA2-associated myelodysplasia without increase in blasts and normal cytogenetics. He received allogeneic stem cell transplant from his haploidentical brother with a 5/10 match. Graft-versus-host disease prophylaxis included post-transplant cyclophosphamide, tacrolimus and mycophenolate mofetil. Neutrophils and platelets recovered on days +15 and +17, respectively. Asymptomatic donor cytomegalovirus reactivation cleared with foscarnet and ganciclovir. Whole blood chimerism was 100% donor at day +30 and has remained 100% in whole blood, myeloid and T cells. Warts improved within weeks while leukopenia persisted. Immune reconstitution remains low but clinical symptoms continue to improve.

Conclusion: GATA2 deficiency is an inborn error of immunity first identified in 2011. HSCT remains the only curative therapy for the disease, although not all clinical presentations respond, such as lymphedema. Our patient's warts and myelodysplasia improved after transplant. There is still more to learn about GATA2 deficiency and HSCT as definitive treatment, especially with timing of intervention and the level of chimerism needed for phenotype reversal. Haploidentical HSCT with post-transplant cyclophosphamide appears to resolve severe HPV infection in GATA2 deficiency likely secondary to restoration of NK cytotoxicity which is described in similar disease conditions.

Keywords: GATA2, hematopoietic stem cell transplant, human papilloma virus, myelodysplasia, monocytopenia, warts

Disclosures: All authors indicated they had no financial relationships to disclose.

(40) DTH to assess cellular immune response after Covid vaccination in young adults

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Introduction: Primary Immunodeficiency diseases (PID) are more frequent among young adults. Covid-19 disease is specially influenced by differences in the immune responses related to physiological changes during the ageing of the immune system. For this reason, diagnostic tests involving measurements of cellular immune responses to SARS-CoV-2 should be studied in different age groups to avoid biased results. Delayed type hypersensitivity (DTH) cutaneous test using RBD antigen (CoviDCELL®) is a feasible in vivo method to assess cellular immune responses to SARS-CoV-2 (1-3). In this report we present the results obtained in 22 young adults to improve the understanding of this new application of the DTH in this group of population.
Methods: DTH skin test protocol was performed according to usual clinical practice, consisting in the intradermal puncture of 25 μL (0.1mg/mL final concentration) of the spike protein in the volar part of the arm. Skin test reaction was evaluated 12h, 24h, and 48 h after injection. A positive response was considered in the case of appearance in the intradermal injection site of a typical induration and/or erythema.
Results: DTH was performed in twenty-two healthy immunocompetent students five months after two doses of Vaxzevria/Vaxzevria or Vaxzevria/Comirnaty vaccines (see table I for details). All participants signed a written consent form included in the HUC_2021_04 protocol approved in the centre. Total positive DTH reactions occurred in 10/ 22 participants. Individuals who had been vaccinated with the homologous vaccination schedule of Vaxzevria had less DTH positive reactions (6/18) than participants with a heterologous schedule (4/4).
Discussion: Humoral immune responses are frequently impaired in PID patients. For this reason, in this group of individuals, the assessment of cellular immune status after Covid vaccination is imperative. In this report we present the use of an in vivo method to assess cellular immune reactivity after vaccination in young immunocompetent adults. The results showed differences in the immunogenicity between homologous/heterologous strategies in this group of participants measured with the DTH skin test.

	GENDER	Age	Disease	Vaccine schedule	Date	DTH response in mm			
						12	24	48	72
1	Male	19	No	**Vaxzevria/Comirnaty**	Feb-Jun	**7**	**7**	**14**	**12**
2	Female	19	No	Vaxzevria/Vaxzevria	Feb-Jun	**5**	**8**	**10**	
3	Female	19	No	Vaxzevria/Vaxzevria	Feb-Jun	**4**	**4**	**4**	0
4	Female	19	No	Vaxzevria/Vaxzevria	Feb-Jun	0	0	0	0
5	Male	19	No	Vaxzevria/Vaxzevria	Feb-Jun	0	0	0	0
6	Female	19	No	Vaxzevria/Vaxzevria	Feb-Jun	**6**	**12**	**8**	**6**
7	Female	19	No	Vaxzevria/Vaxzevria	Feb-Jun	0	0	0	0
8	Female	19	No	Vaxzevria/Vaxzevria	Feb-Jun	0	0	0	0
9	Female	29	No	Vaxzevria/Vaxzevria	Feb-Jun	0	0	0	0
10	Male	19	Yes	**Vaxzevria/Comirnaty**	Feb-Jun	**12**	**18**	**20**	**17**
11	Female	21	No	Vaxzevria/Vaxzevria	Feb-Jun	0	0	0	0
12	Female	19	No	Vaxzevria/Vaxzevria	Feb-Jun	0	0	0	0
13	Female	18	No	Vaxzevria/Vaxzevria	Feb-Jun	0	0	0	0
14	Male	19	No	Vaxzevria/Vaxzevria	Feb-Jun	0	0	8	5
15	Female	20	No	Vaxzevria/Vaxzevria	Feb-Jun	0	0	0	0
16	Male	19	No	Vaxzevria/Vaxzevria	Feb-Jun	0	0	**4**	**4**
17	Male	19	No	**Vaxzevria/Comirnaty**	Feb-Jun	**0**	**5**	**6**	**6**
18	Female	21	No	Vaxzevria/Vaxzevria	Feb-Jun	0	0	0	0
19	Female	19	No	Vaxzevria/Vaxzevria	Feb-Jun	0	0	0	0
20	Female	19	No	**Vaxzevria/Comirnaty**	Feb-Jun	**11**	**16**	**18**	**20**
21	Female	19	No	Vaxzevria/Vaxzevria	Feb-Jun	0	0	4	4
22	Male	20	No	Vaxzevria/Vaxzevria	Feb-Jun	**9**	**9**	**9**	**9**

Keywords: DELAYED TYPE HYPERSENSITIVITY, CELLULLAR IMMUNE RESPONSE COVID, IN VIVO DIAGNOSTIC SKIN TEST, IMMUNOGENICITY COVID VACCINES

Disclosures: yvelise barrios has relevant financial relationships with proprietary interests Biovaxys (Advisory Board). All other authors indicated they had no financial relationships to disclose.

(41) A 7 year-old boy with DeSanto-Shinawi Syndrome and recurrent respiratory infections, bronchiectasis, and hypogammaglobulinemia

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Case: A 4-year-old boy with mild developmental delays, facial dysmorphisms, and asthma presented following multiple hospitalizations for respiratory infections, including recent respiratory failure secondary to Influenza A infection (requiring ECMO support) and associated acute necrotizing leukoencephalitis and myocarditis. During that hospitalization, RANBP2 gene sequencing and duplication/deletion analysis were negative. Immunologic evaluation demonstrated normal immunoglobulins, normal antibody response to tetanus, but low diphtheria antibodies and absent pneumococcus antibodies despite receiving routine immunizations. These did normalize after Tdap and PPSV23 vaccinations. Work-up also revealed mild B cell lymphopenia but normal lymphocyte proliferation to mitogens, dihydrorhodamine, and CH50. A 207 gene panel evaluating for inborn errors of immunity was unrevealing.
From ages 4-7, he was hospitalized numerous times due to hypoxemic respiratory failure secondary to viral or bacterial infections. Sweat chloride testing was negative. Primary Ciliary Dyskinesia genetic testing showed an unsuspicious single variant of uncertain significance. Bronchoscopy was unremarkable, and bronchoalveolar lavage fluid culture grew H. influenzae. High resolution chest CT showed multi-lobar bronchiectasis, as well as scattered mucus plugging and micronodules. Lung wedge biopsy suggested bronchiolitis obliterans syndrome.
Due to the ongoing pneumonias and bronchiectasis, humoral immune work-up was repeated at 7 years-old, revealing new panhypogammaglobulinemia with IgG of 220 mg/dL (386-1470 mg/dL), IgA of 14 mg/dL (29-256 mg/dL) and IgM of 12 mg/dL (37-224 mg/dL). B cell phenotyping showed moderately reduced switched memory B cells and mildly low IgM+ B cells. Subcutaneous immunoglobulin replacement therapy was initiated. Whole exome sequencing identified a de novo pathogenic mutation in WAC c.1616dupA, p.N639KfsX2, diagnostic for DeSanto-Shinawi Syndrome (DESSH).

Discussion: DeSanto-Shinawi syndrome is characterized by dysmorphic features, intellectual disability, and behavioral abnormalities (1). Recurrent respiratory infections are vaguely described in some patients, and there is a single report of a pediatric patient with hypogammaglobulinemia (1,3) . The WAC gene product is an adapter protein that serves as a transcription regulator in several biological processes, including autophagy, microtubule development, pathogen recognition and antigen presentation, Golgi reformation, and cell-cycle checkpoints (2). Our case is the first describing bronchiectasis in DESSH and highlights an association of immune dysregulation and infection susceptibility in WAC haploinsufficiency.

Keywords: DeSanto-Shinawi Syndrome, hypogammaglobulinemia, necrotizing encephalitis, bronchiectasis, bronchiolitis obliterans
Disclosure: Author indicated they had no financial relationships to disclose.

(42) A real-world experience with long-term elapegademase treatment for adenosine deaminase deficiency

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Background: Inherited defects in adenosine deaminase 1 (ADA) cause severe combined immune deficiency (SCID), which can be treated with enzyme replacement therapy (ERT), allogeneic hematopoietic stem cell transplantation, or autologous gene therapy. In 2019, a new recombinant ADA ERT, elapegademase (ELA-ADA) replaced the previously used bovine pegademase. Limited information about the long-term effects of ELA-ADA, including immune reconstitution, is available.
Methods: A retrospective review of 16 patients with ADA-deficient SCID who have received ELA-ADA for 6 months or more.
Results: ELA-ADA was administered to 6 "ERT-naïve" infants and 10 patients who had been receiving pegademase for 3.5 to 26 years. In all ERT-naïve patients, ADA activity in the plasma increased, while dAXP concentrations in red blood cells normalized or were near normalization. These biochemical effects persisted throughout the treatment period in all patients. T and B cell numbers increased rapidly in the ERT-naïve patients, with generation of naïve T and B cells. In 2 of 4 patients, the transition in the frequency of ELA-ADA injections from twice to once a week was associated with a decrease in the number of T cells, which was reversed with the resumption of twice-weekly administration. Thymic output measures (CD3+CD4+CD31+ T Cells), however, were not affected by the frequency of injections.
In most patients who had been treated previously with pegademase, T and B cells numbers remained significantly low after the transition to ELA-ADA, possibly reflecting irreversible damage to either hematopoietic progenitors and/or supportive stroma. One patient was diagnosed with hepatitis and EBV-associated lymphoproliferation 9 months after transitioning to ELA-ADA. Hepatitis and thrombocytopenia of unknown etiology developed in an additional patient. No other significant infections or non-immune complications occurred in the remaining patients. Three patients proceeded to receive allogeneic hematopoietic stem cell transplantations, including the patient suffering from lymphoproliferation.
Conclusions: We present real-world experience with the long-term benefits of ELA-ADA in the treatment of ADA deficiency. Further studies involving a larger number of patients and longer follow-up, as well as assessment of the non-immune abnormalities associated with ADA deficiency will help to further define the best management options for affected patients.

Keywords: adenosine deaminase, SCID, Enzyme replacement, Long-term

Disclosures: Vivian Hernandez-Trujillo has relevant financial relationships with proprietary interests with CSL (Advisory Board), Kaleo (Advisory Board, Consultant, Speaker/Honoraria includes speakers bureau, symposia, and expert witness), Regeneron (Advisory Board), Takeda (Advisory Board, Consultant, Speaker/Honoraria includes speakers bureau, symposia, and expert witness). Jolan Walter has relevant financial relationships with proprietary interests with Octapharma (Research Grant includes principal investigator, collaborator or consultant and pending grants as well as grants already received), Pharming (Consultant), Takeda (Consultant, Research Grant includes principal investigator, collaborator or consultant and pending grants as well as grants already received), and X4 Pharmaceuticals (Consultant). Michael Keller has relevant financial relationships with proprietary interests with Enzyvant (Advisory Board). All other authors indicated they had no financial relationships to disclose.

(43) Comparing Effects of the COVID-19 Pandemic on Patients with Pathogenic Variant of Nuclear Factor Kappa B Subunit 1 (NFKB1) and Cytotoxic T Lymphocyte Antigen 4 (CTLA4)

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Background: Clinical presentation and immune responses to infection and/or immunization to SARS-CoV-2 may depend on the underlying genetic defects, but also the progression of immune dysregulation and comorbidities. Here, we assess and compare disease and immune response to SARS-CoV-2 in a cohort of patients with NFKB1 and CTLA4 deficiencies at our tertiary medical center.
Methods: We performed retrospective chart review and telephone interviews of genetically-confirmed NFKB1 and CTLA4 deficient patients for demographic information, clinical history including SARS-CoV-2 vaccination/infection, symptoms, antibody response, and comorbidities.

Results: Our patient cohort included 3 children and 5 adults (median age 21.5 years, range 15-51) (CTLA4 cohort) and 1 child and 6 adults (median age 26 years, range 17-52) (NFKB1 cohort), both from 5 families. All patients were on immunoglobulin replacement therapy (IgRT) except two asymptomatic children with CTLA4 and one adult with NFKB1 pathogenic variant. Seventy-five percent of patients were vaccinated in each cohort. COVID occurred in 37.5% of CTLA4 and 50% of NFKB1 cohorts. One adult from each cohort received monoclonal antibody therapy with good clinical response. Hospitalization was required for a 42 year-old patient with NFKB1 deficiency, with hypogammaglobulinemia (low compliance on IgRT), moderate persistent asthma and obesity (BMI 30). All infected patients were unvaccinated. SARS-CoV-2 spike IgG antibody level were assessed in 50% of cases. It was fully absent in 4 of 4 NFKB1 deficient adult patients; however, it was preserved in an asymptomatic child and absent to low in 3 of 4 CTLA4 deficient adults. Patients who received monoclonal antibody therapy have not yet been tested.
Conclusions: During this pandemic, most NFKB1 and CTLA4 patients did well except one NFKB1 patient with low compliance and comorbidities. Antibody response to the SARS-CoV-2 vaccine and/or infection were low to absent except for an asymptomatic child. The contribution of underlying gene defects, progression of antibody deficiency/immune dysregulation and comorbidities (asthma, increased BMI) to the risk of severe infection is yet to be determined.

Keywords: COVID, COVID-19, SARS-CoV-2, immunodeficiency, immune dysregulation, CTLA4, NFKB1

Disclosures: Jocelyn Farmer has relevant financial relationships with proprietary interests with Bristol Myers Squibb (Research Grant includes principal investigator, collaborator or consultant and pending grants as well as grants already received), and Pfizer (Research Grant includes principal investigator, collaborator or consultant and pending grants as well as grants already received). Jolan Walter has relevant financial relationships with proprietary interests with Octapharma (Research Grant includes principal investigator, collaborator or consultant and pending grants as well as grants already received), Pharming (Consultant), Takeda (Consultant, Research Grant includes principal investigator, collaborator or consultant and pending grants as well as grants already received) , and X4 Pharmaceuticals (Consultant). All other authors indicated they had no financial relationships to disclose.

(44) A novel missense mutation in XIAP associated with normal protein expression and absent p38 phosphorylation in a patient with recurrent Haemophagocytic Lymphohistiocytosis (HLH).

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Background: X-linked inhibitor of apoptosis protein (XIAP) plays a role in immune regulation through modulation of tumor necrosis factor (TNF)-receptor signalling and regulation of NLRP3 inflammasome activity. XIAP deficiency is a rare inborn error of immunity associated with a range of clinical manifestations including haemophagocytic lymphohistiocytosis (HLH), splenomegaly and cytopenias, hypogammaglobulinemia, severe and recurrent infections in addition to inflammatory manifestations including hepatitis and uveitis. Since the first description of the disease in 2006, over 90 disease causing mutations have been reported. We describe a novel pathogenic variant in XIAP c.641A>G, p.(Asp214Gly) with a clinical phenotype of recurrent episodes of HLH.

Case presentation: We report a case of a now 16 year old boy who initially presented at 14 years of age with fever, hyperferritinaemia, pancytopenia, and hepatosplenomegaly. Two similar prior episodes were noted at age 5 and 12 years. Whilst a diagnosis of HLH was not made at the time of these earlier presentations, the retrospective application of a H-score calculation yielded a value of 259, suggestive of HLH.
At 12 years of age, an episode of prolonged fever self-resolved after several weeks, with the third episode of suspected HLH occurring at 14 years of age presenting with fever, hyperferritinaemia, pancytopenia and hepatosplenomegaly (H-score of 195; 85% probability of HLH).
Initial immunological testing showed reduced NK cell cytotoxicity with normal NK cell degranulation (CD107a), and normal expression of intracellular perforin, SAP and XIAP. However, given a high index of clinical suspicion of an underlying IEI; whole exome sequencing was performed. A hemizygous missense mutation in XIAP was identified, which has not been previously reported. Subsequent functional testing demonstrated normal p38 phosphorylation in response to LPS but absent p38 phosphorylation in response to the NOD2 agonist L18-MDP (see attached flow cytometry histograms of patient vs healthy "travel" control). These results are consistent with a non-functional XIAP, confirming that the genetic variant XIAP c.641A>G, p.(Asp214Gly) is pathogenic.
Discussion: This case describes a novel mutation in XIAP c.641A>G, p.(Asp214Gly) resulting in non-functional XIAP, although XIAP expression was normal.

Keywords: XIAP deficiency, Haemophagocytic Lymphohistiocytosis, XIAP c.641A>G, p.(Asp214Gly)

Disclosures: All authors indicated they had no financial relationships to disclose.

(45) Bending our understanding of actin protein related immune defects: A case report on a likely pathogenic ACTB variant

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Introduction: The actin family of proteins organize into the actin cytoskeleton which serves as an internal cellular structural framework. Actin proteins are crucial for cell motility, structure, integrity, and intercellular signaling. ACTB encodes beta-actin, a non-muscle cytoskeletal actin protein. Pathogenic gain-of-function ACTB variants are associated with Baraitser-Winter Cerebrofrontofacial (BWCFF) syndrome, an autosomal dominant congenital disorder with a broad phenotypic spectrum including characteristic craniofacial dysmorphisms, developmental delay, cleft lip/palate, ptosis, eye defects, hearing loss, cardiac defects and renal malformations. Actinopathies can also be associated with primary immunodeficiencies.
Case history: A 4-year-old male was seen outpatient for evaluation of recurrent viral sinopulmonary infections. His medical history was significant for congenital cardiac defects, surgically corrected submucous cleft, hypospadias, conductive hearing-loss and atopic dermatitis. During infancy, he had frequent episodes of otitis media which resolved with tympanostomy tubes, but relapsed a year later and started occurring monthly.
Immunologic evaluation was significant for natural killer (NK) cell lymphocytosis (1005 /uL), elevated total IgE (141 KU/L), elevated IgA (258 mg/dL), elevated lambda light chains (3.95 mg/dL), low IgM (34 mg/dL) and non-protective measles titer (10.0 AU/mL). Mitogen proliferation was normal to phytohemagglutinin and pokeweed. Chromosomal microarray was unrevealing, but a commercially targeted immunodeficiency

panel revealed a heterozygous ACTB (c.1078dupC) variant which was confirmed on whole exome sequencing. This variant was predicted to be a loss-of-function variant and deemed likely pathogenic. Medical geneticist evaluation excluded a BWCFF diagnosis due to absence of developmental delay and characteristic dysmorphic features.
Additional testing showed persistent NK cell lymphocytosis (1001 /uL), elevated IgA (270 mg/dL), elevated lambda light chains (2.64 mg/dL) and low IgM level (30 mg/dL) over a 15-month period. Dihydrorhodamine assay, G6PD and myeloperoxidase were unremarkable. Neutrophil phagocytosis (76.7% vs 94.5%) and NK cell cytolysis (21.4% vs 32.2%) were both decreased compared to control but still in the normal range.
Discussion: The ACTB variant is suspected to contribute to his underlying immune defects. While gain-of-function ACTB variants are associated with BWCFF, loss-of-function ACTB variants can present with recurrent sinopulmonary infections. Our limited functional characterization showed mildly diminished NK cell lymphocyte and phagocyte function, but further functional studies are needed.

Keywords: Actinopathy, ACTB, beta-actin, Baraitser-Winter Cerebrofrontofacial syndrome, cytoskeleton, immunodeficiency, NK lymphocytosis

Disclosure: All authors indicated they had no financial relationships to disclose.

(46) Gene and pathway-based burden testing of rare variants in bronchiectasis using exome sequencing in patients with immune disorders

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Background: Bronchiectasis is a permanent enlargement of the airways that can occur due to mucociliary clearance disorders including cystic fibrosis and primary ciliary dyskinesia (PCD). Inborn errors of immunity (IEIs) also pose risk for bronchiectasis due to airway damage from opportunistic infections. Most bronchiectasis is idiopathic. Better elucidating the genetic basis of bronchiectasis may allow for risk prediction and prevention among high-risk patients and contribute to management. Given the heterogeneity of bronchiectasis within IEI, PCD, and idiopathic cases, and the notion that the most deleterious variants may be selected against and subsequently rare within a population, we sought to investigate the contribution of rare coding variation to bronchiectasis across a cohort with known or suspected IEI and idiopathic bronchiectasis.
Methods: Participants underwent exome sequencing through a centralized sequencing program with clinical return of CLIA-validated results. The cohort with bronchiectasis included 307 individuals with heterogenous immune phenotypes. Controls consisted of 878 individuals without a molecular diagnosis or a clinical diagnosis of bronchiectasis. Rare variants met the following allele frequencies: TOPMed< 5%, gnomAD popmax< 1%, and internal cohort< 10%. Gene-based burden testing was performed for (1) truncating, (2) missense, and (3) truncating+missense variants using optimal sequence kernel association tests (SKAT-O) with sex, age, age squared, ancestry principal components, and sequencing vendor as covariates. Pathway-based analyses included rare variants in genes involved with cilia, the immune system, and connective tissue.
Results: Gene-based burden testing showed a significant association with missense variants in PIK3CD (Benjamini-Hochberg FDR adjusted p-value=1.4x10-6) and missense variants in STAT3 (p=0.0051). These results were not significant after multiple correction using resampling to generate empirical p-values. Pathway-based analyses were not significant.
Discussion: This global analysis of rare genetic variation underlying bronchiectasis did not reveal a significant pattern of genes or pathways enriched for rare variants in a mixed cohort of individuals with bronchiectasis. Two genes underlying IEIs with risk for bronchiectasis showed nominal significance with FDR adjusted p-values. These results may be limited by small sample size. Future work in an expanded sample as well as incorporating the effect of common variants is warranted to further understand the genetic architecture of bronchiectasis.

Keywords: bronchiectasis, exome sequencing, burden testing, rare variants

Disclosures: All authors indicated they had no financial relationships to disclose.

(47) Genetic profile of patients with Blau syndrome from Chandigarh, India

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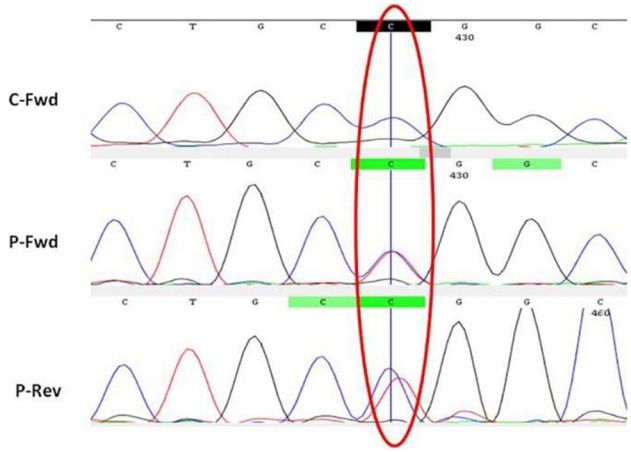
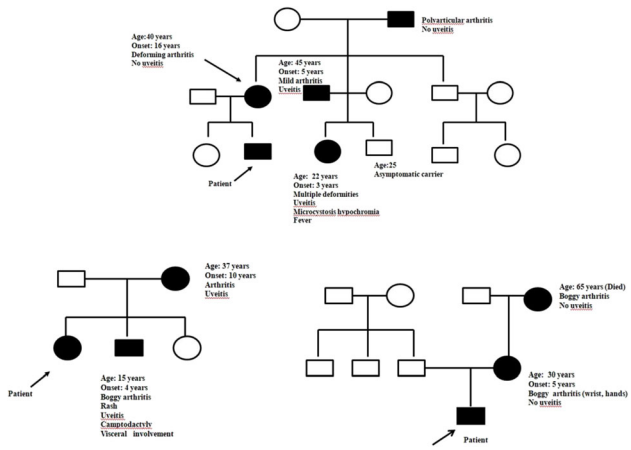
Blau syndrome (BS) is a rare monogenic form of autoinflammatory disease caused by gain-of-function mutation in the Caspase Recruitment Domain (CARD)15/Nucleotide Oligomerization Domain of (NOD)2 gene and is characterized by granulomatous arthritis, dermatitis, and uveitis since early childhood.
Methods: Present study highlights genetic profile of patients with BS from India. The confirmation of genetic diagnosis was carried out at Pediatric Allergy Immunology Laboratory, PGIMER,Chandigarh. Exon-4 of NOD2 gene was amplified using polymerase chain reaction (PCR) at controlled conditions using specific oligonucleotide primers.
Results: BS was genetically confirmed in 11 patients ((10 children, 1 adult; 6 males; 5 females) from 9 families. Molecular confirmation of NOD2 variants were carried in all patients. Missense heterozygous mutation involving amino acid change from arginine to tryptophan at position 334 (hotspot) was identified in the nucleotide-binding domain of NOD2 gene in all (figure 1). Symptomatic parents were noted in 7 (63.6%) patients of 5 families. Mothers were affected in 4 children while fathers in 3 (figure 2). Symptomatic parents had arthritis (6) and uveitis (4) or both (4). Affected symptomatic parents were also found to have same mutation. Asymptomatic carrier sibling (currently at the age of 25 years) with same mutation was identified in one family. Prenatal diagnosis was also performed for a carrier mother.
Conclusions: R334W variant was identified in all patients with clinically suspected BS. We report a series of genetically confirmed Indian patients with BS highlighting evolution of disease. Early genetic screening for this common mutation can aid in early and appropriate diagnosis.



Electropherogram showing NOD2 gene (Exon-4) with missense heterozygous variant (p.R334W). C-Control, P-Patient, Fwd- Forward, Rev-Reverse



Pedigree of patients showing disease manifestations in affected individuals

Keywords: NOD2 mutation, Early onset sarcoid, Blau syndrome

Disclosures: Vignesh Pandiarajan has relevant financial relationships with proprietary interests with Indian Council of Medical Research (Research Grant includes principal investigator, collaborator or consultant and pending grants as well as grants already received) and Jeffrey Modell Foundation (Research Grant includes principal investigator, collaborator or consultant and pending grants as well as grants already received). All other authors indicated they had no financial relationships to disclose.

(48) A mechanistic analysis of podocytopathy and its relevance to lupus nephritis

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Lupus podocytopathy is a rare entity of glomerulonephritis that has been shown to be pathogenically distinct from the widely accepted immune complex-mediated glomerular injury seen in other forms of lupus nephritis. Kidney involvement is a common manifestation of systemic lupus erythematosus and its presence suggests a more aggressive disease course and higher morbidity and mortality rates. Our current report shows that the diagnosis, characterization, and hence treatment of lupus podocytopathy should vary and differ from those of lupus nephritis. Lupus podocytopathy has been characterized by diffuse podocyte foot process effacement (FPE) with lack of endocapillary proliferation, mesangial deposits, or subendothelial and subepithelial immune complex deposition in the glomerular capillary wall and mesangium. Such podocyte injury was shown to be mediated via hyperactivity of the TH1 pathway. Upregulation of Angptl4, a lipoprotein lipase inhibitor in the TH1 pathway, resulted in dysfunction of intermediate filaments and actin-binding proteins responsible for widespread FPE. IL-13 was also found to decrease the expression of the structural proteins of podocytes, thereby increasing glomerular permeability. Furthermore, direct binding of B7-1 (or CD80) was shown to induce Toll-like receptor (TLR) cross-talk and hence greater widespread inflammation and structural damage to the podocyte cytoskeleton. However, it remains unclear the therapeutic implications of these molecular components that lead to lupus podocytopathy; for example, there is no evidence to recommend hydroxychloroquine, which is a TLR inhibitor and a mainstay treatment for lupus nephritis, as a therapeutic agent for lupus podocytopathy.
Cases of minimal change disease pattern seen in lupus podocytopathy were found to be more sensitive to glucocorticoid therapy compared to the focal segmental glomerulosclerosis (FSGS) pattern in lupus podocytopathy. In addition, the FSGS pattern of lupus podocytopathy was shown to be more resistant to disease remission following glucocorticoid therapy as well have higher rates of relapse. These observations question the diverse disease mechanisms of lupus podocytopathy. In the current report, we will provide a systemic and mechanistic analysis of podocytopathy and its relevance to lupus nephritis. Our goal is to provide a framework for prompt and efficacious therapeutic management to improve overall and long-term outcome of lupus nephritis.

Keywords: autoimmunity, podocytopathy, immune dysregulation, IL-13, TLR

Disclosures: All authors indicated they had no financial relationships to disclose.

(49) Biallelic germline mutation in IKZF2, encoding Helios, causes pleiotropic defects of immunity

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Helios, encoded by IKZF2, is one of the five members of the Ikaros family of transcription factors that is predominantly expressed in certain T cell subsets, including thymocytes, activated T cells, regulatory T cells (Tregs) and mucosal-associated invariant T (MAIT) cells. Studies in mice have shown that the conditional deletion of Helios in Tregs leads to the eventual development of autoimmunity, establishing a role for Helios in maintaining the immunosuppressive nature of Tregs through stabilizing Foxp3 expression and silencing the Il2 locus. However, Helios's function in other T cell subsets and its contribution to human immune homeostasis have not yet been elucidated. In our study, we have characterized a patient with recurrent respiratory infections and hypogammaglobulinemia and identified a germline biallelic missense mutation in IKZF2, leading to a valine to leucine amino acid substitution in the region between the N-terminal DNA binding and C-terminal dimerization zinc finger domains of Helios (p.Ile325Val). Our biochemical and proteomic analysis have revealed that HeliosI325V retains DNA binding and dimerization properties but loses interaction with several partners, including epigenetic remodelers and transcription factors. Immune profiling of the patient's peripheral blood mononuclear cells (PBMCs) has indicated a reduction in Tregs with highly diminished MAIT and invariant natural killer T cell populations. Transcriptomic and functional analysis of patient Tregs has revealed a dysregulated transcriptome shown by the downregulation of FOXP3-regulated genes and an increase in IL-2 production. On the other hand, the patient's conventional T cells had diminished IL-2 production upon stimulation as a consequence of reduced accessibility of the IL2 locus in addition to genes involved in T cell activation. Single-cell RNA sequencing of PBMCs revealed a proinflammatory, effector-like gene expression signature in patient CD8+ T cells. Moreover, defective proliferation with delayed expression of surface checkpoint inhibitors was recorded in patient CD4+ T cells, suggesting aberrations in the downstream T cell activation program. Altogether, we identified a previously uncharacterized inborn error of immunity, revealing the importance of maintaining the Helios interactome, which is pertinent for the cell-specific transcriptional programs that enable T cell homeostasis in health and disease.

Keywords: Inborn errors of immunity, Ikaros family of transcription factors, Transcriptional regulation, Epigenetics

Disclosures: All authors indicated they had no financial relationships to disclose.

(50) Asymptomatic Persistently Positive SARS-CoV-2 RNA PCR in a Patient with CVID

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Introduction: Throughout the COVID-19 pandemic, there has been concern regarding how patients with immunodeficiency would fare. Over time reports have demonstrated variable rates of adverse events, from mild symptomatic infection to around 10% case fatality rate in patients with antibody deficiencies. Many of these reports were published prior to widespread availability of COVID-19 vaccines and therefore not much is known of the effect of vaccination on preventing infection in this population. We present a case of a patient with CVID and persistently positive SARS-CoV-2 PCR following vaccination, monoclonal antibody treatment, and subcutaneous immunoglobulin.
Case: 61-year-old male with common variable immunodeficiency (CVID), lymphopenia, bronchiectasis, and type 2 diabetes received Pfizer mRNA COVID-19 vaccine 2 dose series in March–April 2021. Following vaccination, he demonstrated positive spike protein antibodies. In June 2021, he developed fever and cough; tested positive for SARS-CoV-2 via nasal RNA PCR. He received monoclonal antibody infusion, bamlanivimab/estesevimab. His symptoms improved within 5 days of monoclonal infusion; he did not require hospitalization.
Repeat SARS-CoV-2 spike antibodies demonstrated rising titers in the months following his initial vaccination and infection (Table 1). SARS-CoV-2 neutralizing antibody test obtained 4 months after infection returned positive (virus neutralizing titer (VNT):364,ref limit of detection=32 VNT). For pre-screening prior to travel, the patient tested positive for SARS-CoV-2. Four months later, prior to scheduled procedure, he tested positive again. Persistent asymptomatic carriage of SARS-CoV2 virus was noted despite evidence of neutralizing SARS-CoV-2 antibody production, more than 4 months after his infection.
Discussion: Several studies have now demonstrated positive humoral and cellular response to COVID-19 vaccination in immunodeficient patients. Despite this, little is known about how this will translate into protection from carriage/infection or long-term complications from SARS-CoV-2 infection in this population. Prolonged viral shedding has been reported in patients with CVID and other immunocompromised patients, but majority of these cases were in patients not yet vaccinated. The present patient with CVID demonstrates that in immunodeficient patients vaccination, monoclonal antibody infusion, subcutaneous immunoglobulin replacement, and currently available testing modalities may not yet be enough to predict who is at risk for infection or prolonged viral shedding following SARS-CoV-2 infection.

	April 2021 (3 weeks after vaccination)	July 2021 (3 weeks after infection)	October 2021 (4 months after infection)
SARS-COV-2 Spike Ab (<0.80 U/mL)	4.9	117	>250
SARS-COV-2 Neutralizing Ab (> 32 VNT)			364
CD3 (550-2202 cells/mcL)	**249**	**348**	
CD4 (365-1437 cells/mcL)	**160**	**227**	
CD8 (80-846 cells/mcL)	89	123	
CD19 (45-409 cells/mcL)	**2**	**3**	
CD16/56 (59-513 cells/mcL)	94	154	
IgG (767-1590 mg/dL)	1010	1010	
IgM (37-286 mg/dL)	**<5**	**<5**	
IgA (61-356 mg/dL)	**1**	**1**	

VNT = viral neutralizing titer

Table 1: Laboratory Assessment Following Vaccination and Infection

Keywords: COVID-19, Immunodeficiency, CVID

Disclosures: All authors indicated they had no financial relationships to disclose.

(51) A case of hereditary angioedema with early clinical manifestations of the disease caused by heterozygote non-dominant SERPING1 variant

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[2]KREC/clinical research laboratory of the scientific department
[3]Belarusian Research Center for Pediatric Oncology, Hematology and Immunology, Deputy Director for Research

Introduction. Hereditary angioedema (HAE) is a rare autosomal dominant disorder of vascular permeability associated with heterogeneous clinical manifestations. 99% of cases of HAE caused by C1 inhibitor (C1-INH-HAE) deficiency, disease-causing variants lie within the SERPING1 gene (OMIM # 606860). Few variants in the SERPING1 gene have been previously reported with a recessive HAE pattern. Heterozygous for such variants can show a complement profile from normal phenotype to C1-INH-HAE type I and type II phenotype, without disease onset even at the 40-50 age. Here we describe a case of a patient with clinical symptoms of HAE and incomplete dominant SERPING1 variant.
Materials and Methods. For the patient with angioedema without wheals, we performed C3c, C4, C1-INH, C1q, IgE tests; Sanger and next-generation sequencing of SERPING1 gene in its full length (all exons, introns, promoter region and 5′-,3′-UTRs). All subjects consented to the study.
Results. In 2017 a 13-year-old male was referred to our consulting and outpatient department with limb angioedema. The symptoms started when he was 12-year old and consisted of recurrent peripheral angioedema without wheals, these symptoms subsided spontaneously in 48-72 hours. The patient didn't have an autoimmune burden. Laboratory studies presented reduced C1-inhibitor and C4 levels. During three years following-up of patient levels of C1-inhibitor and C4 episodically undergo normalization or slightly low diminished. Plasma C3, C1q and IgE showed normal ranges at every follow-up study. Genetic testing subsequently showed the patient is heterozygous for the previously described non-dominant SERPING1 variant (c.1202T>C; p.Ile401Thr). Sequencing and MLPA analyses of the whole SERPING1 gene haven't found other pathogenic variants. Genetic testing didn't reveal p.Ile401Thr in the DNA samples of the patient's asymptomatic parents. Three years following up showed that patient is still mildly symptomatic and experiencing peripheral angioedema attacks 3-4 times a year. His attacks have a good response to the treatment of C1-INH concentrate.
Conclusion. This is the first reported case of a patient heterozygous for incomplete dominant SERPING1 variant p.Ile401Thr, with early disease onset. This case shows that patients carrying non-dominant variants in heterozygosis should undergo clinical monitoring as potential HAE patients.

Keywords: Hereditary angioedema, HAE, C1-inhibitor deficiency, SERPING1 gene, incomplete dominant variant

Disclosures: All authors indicated they had no financial relationships to disclose.

(52) First report of molecular diagnosis of hemophilia B patients in Belarus

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Introduction. Hemophilia B is a rare genetic bleeding disorder caused by heterogeneous genetic changes in the gene encodes for factor IX (F9, OMIM # 306900). The estimated incidence of hemophilia B is 1 birth per 30,000 male newborns in the world. Genetic testing is essential for the optimal diagnosis and management of patients with hemophilia B.
Materials and methods. 13 male pediatric patients with a clinical diagnosis of hemophilia B were included in the study. The genetic analysis was carried out through a customized NGS platform (QIAseq Targeted DNA Custom Panels; Qiagen, Germany), examining the coding regions and the exon-intron splice junctions of F8, F9, VWF, ADAMTS13, F13A1, F13B genes using a genetic analyzer MiSeq (Illumina, USA). All clinically significant observations were confirmed by Sanger sequencing.
Result. We found the pathogenic variant in all patients with a clinical diagnosis of hemophilia B in the F9 gene. Thirteen unique variants were identified: eight missense c.1135C>G, p.Arg379Gly; c.1064G>A, p.Gly355Asp; c.1240C>A, p.Pro414Thr; c.1153T>C, p.Ser385Pro; c.400T>C, p.Cys134Arg; c.421T>C, p.Cys141Arg; c.173G>A, p.Gly58Glu; c.278A>G, p.Asp93Gly), three nonsense (c.1113C>A, p.Tyr371Ter; c.880C>T, p.Arg294Ter; c.892C>T, p.Arg298Ter), one point mutation of proximal promoter region (c.1-17A>C) and one frameshift variant (c.377delA, p.Lys126ArgFs130Ter). Therefore, missense changes were the most common genetic variants that we found in the F9 gene, the frequency of which was 61.5%. All these variants have been previously reported in the EAHAD F9 and CHBMP databases, except for the frameshift variant c.377delA, p.Lys126ArgFs130Ter present in one patient.
Conclusion. We have performed molecular analysis for the identification of pathogenic variants in hemophilia B patients for the first time in Belarus. The pathogenic variants were identified in 100% of the studied cohort. We found one variant that was not reported previously. Genetic testing of hemophilia B promotes better information of the biology of the disease, to determine the carrier status, for prediction of the likelihood of inhibitor development, and the development of new therapeutic strategies.

Keywords: Hemophilia B, Gene F9, Factor IX, Mutations, Genetic diagnostics

Disclosures: All authors indicated they had no financial relationships to disclose.

(53) Dematiaceous fungal osteomyelitis in an adult with autoimmunity – First report of CGD due to EROS mutation from the Indian subcontinent

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Background: Chronic granulomatous disease (CGD) is an inherited defect in NADPH oxidase that results in defective production of oxygen free radicals by phagocytes. Patients with CGD are unable to effectively clear intracellular infections and are prone to recurrent bacterial and fungal infections. Mutation in the EROS (Essential for Reactive Oxygen Species) protein has been recently described as the 6th novel cause of chronic granulomatous disease.
Case: A 23-year-old female, born to a non-consanguineously married Indian couple, presented with history of being unwell from the age of 20. She initially presented with cough, difficulty in breathing, bilateral cervical lymphadenopathy, and a maculopapular skin rash. Investigations showed very high Angiotensin Converting Enzyme (ACE) levels with granulomas on lymph node biopsy and erythema annulare like lesion on

skin biopsy. A diagnosis of sarcoidosis was considered, and she was treated with high dose steroids followed by Methotrexate following which her symptoms resolved. Subsequently for the next two years she had a stormy course with multiple hospital admissions and received therapy for bacterial pneumonia, fungal pneumonia (Malassezia restricta), disseminated tuberculosis, rib osteomyelitis (Cladophialophora species – dematiaceous fungi) (Figure 1) and sepsis (methicillin resistant coagulase negative Staphylococcus aureus and salmonella). On tapering steroids, she would have a flare of the underlying autoimmune disease requiring continuation of steroids and addition of biologics like Adalimumab and Rituximab.
Her past history was significant as she had been treated for tuberculosis at the age of two and right eye uveitis (autoimmune) at the age of 15.
Evaluation showed normal serum immunoglobulins levels, while dihydrorhodamine (DHR) test showed impaired oxidative burst. Whole exome sequencing reported a pathogenic homozygous mutation c.327dup (p.Val110CysfsTer40) in exon 7 of CYBC1 gene , and a diagnosis of Chronic granulomatous disease (CGD) was established (Table 1). Currently she is doing well on voriconazole and low dose steroids and is being prepared for a bone marrow transplant.
Conclusion: We present a young adult female with polymicrobial infections and autoimmunity and report the first case of EROS-CGD from the Indian subcontinent. Autoimmunity is a challenge to manage in these patients with ongoing infections.

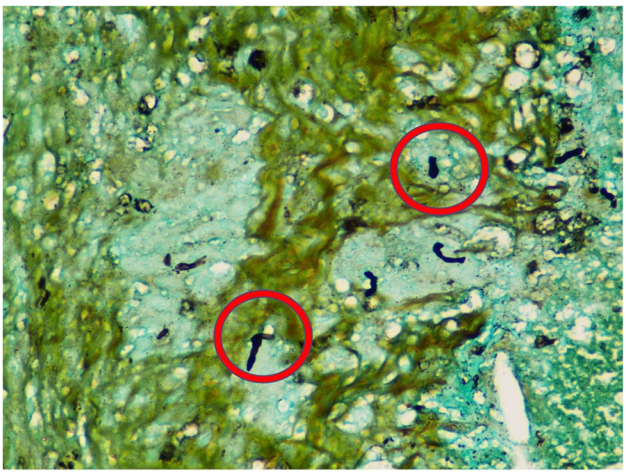

Figure 1: Gomori Methenamine silver stain highlighting fungal structures on rib biopsy specimen

Table 1: Laboratory investigations

Keywords: Chronic granulomatous disease, Dematiaceous fungal osteomyelitis, EROS mutation, Autoimmunity

Disclosures: All authors indicated they had no financial relationships to disclose.

(54) Characterization of thymic epithelial cell and thymocyte function and development in patients with thymic defects using scRNAseq profiling

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The thymus is a specialized primary lymphoid organ of the immune system whose main function is to host the maturation of T-cell lymphocytes. The interaction between thymocytes and thymic epithelial cells (TEC) in the thymus is critical for the correct function and maturation of both cell populations and ultimately for the development of a diverse repertoire of non-self-reactive T-cell lymphocytes. Despite the central role of the thymus in the immune system, limited information is available on lympho-stromal crosstalk in the human thymus, in particular in samples from patients carrying primary or secondary thymic defects. Previously we have demonstrated that DiGeorge syndrome (DGS) and Down syndrome (DS) represent conditions characterized by impaired development or premature ageing of the thymus, respectively. These initial studies have revealed peculiar alterations in thymic architecture and TEC composition, leading to altered T-cell development, in terms of maturation, function and numbers in patients with DS and DGS. Based on these results, we are performing single cell RNAseq (scRNAseq) to explore in more detail the transcriptional landscape of both stromal and hematopoietic components in the human thymus. Thanks to a collaboration with the pediatric cardiothoracic surgery center at the Children's National Medical Center (CNMC) in Washington D.C., we have access to discarded thymic samples obtained from pediatric patients with partial DGS and DS, as well as from patients without immune defects, at the time of heart surgery. Preliminary results of scRNAseq analysis comparing normal tissue with tissue from DS patients revealed a different distribution of cell subsets in both hematopoietic and stromal compartments, with several pathways differentially regulated, such as stress and metabolic processes. Additionally, through a recently established collaboration with the Thoracic and Gastrointestinal Malignancies Branch at the National Cancer Institute (NCI), we are evaluating samples obtained from resected thymic epithelial tumors (TETs). Integration of data obtained from normal and diverse sources of diseased thymic tissue will put us in a unique position to gain significant novel insights into the function and development of the human thymus, which in turn could reveal information that influences the clinical management of patients with thymic defects.

Keywords: Thymus, Stromal cells, Thymocytes, Thymic epithelial tumors, Down syndrome, DiGeorge Syndrome

Disclosures: All other authors indicated they had no financial relationships to disclose.

(55) Homozygous DNASE1L3 mutation leading to lifelong immune dysregulation with late-onset anti-MPO glomerulonephritis

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We report a novel phenotype of monogenic immune dysregulation secondary to homozygous DNASE1L3 mutation. At 2 years of age the patient developed recurrent fever, rash without urticaria, severe abdominal pain, vomiting and intermittent arthritis. A non-specific vasculitis on gut biopsy led to steroid and/or immunosuppressive therapy for 30 years, without a clear diagnosis. At age 46, he developed a marginal zone B-cell lymphoma that was successfully treated with rituximab. Three years later he developed an acute anti-MPO (p-ANCA) nephritic syndrome with focal necrotizing and crescentic glomerulonephritis (GN). He was treated with rituximab for six years with an excellent clinical response. On worsening hypogammaglobulinemia (trough IgG 1.77 g/L), the rituximab was held and he was assessed for immune deficiency. The

hypogammaglobulinemia was deemed secondary and multifactorial in origin however the presence of immune dysregulation since birth suggested an underlying inborn error in immunity. A homozygous pathogenic mutation in DNASE1L3 was found along with lymphopenia of 0.42 *10^9/L, consistently negative anti-nuclear antibody (ANA), extractable nuclear antibodies (ENA), anti-dsDNA, anti-PR3, and normal C3 and C4. Homozygous mutations in DNASE1L3 have been identified as a rare cause of monogenic lupus. Patients present in early childhood with severe lupus, often with lupus nephritis, positive ANA, low complement levels, and anti-dsDNA and ANCA autoantibodies. There is an association between DNASE1L3 and hypocomplementemic urticarial vasculitis (HUV). HUV patients present with significant overlap: early childhood onset, frequent kidney disease, and most fit criteria for lupus or have positive ANA. The key pathophysiology is impaired destruction of neutrophil extracellular traps (NETs) by DNAse, which leads to prolonged exposure of neutrophil intracellular products such as DNA, PR3, and MPO, and consequently the formation of autoantibodies.
In contrast to previous reported cases, our patient did not develop lupus, HUV, or positive ANA in childhood, nor did he have positive autoantibodies or kidney disease most of his life. Only at age 49 did he develop anti-MPO GN without ANA positivity and no criteria for lupus or HUV. Not previously reported, this case highlights that a homozygous DNASE1L3 mutation can result in a variable phenotype of immune dysregulation.

Keywords: DNASE1L3, ANCA, vasculitis, anti-MPO, DNAse, immune dysregulation

Disclosures: All authors indicated they had no financial relationships to disclose.

(56) Disruption of B-cell Population Associated with Increased Infections and Immunosuppressive Regimen

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Rationale: Solid-organ transplant recipients are placed on long-term immunosuppression, preventing graft rejection but increasing risk of infection. We seek to identify biomarkers to predict risk of infection and discover potential causes of the increased susceptibility to infection for pediatric kidney and liver allograft recipients.
Methods: In a single-center registry study, we analyzed 66 kidney and 18 liver pediatric transplant patients. Immunologic labs were collected at 6-month intervals as part of standard institutional solid-organ transplant care and included lymphocyte subsets, immunoglobulins, and vaccine titers. Number of infections and interval health history were recorded in corresponding 6-month intervals along with immunosuppressive regimen and dosage. The relation between immune parameters and number of infections were determined via linear mixed regression model of all consecutive visits while association between individual medications and immune parameters was analyzed via a paired t-test.
Results: For every 1% increase in the ratio of naïve to memory B-cells, there was an increase in number of total infections by 0.04 (β=0.04, $p < 0.0001$). A higher naïve B-cell percentage (β=0.03, p=0.001) and a lower memory B-cell percentage (β=-0.03, p=0.002) were also associated with increased total infections. For every increase by 1% of class-switched memory B-cells (CD27+) resulted in a decrease of 0.04 in total infections (β=-0.04, p=0.003) and non-switched memory B-cells in a decrease of 0.07 in total infections (β=-0.07, p=0.011) across visits. No significant changes were seen in Ig levels, T-cell populations, or vaccine titers. Mycophenolate mofetil (MMF) therapy was associated with increased naïve b-cell percent (β=12.4, $p < 0.001$), decreased CD27 B-cell percent (β=-10.3, $p < 0.001$), and increased naïve:memory B-cell ratio (β=4.5, p=0.009). Azathioprine was associated with the opposite trends.
Conclusion: Disruption of the naïve:memory B-cell ratio could be an indicator of increased infection risk in solid-organ transplant recipients. The changes seen with MMF were associated with increased infections and indicate MMF as a potential culprit for increased infection risk. The ratio of naïve:memory B-cells has potential as a biomarker to predict risk of infection in immunosuppressed solid-organ transplant recipients with MMF as the potential cause of the disruption.

Keywords: memory B cell, transplant, infection

Disclosures: Cathleen Collins has relevant financial relationships with proprietary interests with Enzyvant Therapeutics (Consultant). All other authors indicated they had no financial relationships to disclose.

(57) Fulminant Extensive Transverse Myelitis Treated with Eculizumab in a Young Patient with Complete Complement Factor I Deficiency

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Complement factor I deficiency is a rare autosomal recessive inborn error of immunity that usually presents with repeated encapsulated bacterial infections. Neurological manifestations of this disease are rare and usually present as aseptic encephalomeningitis and hemorrhagic leukoencephalitis, in patients with complete deficiency in complement factor I (CFI).
We describe a case of an 11-year-old girl who presented with fulminant hyperacute quadriparesis due to longitudinal extensive transverse myelitis (LETM), with bulbar involvement and respiratory failure. Based on the clinical presentation and neurological imaging, Neuromyelitis optic spectrum disorder (NOSD) was considered the most likely diagnosis, although aquaporin-4 antibodies were negative. Initial treatment included high-dose methylprednisolone and plasmapheresis, with no clear signs of improvement. Once we evidenced activation of the alternative complement cascade, with reduced C3, undetectable factor B and high soluble C5bC9 plasma levels (Table), we added eculizumab, an anti-C5 blocking agent to her treatment regimen. We observed a slow but gradual improvement over the next few weeks. Six months after treatment initiation, she regained significant motor function of the upper limbs and trunk and was ventilator free. She remained relapse-free.
Extensive etiologic work-up was negative except for the demonstration of compound heterozygous mutations in CFI, each transmitted by one parent (Table). Both mutations have already been described in patients with CFI complete quantitative or qualitative deficiency: the type 1 mutation (c.485G>A) is predicted to alter CFI expression while the type 2 mutation (c.1019T>C) alters CFI function. Interestingly, her 16 year-old sister harbours the same compound heterozygous mutations associated with biological evidence of the alternative complement cascade activation, but remains asymptomatic.
This observation describes the first patient with complete CFI deficiency associated LETM, successfully treated with an anti-C5 agent. It emphasizes that severe demyelinating disease can be a presenting feature of primary immune deficiency, and that the blockage of the complement cascade should be considered in patients with severe neurological diseases associated with signs of activation of the alternative complement pathway.

Table: Complement cascade work-up for the reference patient and her family

(units; normal values)	Patient	Sister	Mother	Father
Clinical presentation	Recurrent upper respiratory tract infections; longitudinal extensive myelitis	Asymptomatic	Asymptomatic	Asymptomatic
Mutations in CFI	c.1019T>C, c.485G>A	c.1019T>C, c.485G>A	c.1019T>C	c.485G>A
C3 (g/L; 0,83-1,52)	0,53	0,52	0,64	0,93
C4 (g/L; 0,13-0,37)	Normal	Normal	Normal	Normal
Classical pathway (C100; U/mL; 31,5-57,6)	Normal	Normal	Normal	Normal
Alternative pathway (AH50; 30-113%)	Not tested (on eculizumab)	0%	19%	73%
Factor I level (U/mL; 0,60-1,40)	Normal	Normal	Normal	-
Factor B level (mg/L; 173-453)	Undetectable	Undetectable	-	-
Soluble c5b-9 levels (ng/mL; < 300)	942	-	-	-

Keywords: Complement Factor I Deficiency, Primary Immune Deficiency, Transverse Myelitis, Neuromyelitis Optica, Demyelinating Disease, Eculizumab

Disclosures: Arnaud Bonnefoy has relevant financial relationships with proprietary interests with Alexion Pharmaceuticals (Advisory Board, Research Grant includes principal investigator, collaborator or consultant and pending grants as well as grants already received, Speaker/Honoraria includes speakers bureau, symposia, and expert witness). Hélène Decaluwe has relevant financial relationships with proprietary interests with Eli Lilly Canada (Advisory Board). All other authors indicated they had no financial relationships to disclose.

(58) Early onset chronic recurrent multifocal osteomyelitis and fluctuating neutropenia in a patient with Majeed syndrome

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Introduction: The LPIN2 gene plays a role in regulation of lipid metabolism, inflammation, and cell division. Homozygous loss-of-function variants cause Majeed syndrome, a rare early-onset autoinflammatory syndrome characterized by chronic recurrent multifocal osteomyelitis (CRMO), congenital dyserythropoietic anemia, and inflammatory dermatosis. We describe a patient with Majeed syndrome with an unreported genetic variant responsive to anakinra.
Case: A 2-year-old Indian male with history of prematurity of 34 weeks, persistent neutropenia, and iron deficiency anemia presented with bilateral elbow pain. Orthopedic evaluation included x-rays of bilateral arms demonstrating periosteal bone formation at the distal humerus and proximal ulna. MRI with and without contrast of the upper extremities showed enhancement of the left and right distal humeri and right proximal ulna with associated edema and elbow effusions concerning for osteomyelitis. Bone biopsy was negative for infection. Concern for CRMO prompted rheumatology evaluation that noted soft tissue swelling, pain, and contractures of elbows. There was no known consanguinity, however, family history was notable for paternal psoriasis. Laboratories exhibited elevated inflammatory markers (C-reactive protein: 37.3 mg/L, sedimentation rate: 60 mm/hr) and anemia (Hemoglobin: 9.4 g/dL) with smear showing microcytic hypochromic anisocytosis. Invitae primary immunodeficiency panel revealed homozygous pathogenic variants in LPIN2 (c.132_135dup; pSer46Valf*22). This nonsense variant creates a premature translational stop signal in the LPIN2 gene resulting in an absent or disrupted protein product. So far, this variant has not been reported in the literature in individuals with Majeed syndrome.
Our patient has been treated with ibuprofen, corticosteroid taper, and anakinra subcutaneous injections (~2 mg/kg/day). Despite anakinra, the patient has experienced recurrent neutropenia (nadir of 240x10^6/L), diarrhea, and rash. Subsequently, a bone marrow and skin biopsy were performed significant for erythropoietic dysplasia with binucleation and granulocytic left shift and perivascular lymphocytic dermatitis, respectively. Findings of skin biopsy were not typical of expected neutrophilic infiltrate.
Conclusion: Majeed syndrome should be a consideration for patients with early-onset CRMO and hematologic abnormalities including anemia and neutropenia. This case reports a new pathologic variant and extends the Majeed syndrome phenotypes. As additional patients are described, it may allow for clarification of clinical variability and long-term outcomes.

Keywords: Auto-inflammatory, Majeed syndrome, Interleukin-1 inhibition, case report

Disclosures: Susan Kirk has relevant financial relationships with proprietary interests BioMarin (Speaker/Honoraria includes speakers bureau, symposia, and expert witness). All other authors indicated they had no financial relationships to disclose.

(59) A Case of Immune Dysregulation Post Hematopoietic Transplant Presenting with Hypergammaglobulinemia, Lymphadenopathy, and HLA-B27 Arthritis in a Patient with a History of Chediak-Higashi Syndrome

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Introduction: Immune dysregulation following bone marrow transplant (BMT) is an evolving field and of clinical interest as the number of BMTs increases. Immune dysregulation may present in many ways. Here we report a unique case of hypergammaglobulinemia, and arthralgia found after BMT.
Case Description: A 14-year-old girl with anxiety and history of Chediak-Higashi s/p bone marrow transplant (BMT) presented for evaluation of arthralgias. She underwent BMT (matched unrelated donor) at 8 months of age. She had graft failure due to EBV and had a subsequent same donor BMT at 12 months of age with excellent chimerism. She was hypogammaglobulinemic after transplant which normalized by age 8. Monitoring at ages 13-14 showed a gradual, but worsening hypergammaglobulinemia with a maximum of 2570 mg/dl. During this time, she developed hip, finger, and knee pain. She was found to have enthesitis and arthritis. There was a family history of ankylosing spondylitis. The patient's HLA B27 was positive and matched as part of her BMT. She was diagnosed with enthesitis related arthritis. Due to the hypergammaglobulinemia, further screening was performed showing hemolytic anemia, lymphadenopathy, hypocomplementemia, and positive histone, DS DNA, ANA, Smith/RNP antibodies. She was ultimately diagnosed with lupus with an overlap enthesitis related arthritis. She started prednisone and hydroxychloroquine. Her venlafaxine was discontinued due to the positive histone AB and association of symptom onset

on starting the medicine. Her serologies and arthritis have improved but did not resolve. She has now started secukinumab with mild improvement.
Discussion: Immune dysregulation after BMT is of evolving clinical concern as the number of BMTs increase. This dysregulation may take many forms as evidenced by this case. This case shows that HLA-B27 arthritis remains a consideration after BMT given the desire to match HLAs during the BMT process. Additionally, it shows that unexplained hypergammaglobulinemia may provide a clue to unique post-BMT immune dysregulation. Lastly, patients after BMT remain susceptible to lupus like phenomenons that may be atypical in presentation. In particular venlafaxine, has been very rarely associated with drug-induced lupus and a history of a BMT may elicit a higher suspicion for uncommon drug-induced lupus.

Keywords: Bone Marrow Transplant, Immune Regulation, Lupus, HLA B27, Chediak-Higashi

Disclosures: All authors indicated they had no financial relationships to disclose.

(60) HIV-negative Kaposi sarcoma as a novel presentation of Dominant Negative CARD11 Deficiency

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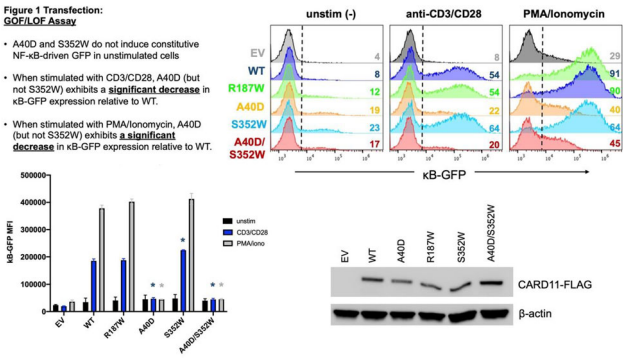
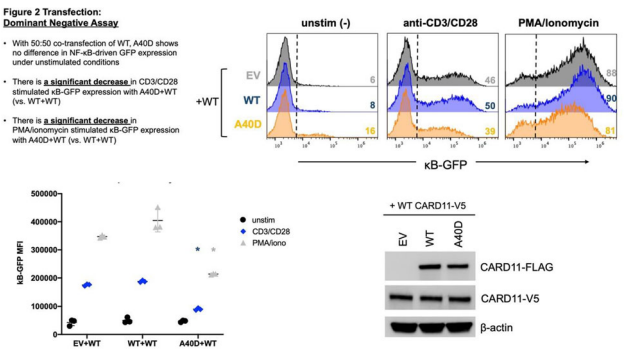
Aberrant immune control of Kaposi sarcoma herpesvirus (KSHV AKA human herpesvirus 8) is associated with the development of Kaposi sarcoma (KS). Most KS is the result of acquired immune defects including HIV infection and iatrogenic immunosuppression (1). Additionally, rare inborn errors of immunity (IEI) have been associated with KS including defects in Ox40, MagT1, IFNgR1, CTLA4, STIM1 and WAS (2-4). Here, we report a series of patients with HIV-negative KS followed at the NIH including a patient with a dominant negative variant in CARD11.
Seven patients with HIV-negative KS were investigated for IEI. All are men aged 25 years to 66 years at the time of KS presentation. Four of 7 patients had autoimmune disease including systemic lupus erythematosus (SLE), inflammatory bowel disease, and Type I diabetes mellitus. Atopy was present in 5 of 7 patients. Five of 7 patients had complicated KS disease: 3 with multicentric Castleman disease, 1 with primary effusion lymphoma, and 1 with KSHV inflammatory cytokine syndrome (KICS). Four patients had isolated dermatologic disease, 3 had visceral disease, and 1 is deceased due to KICS-related complications.
All patients were investigated using whole exome sequencing. One patient with severe atopy, SLE, and angioedema presented with KS at 45 years of age complicated by KICS. He subsequently developed refractory Pneumocystis Jirovecii pneumonia and died at 46 years of age with disseminated KS, KICS, and polymicrobial pneumonia. Posthumously, he was found to have two heterozygous missense variants in CARD11: c.119C>A, p.Ala40Asp and c.1055C>G, p.Ser352Trp. Functional testing revealed p.Ala40Asp as the pathogenic mutation by exhibiting dominant interference of wild-type CARD11-dependent NF-kB signaling.
In conclusion, we present a series of 7 patients with HIV-negative KS, many with concurrent immune dysregulation, concerning for IEI. Thus far, one patient with KS, KICS, and severe atopy at presentation has been identified with a dominant negative CARD11 variant consistent with CADINS. The expanding number of IEI with KS supports a role for genetic testing of patients with HIV-negative KS.



GOF/LOF Assay



Dominant Negative Assay

Keywords: Kaposi Sarcoma, HHV8, Kaposi Sarcoma Herpesvirus, Immune dysregulation, CARD11, KSHV Inflammatory Cytokine syndrome, CADINS disease.

Disclosures: Robert Yarchoan has relevant financial relationships with proprietary interests with Celgene (Contracted Research, CRADA), Janssen Pharmaceuticals (Contracted Research, drug supply for laboratory research), Merck,EMD Serano, Eli Lilly, CTI BioPharma (Contracted Research, CRADA), Patent (Intellectual Property / Patents, US Patent 10,001,483), Patent (Intellectual Property / Patents, a peptide vaccine for HIV and on the treatment of Kaposi sarcoma with IL12) and Patent (Intellectual Property / Patents, co-inventor on patents related to internalization of target receptors). All other authors indicated they had no financial relationships to disclose.

(61) 2 Novel Variants in SOCS1 lead to immune dysregulation as well as increased infectious susceptibility

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SOCS1 haploinsufficiency is characterized by early onset autoimmunity and lymphoproliferation. Here we describe 3 unrelated patients with SOCS1 variants.

P1 is a 45 year old male with early onset sinopulmonary infections leading to bronchiectasis, bacterial meningitis, lymphocytic colitis, splenomegaly, and nodular regenerative hyperplasia complicated by cirrhosis. He did not respond to a trial of sirolimus and developed acute portal venous thrombosis while on tofacitinib necessitating discontinuation. He is currently treated with tocilizumab therapy, supplemental immunoglobulin, and prophylactic antimicrobials. He was found to have a novel heterozygous missense variant in SOCS1 c.421C>G (p.Arg141Gly) on whole exome sequencing.

P2 is a 54 year old female with non-malignant lymphoproliferation, sinopulmonary infections, sensorineural hearing loss, cyclic neutropenia and atopy. Whole exome sequencing detected a novel heterozygous missense variant in SOCS1 c.392A>C (p.Gln131Pro).

P3 was a 30 year old male when first seen at NIHCC with childhood onset recurrent sinopulmonary infections, lymphoproliferation and multiple autoimmune manifestations including Evan's syndrome status post splenectomy, recurrent aphthous ulcers, aseptic meningitis, optic neuritis, and idiopathic sensorineural hearing loss. He was managed with mycophenolate mofetil, prednisone, and filgrastim; as well as trials of hydroxychloroquine and supplemental immunoglobulin. He died at 36 years of age from streptococcal bacteremia. He was posthumously found to have a heterozygous frameshifting variant in SOCS1 c.476_480dup (Met161AlaFSTer46) which was previously reported in the literature. (1)

Laboratory evaluation revealed low IgA and decreased memory B cells in all 3 patients (Table1). Lymphocyte functional testing showed enhanced lymphocyte proliferation in P1, but not P2 (Fig1). IFNg-induced phosphorylation of Stat1 was increased in patients with SOCS1 variants (Fig2). Furthermore, IFNg production in memory CD4+ T cells was elevated as compared with historical controls (Fig3). P1 and P2 were also noted to have decreased CD27+CD38+ plasmablasts as well as decreased IgG and IgA secretion by B cells (Fig4; Fig5).

In summary, we present 3 unrelated patients, 2 with novel variants in SOCS1. Notably, infections are more prominent in this case series than previously reported. Continued investigation of the IEI phenotype attributable to SOCS1 will hopefully reveal appropriate targeted therapies, including JAK inhibition and anti-IL-6 therapy.

Table 1:

Laboratory Evaluation	P1 (*SOCS1* c421C>G)	P2 (*SOCS1* c.392A>C)	P3 (*SOCS1* c.476_480dupGCCGC)	Normal Range
White Blood Cell Count (K/uL)	0.9	1.92	11.26	4.23-9.07
Absolute Lymphocyte Count (K/uL)	0.23	0.797	2.39	1.32-3.57
Absolute Neutrophil Count (K/uL)	0.57	0.852	3.64	1.78-5.38
Platelet Count (K/uL)	37	186	442	161-347
IgG (mg/dL)	833*	921	969	700-1600
IgA (mg/dL)	<5	47	<7	70-400
IgM (mg/dL)	<5	126	854	40-230
CD4+ T cell count (cells/uL)	142 (52.6%)	357 (25.7%)	1331 (55.7%)	359-1565 (31.9-62.2%)
CD8+ T cell count (cells/uL)	73 (27.1%)	759 (54.6%)	413 (17.3%)	178-853 (11.2-34.8%)
CD19+ B cell count (cells/uL)	34 (12.7%	88 (6.3%)	148 (6.2%)	61-321 (3.3-19.3%)
CD20+/CD27+ Memory B cells (cells/uL)	0 (0%)	7 (0.5%)	7 (0.3%)	12-68 (0.8-3.6%)

Key
*on IVIG therapy
Low
High

Baseline laboratory values of three affected patients at the time of presentation to the National Institutes of Health Clinical Center.

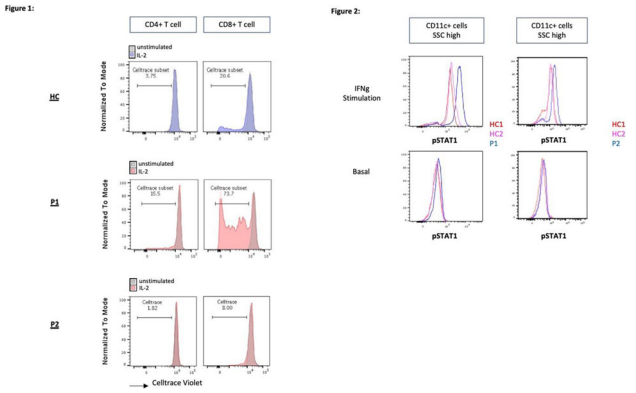

Figure 1: Proliferation as measured by celltrace violet in unstimulated PBMCs (grey) and after stimulation of PBMCs with IL2 (blue in healthy control, pink in P1 and P2). Proliferation of both CD4+ T cell and CD8+ T cells was enhanced in patient P1 as compared with healthy control. Figure 2: STAT1 phosphorylation in unstimulated (bottom panel) and after IFNg stimulation (top panel) in CD11c+/SSC high cells from patients and healthy controls (HC). Phosphorylation of STAT1 was increased in both P1 and P2 after IFNg stimulation as compared with healthy controls.

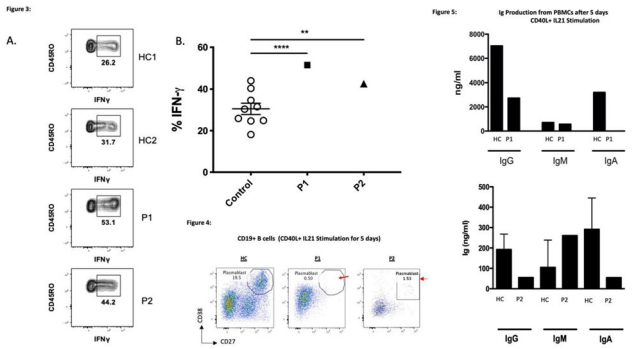

Figure 3: IFNg production in memory T cells is significantly increased in P1 and P2 as compared with healthy controls. Figure 4: Proportion of CD38+CD27+CD19+ plasmablasts were measured 5 days after stimulation with CD40L and IL-21. Plasmablasts were markedly reduced in P1 and P2 as compared with healthy controls. Figure5: Immunoglobulin production from bulk PBMCS was measured 5 days after stimulation with CD40L and IL-21. IgG and IgA production were decreased in P1 and P2 as compared with healthy controls; IgM production was similar (P1) or enhanced (P2).

Keywords: SOCS1 haploinsufficiency, Autoimmunity, Lymphoproliferation

Disclosures: All authors indicated they had no financial relationships to disclose.

(62) A Novel Presentation of PSTPIP1 Gene in a 5-month-old with PSTPIP1-associated myeloid-related proteinemia inflammatory (PAMI) syndrome

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Proline-Serine-Threonine Phosphatase Interacting Protein 1 (PSTPIP 1) is a protein commonly found in hemopoietic tissues, that is involved in regulation of immune and inflammatory processes. PSTPIP1-associated myeloid-related proteinemia inflammatory syndrome (PAMI syndrome) is a rare disease that has been associated with E250K and E257K mutations in the PSTPIP1 gene. Reported clinical findings of PAMI syndrome include recurrent fevers, pancytopenia, neutropenia, dermatitis, hepatosplenomegaly, arthralgia, failure to thrive, hyperzincemia, hypercalprotectinemia, and elevation of inflammatory markers.
Our case report is of a patient with alpha thalassemia trait who was seen at 5-months of age for recurrent fevers and rash. The patient first developed these symptoms at 1-month of age. Her prenatal birth history was unremarkable. The rash was generalized, blanching, and maculopapular, but sparing the palms and soles. She was also fussy when moving her lower extremities suspected to be secondary to arthralgia. Laboratory evaluation at initial presentation was significant for an absolute neutrophil count of 490, elevated CRP (24.20 mg/dl, normal: < 0.30 mg/dl), and elevated ferritin level (2,551 ng/ml, normal: 10-291 ng/ml). Skin biopsy was consistent with neutrophilic urticarial dermatitis. A primary immunodeficiency gene panel revealed a variant of unknown significance (VUS) in the PSTPIP1 gene c.708C>A(p.Asn236Lys). This sequence change replaces Asparagine with Lysine in codon 236 of the PSTPIP1 gene. PSTPIP1 gene mutations are commonly associated with Pyogenic Arthritis, Pyoderma gangrenosum, and Acne (PAPA) syndrome. However, our patient showed findings more consistent with PAMI. Further studies revealed a persistently elevated ferritin (peak: 2,551 ng/ml) and zinc levels (peak: 1287 mcg/dl, normal: 31-120 mcg/dl). The VUS was confirmed with whole-exome gene sequencing. Parents were not found to have the variant. The patient was started on Anakinra at 5-months of age, and her symptoms are well controlled on the medication. She is now 21-months of age and continues to have neutropenia and recurrent fevers, but no recurrent infections. She is currently awaiting bone marrow transplantation for severe neutropenia.
We report a de novo heterozygous mutation in the PSTPIP1 gene(c.708C>A, p.Asn236Lys), that is "likely pathogenic" based on our patient's clinical presentation and laboratory studies being consistent with PAMI syndrome.

Keywords: PSTPIP1 gene, PAMI syndrome, Immune dysregulation, Neutropenia, Anakinra

Disclosures: All authors indicated they had no financial relationships to disclose.

(63) Comparison of different immunization schemes immunogenicity with adjuvant influenza vaccines in patients with common variable immune deficiency

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Objective. The problem of vaccination of patients with primary immunodeficiency, and especially patients with humoral defects of immunity, who respond with a low level of specific antibodies or even a complete absence of antibody synthesis after vaccination, is especially urgent now, when vaccination is assigned the main role in preventing the spread of infectious diseases.
Design and methods. In the prospective, single-center study, formation of humoral response in patients with common variable immune deficiency (CVID) after adjuvant influenza vaccines administration in hemagglutinin inhibition test was studied. In 2018-2019 influenza season 6 patients with CVID received 1 dose of the adjuvant subunit quadrivalent influenza vaccine, and in 2019-2020, 9 patients with CVID received 2 doses of the adjuvant subunit trivalent influenza vaccine. Blood samples were taken before and 3 weeks after vaccination. Intravenous immunoglobulin therapy (IVIG) was suspended for 7 weeks - 4 weeks before and 3 weeks after vaccination. Geometric mean titer (GMT) and geometric mean ratio (GMR) were estimated.
Results. Statistically significant increase in GMT relative to baseline to A/H1N1 and A/H3N2 (25 [12; 54] to 34 [16; 75] ($p = 0.02$) and 11 [6; 19] to 17 [10; 29] ($p = 0.05$), respectively and in GMR - 1.36 [1.03; 1.80) versus 0.79 [0.55; 1.16] ($p = 0.03$) and 1.59 [1.00; 2.52] versus 1.00 [0.63; 1.58] ($p = 0.07$), respectively was observed in the group of patients vaccinated with 2 doses. An increase in GMT to strain B/Colorado in the group of vaccinated with 2 doses was also statistically significant: from 7 [5; 10] to 11 [7; 18] ($p = 0.02$). Cochran-Mantel-Hensel criterion showed that the chance of an increase in antibodies as a result of vaccination with two doses is in 9.3 [1.6; 51.4] times higher (the Mantel-Hensel odds ratio) than after single dose vaccination ($p = 0.02$), regardless of the strain.
Conclusions. Immunogenicity of simultaneous administration of two doses of influenza vaccines is higher in patients with CVID than after single dose. But the search for new vaccination schemes is the subject of further investigations, as well as effectiveness of boosterization with immunoadjuvant vaccines in CVID patients.

Keywords: Influenza, Vaccination, CVID, effectiveness

Disclosures: All authors indicated they had no financial relationships to disclose.

(64) Don't Underestimate a Heterozygous TACI Mutation

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Introduction: TACI is mainly expressed on B lymphocytes particularly on marginal zone B cells, CD27+ memory B cell subsets and plasma cells and is part of a complex signaling network responsible for B cell survival and differentiation. Associated gene defects have been shown to cause CVID, particularly in TNFRSF13B. Two allelic variants C104R and A181E are frequently identified and occur in around 80% of TACI sequence variants. This case presents a patient with TACI heterozygous mutation in TNFRSF13B c.310T>C associated with CVID diagnosis, presenting with hypogammaglobulinemia in the presence of recurrent respiratory infections responding to immunizations.
Case Presentation: Case of 4-year-old male born 38WGA with recurrent respiratory infections. At 15-days-old he presented with nasal congestion and cough without associated fever taken to the hospital where he was treated with bronchodilator therapies and discharged home. He had a total of seven hospitalizations in two years. Mother refers only one throat infection, denies skin infections, ear infections, pneumonia, meningitis, or GI infections.

He is followed by a pediatric pneumologist who, due to history of respiratory infections ordered a genetic panel for primary immunodeficiencies. TNFRSF13B c.310T>C (p. Cys 104 Arg) heterozygous mutation was identified, and patient was referred to our immunology clinics. Upon evaluation, lymphocyte subset panel was normal for age, proliferation studies were normal for age and chest x-ray was normal. Immunoglobulin levels were decreased for age and pneumococcal titers were below normal. He was re vaccinated and one month later his titers were within normal protective values.
Discussion: Patient presented with several respiratory infections and associated hypogammaglobulinemia with a heterozygous mutation at TNFRSF13B, likely pathogenic variant [c.310T>C (p.Cys104Arg)]. A.B Barroeta Seijas et al. found that recurrent infections were the most relevant clinical findings in pediatric patients with TACI mutations and their data suggests that the impact of TACI genetic mutations can range from hypogammaglobulinemia of infancy to autoimmunity in adults. Nevertheless, it is important to continue to explore functional studies such as the potential role of environmental factors in its pathogenesis among others that could lead to better classification and understanding of patients with recurrent infections and hypogammabulinemia.

Keywords: TACI, CVID, Pediatric, Hypogammaglobulinemia

Disclosures: All authors indicated they had no financial relationships to disclose.

(65) A retrospective chart review evaluating fever in PFAPA after tonsillectomy in patients with PFAPA seen in a pediatric tertiary care center

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The syndrome of periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA) is the most common autoinflammatory fever disorder during childhood. Corticosteroids, colchicine, and cimetidine have been used for management with variable results. Tonsillectomy is reserved as an option in patients for refractory PFAPA. Limited data exists evaluating patients' response to tonsillectomy as treatment for PFAPA.
A retrospective chart review was performed at Nationwide Children's Hospital in Columbus, Ohio, a pediatric tertiary care center, to identify patients with PFAPA. ICD-10 codes were used for patients with recurrent fever and PFAPA who were seen by a pediatric infectious disease or pediatric rheumatology specialist between January 1, 2017 and August 10, 2021. Data collected included demographics, steroid use, tonsillectomy date, patient follow up, and fever pattern post tonsillectomy.
Of the 704 patients evaluated for recurrent fever and/or PFAPA during the study period, 80 (11%) underwent tonsillectomy as treatment. All the patients with tonsillectomy had documented periodic fevers, 53 (66%) had documented aphthous stomatitis and pharyngitis. 38 patients were females (1-14 years; average: 6 years) and 42 were males (1-14 years; average 5 years) at the time of initial evaluation. 33 (41%) patients received a trial of steroids. 20 (25%) patients had no further follow-up. 48 (60%) patients had documented resolution of fever, post tonsillectomy. 73% (8/11) of patients referred by Rheumatology had resolution of fever, 82% (9/11) referred by Infectious disease had resolution of fever and 57% (31/54) referred by ENT had resolution of fever. Of those referred by Sleep Medicine, Neurology, or multiple specialties, 0% (0/4) had resolution of fever. 32 patients (42%) had recurrences of fever episodes and were later diagnosed with either unclassified immunodeficiency, recurrent viral illness, or other autoimmune diseases.
In this retrospective study, documented resolution of fever was 60% post-tonsillectomy even though some patients had only periodic fevers and did not meet classic diagnostic criteria for PFAPA. Of the 66% patients with documented aphthous stomatitis and pharyngitis, 62% had resolution of fever. 25% of these patients were lost to follow up, thus likely they too did not have recurrence of fever episodes.

Keywords: Periodic fever, Tonsillectomy, PFAPA

Disclosures: All authors indicated they had no financial relationships to disclose.

(66) DiGeorge Syndrome in a patient with TBX1 mutation and normal chromosomal microarray

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Introduction: DiGeorge syndrome (DGS) is classically associated with the genetic deletion of 22q11. However, other etiologies are possible for this syndrome and related congenital athymia.
Case description: A female neonate was referred to our immunology office with low T-cell receptor excision circles on the newborn screen (NBS), with values of 0, 130, 212, 0, 0, 202. Pregnancy was complicated by gestational diabetes controlled through diet. She was born vaginally with no postnatal complications and no obvious facial dysmorphisms, and was eating and gaining weight appropriately. Initial bloodwork was significant for T cell lymphopenia, with CD3 1674 cells/uL, and CD4 1061 cells/uL. Mitogen proliferation studies were normal. She was hypocalcemic (5.7mg/dL) with hypoparathyroidism (14 pg/dL). She was sent to the hospital for stabilization. While electrolytes were normalized, a chest X-ray failed to visualize the thymus; an echocardiogram was normal. Upon recheck, her lymphopenia worsened, with CD3 918 cells/uL, CD4 669 cells/uL, and CD8 315 cells/uL. Of the CD4 T cells, 19% (237 cells/uL) were CD45RO+ and 81% (1000cells/uL) were CD45RA+, of which 80% (804 cells/uL) were CD4+CD31+. Chromosomal microarray (CMA) was normal, but a commercial primary immunodeficiency genetic panel identified a heterozygous pathogenic variant c.1036C>T (p.Gln346*) resulting in a premature stop codon in the TBX1 gene. While the recent thymic emigrant T cells are higher than expected in congenital athymia, her presentation and genetic defect are concerning for complete DGS. She is currently on antifungal and pneumocystis prophylaxis and awaiting a consult for thymus transplantation.

Discussion: DGS most often involves a microdeletion in chromosome 22q11.2, leading to a diverse clinical phenotype involving congenital heart defects, immunodeficiency, athymia, hypocalcemia, and dysmorphic facies. However, patients can have single gene pathogenic variants that lead to the DGS phenotype, irrespective of the microdeletion. If further evaluation had not been pursued after a normal CMA, appropriate diagnosis and treatment would have been missed. Thus, in patients with high clinical suspicion for DGS, it may be prudent to check a targeted genetic panel in addition to CMA.

Keywords: DiGeorge syndrome, TBX1, Normal chromosomal microarray, Newborn screen, Athymia, Thymus transplant, Genetic screening

Disclosures: All authors indicated they had no financial relationships to disclose.

(67) Clinical Significance of Inherited Chromosomally Integrated HHV-6 (iciHHV-6) in the Setting of ADA-Deficient SCID

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Introduction: Human herpesvirus-6 (HHV-6) causes mild illness in immunocompetent individuals but may be associated with severe disease in patients with primary immunodeficiency. A unique feature of HHV-6 is its ability to integrate into the chromosomes of germ cells, resulting in chromosomally integrated HHV-6 (ciHHV-6) which may be transmitted to offspring. The possibility of ciHHV-6 causing active HHV-6 infection must be considered in patients with a primary immunodeficiency.
Case Presentation: A 5-week-old infant with Adenosine Deaminase Deficient (ADA) Severe Combined Immunodeficiency (SCID) presented with a 3-week history of cough, failure to thrive, and bilateral pulmonary opacities on chest x-ray. Subsequent inpatient evaluation revealed ground glass attenuation on chest CT prompting bronchoscopy with bronchoalveolar lavage (BAL) fluid studies including pneumocystis PCR, mycoplasma, mycobacterial, and fungal cultures, which were negative. Additional negative studies included a respiratory viral panel, COVID-19, HSV, and CMV. Interestingly, results of serum HHV-6 PCR viral testing were positive at 29,200 copies/ml with subsequent HHV-6 PCR testing on BAL fluid revealing 1.6 million copies/ml. Due to concern for HHV-6 viremia and pneumonitis, intravenous antiviral therapy was initiated. Chromosomal integration studies later revealed that the patient and his mother were positive for ciHHV-6. Antiviral therapy was discontinued, and he remained clinically stable off treatment. His cough resolved after starting ADA enzyme replacement therapy suggestive of possible pulmonary alveolar proteinosis as a cause.
Conclusion: A prior case report has illustrated that active HHV-6 infection can result from ciHHV-6 in a patient with X-linked SCID. Additional cases have also demonstrated active HHV-6 infection following hematopoietic stem cell transplantation with either donor or recipient ciHHV-6. Quantitative PCR testing on serum or tissue specimens from patients with ciHHV-6 are unreliable for determining active infection versus chromosomal integration as these patients have high levels of HHV-6 DNA at baseline. Therefore, clinical judgment, testing for ciHHV-6, and assessing for improvement on antiviral therapy is paramount in determining the likelihood of active infection, especially in patients with an underlying primary immunodeficiency.

Keywords: Active HHV-6 Infection, ciHHV-6, ADA-deficient SCID

Disclosures: Talal Mousallem has relevant financial relationships with proprietary interests with Chiesi (Advisory Board, Research Grant includes principal investigator, collaborator or consultant and pending grants as well as grants already received). All other authors indicated they had no financial relationships to disclose.

(68) Chronic mucocutaneous candidiasis with IL17RC gene mutation

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Background: Chronic mucocutaneous candidiasis (CMC) is characterized by persistent or recurrent Candida infection, usually Candida albicans, that affects the oral and genital mucosae, nails, and skin. CMC has been associated with several inborn errors of immunity that affect the IL-17 signaling pathway, including loss-of-function mutations in the IL-17 receptor C (IL17RC) gene. We report the fourth known case of autosomal recessive (AR) IL17RC deficiency.
Case description: A 53-year-old female born to consanguineous parents suffered from recurrent and severe oropharyngeal candidiasis associated with odynophagia and dysphagia since early in infancy, recurrent candida skin infections, and recurrent episodes of urinary frequency and urgency. Her medical history was also relevant for a generalized corticosteroid-responsive dermatitis as an infant, chronic urticaria with angioedema, and a recently diagnosed stage 1A cutaneous mycosis fungoides-subtype T cell lymphoma (CTCL). Her history of early-onset CMC and CTCL prompted an immune workup for an underlying cellular immunodeficiency. She had normal lymphocyte subsets (CD4+T, CD8+T, B, and NK cells). Lymphocyte proliferation assays showed normal lymphocyte response to candida, PHA, ConA, and Pokeweed with low but present response to tetanus. EBV PCR in blood was undetectable. She had normal serum IgG, IgA, and IgM levels, and a normal humoral response to protein and polysaccharide antigens. ANA was positive (homogeneous pattern) but anti-Jo, SCL-70, RNP, Smith, SSA and SSB antibodies were all negative. Targeted genetic testing for 407 genes associated with inborn errors of immunity revealed that the patient was homozygous for the IL17RC c1132C>T (p.Arg378*) variant, which was previously reported in a patient with AR IL17RC deficiency and was shown to result in loss of membrane IL17RC expression. Because the patient was not having frequent fungal infections as an adult, prophylactic antimycotic therapy was not initiated due to the risk for antifungal resistance. She achieved complete remission of her CTCL with narrowband UVB therapy.
Conclusion: This case reinforces the link between AR IL-17RC deficiency and CMC. AR IL-17RC deficiency is a very rare disease and its clinical presentation may extend beyond MCM. Further studies are required to evaluate whether IL17-RC plays any role in the pathogenesis of CTCL.

Keywords: Autosomal recessive IL17 deficiency, Chronic mucocutaneous candidiasis, Rare disease, Inborn errors of immunity

Disclosures: All authors indicated they had no financial relationships to disclose.

(69) Genetic Testing for Inborn Errors of Immunity Using a Primary Immunodeficiency Panel or a Comprehensive Immune and Cytopenia Panel

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Introduction: Primary immunodeficiencies (PID) are a group of inherited disorders affecting immune system development or function. Identifying the genetic etiology significantly impacts patient management but can be challenging if the PID overlaps with hematological disorders like cytopenia and bone marrow failure. We developed an NGS panel, the Comprehensive Immune Cytopenia (CIC) Panel, to address this need and compared the results of the panel to those from a Primary Immunodeficiency Panel (PID) during the same period.
Methods: We performed a retrospective review of deidentified results from 1,243 consecutive patients tested with the CIC Panel (642 genes) or the PID Panel (298 genes). Genetic test results, patient age, clinical information and panel used were extracted from the internal laboratory database.
The panels share 329 genes in common, with the PID Panel and the CIC Panel having 7 and 313 unique genes, respectively. Target regions included all coding exons (unless otherwise indicated), 20 base pairs at intron-exon boundaries, and select, clinically relevant noncoding variants. Copy number variants (CNVs) were analyzed bioinformatically with 2 pipelines, including a proprietary pipeline developed to detect exon-level CNVs. Variant interpretation was performed using a point-based modification of the ACMG guidelines.
Results: Results are summarized in Table 1. For the cohort tested with the PID Panel, the genes responsible for the most diagnoses were BTK (9%) and STAT3 (6%). For the cohort tested with the CIC Panel, the gene responsible for the most diagnoses was XIAP (9%). CNVs were responsible for the diagnosis in 15% of patients while noncoding variants were responsible for the diagnosis in 7% of patients. Variants in difficult-to-sequence (DTC) genes accounted for 10% of the diagnoses.
Conclusion: We demonstrate the clinical utility of performing genetic testing for IEI and its hematologic phenocopies. While both panels had a similar diagnostic yield, the most frequent diagnostic genes are panel specific. Small and large CNVs, noncoding variants and DTC genes are important contributors to the diagnostic potential highlighting the value of panels with high-resolution CNV capabilities, methods to resolve DTC regions, and the inclusion of clinically relevant noncoding variants for this patient population.

	Primary Immune Deficiency Panel	Comprehensive Immune and Cytopenia Panel
Number of patients tested	882	361
Median age at testing	14 years	12 years
Percent of cohort 0-18 years	61%	69%
Percent of cohort >18 years	39%	31%
Number of diagnoses	66 (7%)	32 (9%)
Number of diagnoses due to a copy number variant	11 (16.7%)	4 (12.5%)
Number of diagnoses due to an intragenic copy number variant	6/11	1/4
Number of diagnoses due to a non-coding variant	6 (11%)	1 (3%)
Number of diagnoses in a difficult-to-sequence gene	3 (4.5%)	7 (32%)

Table 1. Primary Immune Deficiency Panel and Comprehensive Immune Cytopenia Panel Results

Keywords: cytopenia, inborn errors of immunity, next-generation sequencing, panel testing, genetic diagnostics

Disclosures: Kim Gall has relevant financial relationships with proprietary interests with Blueprint Genetics (Employment). Zoe Powis has relevant financial relationships with proprietary interests with Blueprint Genetics (Employment). Julie Hathaway has relevant financial relationships with proprietary interests with Blueprint Genetics (Employment). Alicia Scocchia has relevant financial relationships with proprietary interests with Blueprint Genetics, a Quest Diagnostics Company (Employment). Elina Hirvonen has relevant financial relationships with proprietary interests with Blueprint Genetics (Employment). Paivi Kokkenen has relevant financial relationships with proprietary interests with Blueprint Genetics (Employment). Inka Saarinen has relevant financial relationships with proprietary interests with Blueprint Genetics (Employment). Jennifer Schleit has relevant financial relationships with proprietary interests with Blueprint Genetics (Employment). Lotta Koskinen has relevant financial relationships with proprietary interests with Blueprint Genetics (Employment). Samuel Myllykangas has relevant financial relationships with proprietary interests with Blueprint Genetics (Employment). Juha Koskenvuo has relevant financial relationships with proprietary interests with Blueprint Genetics (Employment). Jussi Paananen has relevant financial relationships with proprietary interests with Blueprint Genetics (Employment). Pertteli Salmenpera has financial relationships with proprietary interests with Blueprint Genetics (Employment). Massimiliano Gentile has relevant financial relationships with proprietary interests with Blueprint Genetics (Employment). Emma Martensson has relevant financial relationships with proprietary interests with Blueprint Genetics (Employment). All other authors indicated they had no financial relationships to disclose.

(70) CTLA4 haploinsufficiency presenting as celiac-like disease and treatment considerations in the setting of previous disseminated coccidioidomycosis

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A 16-year-old female with reported celiac disease since infancy was referred for inadequate weight gain and persistent abdominal pain. Her calprotectin was repeatedly elevated at 200-400 ug/g (normal 0-120 ug/g) despite optimal management. EGD and colonoscopy visually demonstrated a duodenum with diffuse scalloping despite adherence to a gluten free diet. Pathology showed villous blunting and increased intraepithelial lymphocytes in the duodenum and ileum. HLA celiac testing showed absence of HLA DQ2 or DQ8. Gene panel testing was sent to rule out autoimmune enteritis. A previously unreported de novo heterozygous variant in CTLA4 in exon 1, c71_72del (p.Leu24Profs*35), was identified suggesting a diagnosis of autosomal dominant CTLA4 haploinsufficiency. Immunological laboratories demonstrated B cell lymphopenia (absolute CD19 of 139/ul with normal 200-600), decrease memory B cells (absolute CD19+CD27+ of 9.6/ul with normal 50-200), mild hypogammaglobulinemia (580 mg/dl) and poor response to polysaccharide pneumococcal vaccine.
She is about to start IVIG. Initial therapeutic options for CTLA4 haploinsufficiency with gastrointestinal involvement include systemic/topical steroids, abatacept or sirolimus. The treatment decision for this patient was complicated by a history of disseminated coccidioidomycosis (DCM) 3 years prior to her presentation. At the time of her referral, she was off antifungal therapy and did not have clinical or radiographic evidence of infection. She continued to live in a Coccidioides endemic region. Our infectious disease colleagues had no contraindications to starting abatacept and recommended no prophylactic antifungal therapy

as long as close monitoring for recurrence of infection was pursued. We ruled out the presence of a non-reported, common heterozygous variant in PLCG2 (p.Arg268Trp) as this specific variant was found in 5 out of 66 patients with DCM. To minimize medication induced immunosuppression, treatment with weekly subcutaneous abatacept was initiated. Soluble IL-2 receptor levels have decreased since starting therapy and there has been no recurrence of DCM. HSCT will be considered in the future.
CTLA4 haploinsufficiency can present with an isolated celiac-like diagnosis. Suspicion of early onset autoimmune enteritis not responding to traditional therapy should trigger the evaluation for possible monogenic causes of disease. Special considerations should be taken when choosing medical therapy to prevent recurrence of serious infections.

Keywords: CTLA4 haploinsufficiency, Celiac disease, Disseminated coccidioidomycosis, PLCG2

Disclosures: Alka Goyal has relevant financial relationships with proprietary interests with Rapt Therapeutics (Employment, Ownership Interest includes stock, stock options, patent or other intellectual property) and Talaris (Consultant). All other authors indicated they had no financial relationships to disclose.

(71) Congenital hypothyroidism associated with IPEX Congenital hypothyroidism associated with IPEX Congenital hypothyroidism associated with IPEX Congenital hypothyroidism and IPEX

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Congenital hypothyroidism associated with IPEX
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IPEX (Immune dysregulation polyendocrinopathy enteropathy X-linked syndrome) represents one of the few Inborn Errors of Immunity that may manifest in the fetal period. Twenty-one cases of fetal loss from hydrops in mid-pregnancy have recently been described. Histopathology showed multivisceral infiltrates with T lymphocytes and other cells, the pancreas being affected in most cases, and the thyroid gland was infiltrated in part of these cases. We describe here the case of a 12-month-old infant referred due to a persistent diarrhea, failure to thrive, neurologic development retardation (probably due to perinatal asphyxia) and bronchopulmonary dysplasia. He was born at term after an uneventful pregnancy with 3,330g; positive neonatal screening for hypothyroidism - subsequently confirmed and difficult to control - associated with anti-TPO: 209 (nl: < 9), reagent to anti-TGB and TRAB. Anti-GAD: 38 (nl < 10), IgE: 1,579 IU/mL (VR: 2-97). The patient had a mutation in FOXP3: c.751_753delGAG; p(GLU251del), already described as a pathogenic variant. After hospitalization, the patient's evolution worsened progressively, with several episodes of electrolytic disturbances, disseminated eczema, persistent thrombocytopenia and poor response to corticosteroids and tacrolimus. He also presented septicemia, with isolation of Enterococcus faecalis and Pseudomonas aeruginosa, and died before undergoing HSCT. As far as the authors are aware, this is the first description of congenital onset Hashimoto's disease caused by a FOXP3 mutation leading to autoimmune thyroiditis as part of intrauterine IPEX clinical picture. Therefore, FOXP3 should be included in the gene panel used to identify monogenic causes of congenital hypothyroidism.
Funding: this work was supported by the FAPESP grant no. 2014/50489-9.

Keywords: PID, IPEX, Congenital Hypothyroidism

Disclosures: All authors indicated they had no financial relationships to disclose.

(72) Activated PI3K-Delta Syndrome: A Tale of Two Siblings With Variable Clinical Phenotypes

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Introduction: Activated phosphoinositide 3-kinase (PI3K) delta syndrome (APDS) is an autosomal dominant, combined immunodeficiency that presents with variable clinical phenotypes. We describe two siblings with APDS bearing heterozygous variants at p.E81K whose presentation differed by over a decade.
Case Description: The proband was healthy until 6 months of age, when he developed a skin abscess that required admission and IV antibiotics. He also had recurrent otitis media, skin abscesses, one episode of pneumonia at 18 months of age, and eczema. At 4 years he presented with bloody stools and required bowel resection, with pathology returning as marginal zone hyperplasia. No further treatment was required. At 7 years he developed inguinal lymphadenopathy with biopsy suggesting EBV lymphadenitis. Over the next decade he was clinically well. At 17y, he developed IgA vasculitis. At 18y, he developed bloody stools, abdominal pain, and flaring IgA vasculitis. PET-CT revealed global lymphadenopathy as well as mild splenomegaly. His labs were notable for low T and NK cells, increased immature B-cells, normal switched memory B-cells and elevated IgG with normal IgM and IgA. He underwent lymph node biopsy that revealed follicular hyperplasia but not lymphoma.
His older sister was totally asymptomatic throughout early childhood, and then presented with IgA vasculitis at age 16. She then presented two years later with abdominal pain and bloody stools, with endoscopy revealing extensive ulceration in the colon. She underwent left hemicolectomy with pathology consistent with marginal zone B-cell lymphoma. She received treatment with Rituximab and has been stable for the subsequent four years. Both siblings are being considered for compassionate treatment with Leniolisib, a selective oral PI3Kδ inhibitor.
Discussion: The factors that control variability in the clinical and immunological phenotypes of APDS are unknown. The p.E81K variant shows milder mTOR activation than the more common p.E1021K variant, but even with the identical variants, these siblings showed more than a decade-long gap in their presentations. Other modifying factors, like age, infections, and stimulation of autoreactivity by commensal microbes, will be discussed.

Keywords: combined immunodeficiency, APDS, activated phosphoinositide 3-kinase delta syndrome

Disclosures: All other authors indicated they had no financial relationships to disclose.

(73) Disseminated Mycobacterium Avium Intracellulare Infection in a Patient with NLRP12 variant

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Introduction: NLRP12, a member of NOD-like receptor (NLR) proteins, has been implicated in regulating innate and adaptive immunity. Mutations in NLRP12 have been associated with systemic autoinflammatory diseases in patients. Murine studies demonstrated that loss of NLRP12 resulted in autoimmunity and impaired control of viral and bacterial infections. We present a case of a patient with disseminated Mycobacterium Avium Intracellulare (MAI) infection and hemophagocytic lymphohistiocytosis (HLH) who carries a heterozygous variant in NLRP12 gene.
Case Description: 37-year-old woman with history of anaplastic astrocytoma and follicular hyperplasia initially presented with left knee pain associated with fatigue, weight loss and arthralgia. Synovial cultures from the affected knee were positive for MAI. Due to systemic symptoms, there was concern for disseminated infection and immunology was consulted to evaluate for underlying immunodeficiency. Patient was lymphopenic (ALC 400) and had normocytic anemia (Hgb 10.1). Inflammatory markers including ESR (131), CRP (14.8) and ferritin (1207) were elevated. Flow cytometry showed marked decrease in T cells (151, normal: 629-2465), and mild reduction in B cells (72, normal: 117-503) and NK cells (57, normal: 69-399), with a CD4:CD8 ratio of 5:1. Immunoglobulins were notable for an elevated IgG (4075). Autoimmune work up showed a high ANA antibody titer (1:1280) and presence of anti-SSA Ro and anti-Ribosomal P autoantibodies. Complements C3 and C4 levels were reduced. Treatment for disseminated MAI infection was started.
Patient subsequently re-presented with fever, lethargy and altered mental status. Repeat infectious work up, including lumbar puncture, was negative. Given elevated ferritin of 1796 and low NK cells, bone marrow evaluation was pursued and revealed histiocytes with erythrophagocytosis concerning for HLH. Soluble IL-2 receptor (1941) was elevated. Patient met diagnostic criteria for HLH and was started on systemic corticosteroids, to which she responded. Invitae primary immunodeficiency genetic testing showed heterozygous in frame exon 5 deletion in the NLRP12 gene.
Discussion: Alterations in NLRP12 have been linked to immune dysregulation. NLRP12 variant in our patient may be contributing to her phenotype of disseminated mycobacterial infection and autoimmunity. Additional studies such as functional testing are needed to elucidate how this variant alters NLRP12 function.

Keywords: Immune Dysregulation, Autoimmunity, Mycobacterial Infection

Disclosures: Fei Li Kuang has relevant financial relationships with proprietary interests with AstraZeneca (Research Grant includes principal investigator, collaborator or consultant and pending grants as well as grants already received). All other authors indicated they had no financial relationships to disclose.

(74) Correlates of psychological adaptation in adults with inborn errors of immunity

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Background: Adjusting to and living with a chronic health condition can be challenging. While there is a broad literature on how individuals cope and adapt to some health conditions such as cancer, there is a dearth of information on how individuals with inborn errors of immunity (IEI) adapt to and manage their illness. We implemented a cross-sectional survey study to investigate levels of psychological adaptation, anxiety, depression, perceived personal control, and other important psychosocial variables in individuals with IEI to detect areas for potential intervention to improve adaptation.
Methods: A RedCap survey assessing various psychological variables and illness characteristics using validated measures was emailed to adults undergoing genetic sequencing in the National Institute of Allergy and Infectious Diseases Centralized Sequencing Program and who were also suspected to have an IEI. Data was analyzed using R statistical software.
Results: We received 314 responses from a pool of 1,038 invited individuals (30.3% response rate). Respondents were heterogenous for specific IEI diagnoses. Levels of adaptation to illness were similar to previously published cohorts of individuals with health conditions (mean: 3.89, where 5 represents being totally adapted to implication of one's illness, SD: 0.67). Multiple linear regression analysis detected that perceived present control was the most significant correlate of adaptation analyzed ($B= 0.26$, $p < 0.001$). Higher levels of anxiety and depression were negatively correlated with psychological adaptation ($B = -0.19$, $p < 0.05$). Specific illness diagnosis, gender, sleep quality, functional level, and pain level were not found to be significantly associated with adaptation. Adjusted R2 for the model was 0.11.
Conclusion: Individuals who had higher levels of perceived personal control of their present situation were significantly more likely to report being better adapted to their illness. Interestingly, sleep quality, pain, and functional status were not significantly associated with adaptation. These data indicate the possibility that psychological adaptation is more dependent on personal characteristics than specific illness diagnosis. Finally, these data suggest that identifying areas of control for our patients with IEI may be useful to aid adjustment and coping.

Keywords: Genetics, Counseling, Adults, Coping, Psychosocial

Disclosures: All authors indicated they had no financial relationships to disclose.

(75) Characterization of CXCR4(S341Y) Variant of Uncertain Significance in the Setting of Infections, Hypogammaglobulinemia, and Warts

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Warts, Hypogammaglobulinemia, Infections, Myelokathexis (WHIM) syndrome is a rare primary immunodeficiency disorder commonly caused by nonsense, frameshift, or missense gain-of-function, autosomal dominant mutations in the C-terminus of CXCR4. The clinical presentation of patients with WHIM varies, even in familial forms; neutropenia accompanied by recurrent infections and myelokathexis and/or identification of a pathogenic CXCR4 variant can expedite diagnosis. Here, we report in vitro functional characterization of CXCR4 p.S341Y, a novel missense variant of uncertain significance (VUS) detected in several family members with variable clinical features of WHIM syndrome.
CXCR4 including wild-type (WT), novel VUS S341Y, and known pathogenic variants R334X (nonsense) and E343K (missense) were expressed in the CXCR4-negative K562 cell line. Functional activity of CXCR4 was tested with assays for CXCL12-induced, extracellular signal-regulated kinase (ERK)/PI3K-Akt (AKT) activation, cellular chemotactic response, and CXCR4 receptor internalization.
The heterozygous CXCR4 (c.1022C>A, p.S341Y) VUS was originally discovered in a male aged 19 years with a heterozygous loss-of-function NFkB1 mutation and warts (W), hypogammaglobulinemia (H), recurrent infections (I), moderate neutropenia, and thrombocytopenia; however, there was no evidence of myelokathexis (M) in the bone marrow biopsy. Genetic screening revealed 3 family members with the same CXCR4 variant (no NFkB1 mutation) but with variable clinical presentation. Functional studies were initiated for VUS resolution. Analysis of the downstream signaling revealed hyperactivation of ERK and AKT signaling pathways in the CXCR4(S341Y), comparable to effects observed in pathogenic variants R334X and E343K. CXCR4(S341Y) also showed increased chemotaxis toward CXCL12, similar to the pathogenic variants. Interestingly, upon stimulation with CXCL12, CXCR4(S341Y) showed an internalization response comparable to CXCR4(WT), while CXCR4(R334X) and CXCR4(E343K) displayed impaired internalization.
Here, we describe functional characterization of a novel CXCR4 VUS p.S341Y identified in a family with manifestations across the clinical spectrum of WHIM syndrome. Our functional studies in parallel with clinical presentation of patients may contribute to the reclassification of p.S341Y VUS as a likely pathogenic variant. Even with WT-like internalization of the receptor (correlating with lack of myelokathexis), VUS's such as S341Y can be classified as pathogenic due to other, related impaired cellular mechanisms when shown to contribute to the clinical phenotype of the patient.

Keywords: WHIM Syndrome, Variant of Uncertain Significance, CXCR4, Primary Immunodeficiency, CXCR4 Signaling and Internalization

Disclosures: Katarina Zmajkovicova has relevant financial relationships with proprietary interests with X4 Pharmaceuticals (Employment, Ownership Interest includes stock, stock options, patent or other intellectual property), Sumit Pawar has relevant financial relationships with proprietary interests, X4 Pharmaceuticals (Employment). Sabine Maier-Munsa has relevant financial relationships with proprietary interests with X4 Pharmaceuticals (Employment). Barbara Maierhofer has relevant financial relationships with proprietary interests with X4 Pharmaceuticals (Employment).
Christoph Geier has relevant financial relationships with proprietary interests with X4 Pharmaceuticals (Speaker/Honoraria includes speakers bureau, symposia, and expert witness). Henry Kanarek has relevant financial relationships with proprietary interests with AstraZeneca Pharmaceuticals (Speaker/Honoraria includes speakers bureau, symposia, and expert witness), Biocryst (Speaker/Honoraria includes speakers bureau, symposia, and expert witness), Kedrion (Research Grant includes principal investigator, collaborator or consultant and pending grants as well as grants already received), Novartis (Research Grant includes principal investigator, collaborator or consultant and pending grants as well as grants already received) , Octapharma (Research Grant includes principal investigator, collaborator or consultant and pending grants as well as grants already received) , Pharming Pharmaceuticals (Speaker/Honoraria includes speakers bureau, symposia, and expert witness) , Regeneron (Research Grant includes principal investigator, collaborator or consultant and pending grants as well as grants already received), Takeda (Research Grant includes principal investigator, collaborator or consultant and pending grants as well as grants already received), and Teva Pharmaceuticals (Speaker/Honoraria includes speakers bureau, symposia, and expert witness). Michael Jaglal has relevant financial relationships with proprietary interests with Agios Pharmaceuticals (Advisory Board), and Sanofi (Advisory Board). Adriana Badarau has relevant financial relationships with proprietary interests with X4 Pharmaceuticals (Ownership Interest includes stock, stock options, patent or other intellectual property, Previous employer). Arthur Taveras has relevant financial relationships with proprietary interests with X4 Pharmaceuticals (Employment, Ownership Interest includes stock, stock options, patent or other intellectual property). Jolan Walter has relevant financial relationships with proprietary interests with Octapharma (Research Grant includes principal investigator, collaborator or consultant and pending grants as well as grants already received), Pharming (Consultant), Takeda (Consultant, Research Grant includes principal investigator, collaborator or consultant and pending grants as well as grants already received), and X4 Pharmaceuticals (Consultant). All other authors indicated they had no financial relationships to disclose.

(76) A Case Series: Inflammatory Bowel Disease in Children with X-Linked Agammaglobulinemia

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Introduction: Ten percent of patients with X-Linked Agammaglobulinemia (XLA) are estimated to have auto-inflammation presenting as inflammatory bowel disease (IBD). While the relationship between XLA and IBD is a recent area of interest, the severity of patients' gastrointestinal symptoms and effective therapy remains unclear. We herein present two cases of XLA with IBD, outlining the presentation and treatment.
Case Description: Patient 1 is a healthy male who presented at age two years during admission for treatment of (lobar) pneumonia complicated by empyema. Work-up during admission showed low IgG (40 mg/dL), undetectable IgA, and low IgM (7 mg/dL). On follow up testing, his monocytes had low BTK expression, consistent with a diagnosis of XLA. He started Immune globulin replacement. Over the next year, he began treatment for low iron (Hgb 8.6 g/dL, Iron 15 mcg/dL). IgG levels were difficult to maintain at goal (>800 mg/dL) despite stable weight and dosing adjustments. Two years after presentation, he was diagnosed with IBD and the disease was controlled with subcutaneous Methotrexate. Patient 2 presented at age 2 with recurrent sinopulmonary infections. Labs showed undetectable IgG, IgA, and IgE with low IgM (28.9 mg/dL) and < 1% B cells on flow cytometry. BTK analysis showed lack of BTK expression in monocytes and XLA was diagnosed. Four years later, he was diagnosed with concurrent Chronic Granulomatous Disease given granulomatous gingivitis, low neutrophilic oxidative burst and a missense

variant in CYBB (c.272G>T). He developed blood in the stool, granulomatous colitis and issues maintaining IgG levels attributed to colonic inflammation. Therapy began with mesalamine, was switched to mercaptopurine and oral budesonide and then to vedolizumab (α4β7 integrin antibody) on which he was controlled. However, due to infections and liver involvement, stem cell transplant was ultimately pursued.
Discussion: IBD in XLA patients can present a unique challenge in terms of diagnosis and treatment. Clinical suspicion in XLA patients with falling IgG levels despite stable therapy, vitamin deficiencies or poor growth can be clues to a co-diagnosis of IBD. These cases highlight the variety in patient presentation in those with XLA and IBD and provide examples of possible therapies and interventions.

Keywords: XLA, Inflammatory Bowel Disease, vedolizumab

Disclosures: All other authors indicated they had no financial relationships to disclose.

(77) Humoral Immunodeficiency in a Patient with Malan Syndrome Secondary to Chromosome 19p13.2 Microdeletion.

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Introduction: Malan syndrome (Sotos Syndrome 2, MIM 614753) is A rare Autosomal dominant overgrowth genetic disorder characterized by dysmorphic facial features, macrocephaly, intellectual disability and behavioral issues. Malan syndrome is caused by either chromosomal 19p13.2/19p13.13 microdeletion or NFIX gene haploinsufficiency. Herein, we present a case of Malan syndrome who presented to the immunology clinic with recurrent bacterial infection and significant humoral immunodeficiency.
Case report: This is a 5-year-old girl who presented to the immunology clinic with a history of recurrent infections. She was born full-term and was admitted to the NICU due to feeding difficulties and recurrent desaturation. She was found to have hypercapnia and sleep study suggestive of obstructive apnea and was started on CPAP. Cranial 3D CT was done, which showed Pierre robin sequence and craniosynostosis. Mandibular reconstruction was done at the age of 3 months. She was diagnosed with lissencephaly based on MRI shortly after birth and subsequently was found to have seizures and started on antiepileptics. Microarray was done and showed Chromosome 19 microdeletion 19p13.2-19p13.3.
Over the following years, she had multiple ear infections (almost once per month) and had two sets of ear tubes by the age of 3 years. She also has three episodes of Pneumonia, all proven on chest X-ray. She missed 3-5 days/month of school on average due to illness. She did not have a history of skin abscesses or oral thrush. The immunology evaluation revealed low IgG 115mg/dL (RR 445-1,187mg/dL), low IgA 21.6mg/dL (RR 25-153mg/dL), IgM 20.8 mg/dL (RR 41-186mg/dL) and a poor response to Hib (< 0.11mg/L) Low and Prevnar (6 out of 12 serotypes were > 1.3). She had a normal response to the tetanus vaccine and a low switched memory B cells percentage. She was started on IgG replacement which led to a major improvement in the frequency of bacterial infections.
Conclusion: Immunology workup should be considered in patients with chromosomal disorders and a history of recurrent infections. In this case, the Immunology evaluation was delayed because recurrent infections were initially attributed to anatomical anomalies. Malan syndrome can be associated with significant humoral immunodeficiency requiring IgG replacement therapy.

Keywords: Malan Syndrome, Sotos Syndrome, hypogammaglobulinemia, Chromosome 19p13.2

Disclosures: All authors indicated they had no financial relationships to disclose.

(78) Cutaquig® is well tolerated in patients who did not tolerate other subcutaneous immunoglobulin products

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Subcutaneous immunoglobulin (SCIG) treatment offers many clinical advantages over intravenous immunoglobulin to immunodeficient patients. SCIG is generally tolerable, but some patients may experience adverse events to one or more SCIG products. We investigated treatment tolerability, safety and quality of life of ten immunodeficient patients who were treated with 16.5% Cutaquig due to intolerability or adverse events to other 20% SCIG product(s).
During a one-year follow-up period, seven patients completed the study without any administration changes, such as slowing, interrupting, or stopping the infusion. There were no serious or severe adverse events related to the treatment with SCIG reported during the study. Three moderate infections were reported (two urinary tract infections and one injection site infection). Serum IgG level at the end of the study was comparable to baseline 9.6 ± 4.5 vs 7.6 ± 4.3 g/L, $p = 0.26$. Overall health, health changes, and quality of life by the SF-36 survey and EQ visual analog scale improved by 21.5%, 16.7% and 7.7%, respectively. While several domains in quality-of-life measurement such as emotional and social aspects declined due to Coronavirus disease 2019 pandemic, Cutaquig offers an alternate treatment option for patients who did not tolerate 20% SCIG products.
Therefore, the availability of 16.5% Cutaquig expands choices for patients requiring chronic IG treatment.

Keywords: Cutaquig, subcutaneous immunoglobulin, tolerability, adverse event

Disclosures: Juthaporn Cowan has relevant financial relationships with proprietary interests with Alexion Pharmaceuticals (Speaker/Honoraria includes speakers bureau, symposia, and expert witness), CSL Behring (Research Grant includes principal investigator, collaborator or consultant and pending grants as well as grants already received), EMD Serono (Speaker/Honoraria includes speakers bureau, symposia, and expert witness), Grifols (Research Grant includes principal investigator, collaborator or consultant and pending grants as well as grants already received), GSK (Speaker/Honoraria includes speakers bureau, symposia, and expert witness), Octapharma (Other Financial or Material Support, Research Grant includes principal investigator, collaborator or consultant and pending grants as well as grants already received, Speaker/Honoraria includes speakers bureau, symposia, and expert witness), and Takeda Development Center Americas, Inc. (Other Financial or Material Support, Educational funding). D. William Cameron has relevant financial relationships with proprietary interests with Takeda (Speaker/Honoraria includes speakers bureau, symposia, and expert witness). All other authors indicated they had no financial relationships to disclose.

(79) Expanding the clinical and immunological phenotypes and natural history of MALT1 deficiency

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Purpose: MALT1 deficiency is a combined immune deficiency characterized by recurrent infections, eczema, chronic diarrhea, and failure to thrive. Clinical and immunological characterizations of the disease have not been previously reported in large cohorts. We sought to determine the clinical, immunological, genetic features, and the natural history of MALT-1 deficiency.

Methods: The clinical findings and treatment outcomes were evaluated in nine new MALT1-deficient patients. Peripheral lymphocyte subset analyses, cytokine secretion, and proliferation assays were performed. We also analyzed ten previously reported patients to comprehensively evaluate genotype/phenotype correlation.

Results: The mean age of patients and disease onset were 33±17 and 1.6 ±0.7 months, respectively. The main clinical findings of the disease were recurrent infections (100%), skin involvement (100%), failure to thrive (100%), oral lesions (67%), chronic diarrhea (56%), and autoimmunity (44%). Eosinophilia and high IgE were observed in six (67%) and two (22%) patients, respectively. The majority of patients had normal T and NK cells, while eight (89%) exhibited reduced B cells. Immunoglobulin replacement and antibiotics prophylaxis were mostly ineffective in reducing the frequency of infections and other complications. One patient received hematopoietic stem cell transplantation (HSCT) and five patients died as a complication of life-threatening infections. Analyzing this cohort with reported patients revealed overall survival in 58% (11/19), which was higher in patients who underwent HSCT (P=0.03).

Conclusion: This cohort provides the largest analysis for clinical and immunological features of MALT1 deficiency. HSCT should be offered as a curative therapeutic option for all patients at the early stage of life.

Keywords: Inborn errors of immunity, primary immunodeficiency, MALT1, combined immune deficiency, immune dysregulation, recurrent infections, skin involvement, failure to thrive, hematopoietic stem cell transplantation

Disclosures: Hassan Abolhassani has relevant financial relationships with proprietary interests with Jonas Söderquist scholarship and Åke Wibergs foundation (Research Grant includes principal investigator, collaborator or consultant and pending grants as well as grants already received). Daniel Krappmann has relevant financial relationships with proprietary interests with Deutsche Forschungsgemeinschaft (ID 360372040 – SFB 1335 P07) (Research Grantincludes principal investigator, collaborator or consultant and pending grants as well as grants already received). Talal a. Chatila has relevant financial relationships with proprietary interests with National Institutes of Health (R01AI085090 and R01AI128976) (Research Grant includes principal investigator, collaborator or consultant and pending grants as well as grants already received). Safa Baris has relevant financial relationships with proprietary interests with Scientific and Technological Research Council of Turkey (318S202) (Research Grantincludes principal investigator, collaborator or consultant and pending grants as well as grants already received). All other authors indicated they had no financial relationships to disclose.

(80) Complement Deficiency and T-cell Functional Defects with Associated Recurrent Streptococcus Bacteremia as a Unique Presentation of RTEL1 Variant Heterozygosity

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Background: RTEL1 variants are classically associated with a bone marrow failure, pulmonary and/or liver fibrosis consistent with a telomeropathy phenotype. While lymphopenia is documented in patients with RTEL1 variants, functional, including complement defects, are not fully characterized.
Case Presentation: At 18-months of age a fully immunized Caucasian boy developed Viridans streptococci bacteremia following otitis media treatment. An echocardiogram was negative for endocarditis. Following antimicrobial therapy, fevers returned. Repeat blood cultures revealed Streptococcus pneumoniae. An immunodeficiency evaluation was completed. Quantitative immunoglobulins were normal. Lymphocyte analysis, including naïve and memory T-cell assessment, showed normal absolute values. B-cell subset analysis was overall reassuring, including class-switched cells, but did note reduced absolute plasmablasts (CD38+/IgM-). Lymphocyte mitogen proliferation was appropriate, but antigen proliferation showed significantly decreased CD45+ total lymphocytes and CD3+ T-cell proliferative responses to Candida and Tetanus toxoid antigens. Diphtheria, Tetanus and Streptococcus pneumoniae vaccination titers were normal. A spleen was present on imaging. Complement level testing was significant for reduced CH50 and AH50 levels on numerous lab draws with nadir values of 25 U/mL (normal > 41 U/mL) and 17% (normal > 46%), respectively. Further clinical assessment was reassuring against a classical complement deficiency secondary to hepatic dysfunction, proteinuria or an underlying autoimmune condition (negative ANA). Individual complement component testing, including C2-C9, C3c, Factor B, Ba, Bb, Factor H, Factor I, Properdin, and soluble C5b-9, were unremarkable. Alternative pathway activity testing, as well Factor B and Factor H autoantibody screening, was additionally normal. Whole exome sequencing revealed heterozygous variants in RTEL1 (paternally derived c.1031 T>C, p.M344T and maternally derived c.2744 C>T, p.A915V). Telomere testing revealed telomere length < 1%ile in natural killer cells, memory T-cells and granulocytes with low telomere length (1-10%ile) in lymphocytes, naïve T-cells and B-cells. Complete blood cell counts have been normal. Parental telomere length testing normal. The patient continues on daily amoxicillin prophylaxis with additional optimization of vaccination status against encapsulated organisms.
Conclusion: Our patient expands the clinical and laboratory phenotype seen in association with autosomal recessive RTEL1-associated disease through functional T-cell defects and complement deficiency leading to recurrent streptococcal bacteremia episodes.

Keywords: RTEL1, complement deficiency, telomere biology disorder, immunodeficiency

Disclosures: Kelly Walkovich has relevant financial relationships with proprietary interests with AstraZeneca (Advisory Board), Horizon Pharma (Advisory Board), Pharming Health Inc (Advisory Board), Sobi Pharmaceuticals (Other Financial or Material Support, Steering committee member), X4 Pharma (Other Financial or Material Support, Local principal investigator for industry sponsored study). All other authors indicated they had no financial relationships to disclose.

(81) Hemophagocytic lymphohistiocytosis (HLH) preceded by recurrent fevers in a pediatric patient with DNASE2 deficiency

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DNASE2 deficiency is a rare type 1 interferonopathy. Previously, only four patients from three families were reported carrying a hypomorphic homozygous missense mutation in DNASE2, presenting with autoinflammation, failure to thrive, recurrent fevers, and anemia. One patient also presented with HLH and cytokine dysregulation. Here we describe a case likely due to DNASE2 deficiency with HLH after a period of recurrent fevers and malaise.
A 12-year-old boy of Indian descent with no consanguinity presented after 5 months of recurrent weekly fevers to 103F, chills, fatigue, malaise, and anorexia. His initial exam found him to be thin, with mobile cervical lymphadenopathy and mild splenomegaly. Laboratory investigation demonstrated multiple derangements including neutropenia, anemia, thrombocytopenia, hyperferritinemia, hypertriglyceridemia, sIL-2R elevation (924 U/ml), IL-18 elevation (1,197 pg/ml), low NK cell activity, and hemophagocytosis. He additionally had poor pneumococcal titers, but normal immunoglobulins, lymphocyte numbers, and mitogen studies. Infectious disease and rheumatologic testing was notable only for positive ANA and elevated EBV IgM with negative EBV PCR. He had various thyroid abnormalities leading to a diagnosis of autoimmune thyroiditis.
He received several blood transfusions during a 4-week admission and continued to have weekly fevers. Due to ongoing workup, he did not receive immunosuppressive treatments. After 3-4 weeks, his fevers resolved and he started to regain weight, with normalized cell lines. He was discharged and remained asymptomatic for several months. However, he recently experienced a recurrence of symptoms.
Immunology-focused exome analysis was performed and demonstrated an extremely rare homozygous DNASE2 variant (NM_001375.3, c.1040G>A, p.Cys347Tyr) affecting the last highly-conserved residue of the phospholipase D family consensus sequence. Because this variant has previously been reported in an infant with growth delay, microcephaly, hepatosplenomegaly, and thrombocytopenia, it is likely deleterious and the cause of the DNASE2 deficiency in our patient. HLH associated with DNASE2 deficiency has only been reported in one other patient previously. Occurrence of HLH in two out of five total patients with this mutation suggests that the phenotype of DNASE2 deficiency may need to be expanded, and screening for DNASE2 considered in the evaluation of patients without known familial HLH gene mutations.

Keywords: HLH, genetics, recurrent fevers

Disclosures: All authors indicated they had no financial relationships to disclose.

(82) A known homozygous mutation in FADD gives rise to clinical features of FADD deficiency in the absence of ALPS biomarkers

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FAS-associated protein with death domain (FADD) deficiency is a rare autosomal recessive disorder due to a disruption of FAS-mediated apoptosis. It is characterized by recurrent febrile episodes of encephalopathy and seizures, with variable degrees of lymphoproliferation, cerebral atrophy and cardiac abnormalities. In all reported cases, biomarkers of Autoimmune lymphoproliferative syndrome (ALPS) were markedly elevated, consistently with a defect in the extrinsic pathway of apoptosis. Herein we report a new case of FADD deficiency characterized by atypical laboratory features.
A 17 years-old female came to our attention for three recurrent episodes of fever, seizures and encephalopathy requiring hospitalization in intensive care unit. In one case a concomitant EBV infection was detected,

while infectious workup was negative in the other two events. All cases resolved after anticonvulsant treatment (Levetiracetam), together with steroids and intravenous immunoglobulins. Neurologic follow-up showed dysarthria and sensorimotor polyneuropathy. Clinical history revealed three episodes of pneumonia in the past, together with recurrent upper respiratory infections since her first year of age. She also displayed dyshidrotic eczema and mild liver steatosis despite normal body mass index. Family history showed a similar episode of encephalopathy in her brother, who also presents a specific learning disorder (SLD). Moreover, a maternal cousin suffers from epilepsy and SLD.
Whole exome sequencing (WES) revealed a homozygous p.C105W mutation in FADD, already reported as pathogenic. Both parents resulted heterozygous, while her brother also resulted homozygous for the same mutation. Laboratory tests were performed seeking ALPS biomarkers (TCRαβ+ double negative T cells, vitamin B12, IL-10), which unexpectedly resulted in normal range, as well as serum immunoglobulins. FAS-mediated apoptosis testing is currently being processed, while further functional investigations are planned in both the patient and her brother. Interestingly, she was recently infected with SARS-CoV-2 but only displayed mild symptoms of Covid-19, despite the relevant role of FADD in type I Interferon response.
This case increases the number of reported patients with FADD deficiency, showing that this disorder may present variable expressivity. Further studies may reveal a potential role of epigenetics and immune system plasticity in the development of atypical phenotypes of this inborn error of immunity.

Keywords: FADD deficiency, Autoimmune lymphoproliferative syndrome, Apoptosis, Immune dysregulation, Inborn errors of immunity

Disclosures: All authors indicated they had no financial relationships to disclose.

(83) Early onset CVID and hypereosinophilia with novel VUS NFKB2 mutation c.1993A>T (p.Thr665Ser)

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Introduction. Common variable immunodeficiency (CVID) is an inborn error of immunity with defects in B cell maturation leading to low serum immunoglobulins and poor antibody response. Genetic causes for CVID account for up to 20% of cases and include defects such as ICOS, TACI, LRBA, and NFKB1. Here we present a 4 year old Hispanic female with early onset CVID and hypereosinophilia with novel VUS NFKB2 mutation c.1993A>T (p.Thr665Ser).
Case Presentation: Our patient initially presented at 20 months of age with left labial majora pseudomonas and enterococcus abscess. Labs were significant for neutropenia (61.0 10k/uL), B cell lymphocytopenia (301.92 cells/uL), low IgG (217 mg/dL) and IgM (9.7 mg/dL) with normal IgA, low vaccine titers (tetanus antitoxoid 0.02 IU/mL, diphtheria antitoxoid 0.02 IU/mL, haemophilus influenza IgG 0.11 mg/L, and pneumococcal titers 0/14 (all < 0.1 ug/dL)), and normal oxidative burst. She received antibiotics, G-CSF, and IVIG with improvement. Previous infectious history of three episodes of otitis media, with no prior hospital admissions. She had no other physical exam abnormalities or pertinent family medical history. Normal development. Normal hair, skin, and nails.
During the COVID-19 pandemic she was quarantined at home and free of infections. Follow up testing revealed persistent hypogammaglobulinemia and loss of antibody titers after initial response to boosters. She was started on immunoglobulin replacement. She had low IgG subclass 1 (191 mg/dL) with normal other IgG subclasses and normal lymphocyte mitogen proliferation. More recently, she developed acute bilateral submandibular swelling and hypereosinophilia (4.4 10k/uL). Invitae CVID panel +VUS NFKB2 mutation c.1993A>T (p.Thr665Ser).
Discussion: NFKB2 defects have been recently identified in association with early onset CVID and central adrenal insufficiency. Identified pathologic mutations are in the C-terminus and cause nonsense or frameshift alleles. Our patient's variant is located near to but not in the C-terminus and it is a heterozygous missense mutation. Testing was limited to the Invitae CVID panel, therefore it is unknown if she may have additional mutations contributing to her phenotype. She also has persistently elevated T cells and decreased B cells, all of which may be related to her underlying CVID phenotype.

Keywords: CVID, NFKB2, Inborn error of immunity, Hypogammaglobulinemia, Primary immunodeficiency, Variant of unknown significance

Disclosures: Vivian Hernandez-Trujillo has relevant financial relationships with proprietary interests CSL (Advisory Board), Kaleo (Advisory Board, Consultant, Speaker/Honoraria includes speakers bureau, symposia, and expert witness), Regeneron (Advisory Board), and Takeda (Advisory Board, Consultant, Speaker/Honoraria includes speakers bureau, symposia, and expert witness). All other authors indicated they had no financial relationships to disclose.

(84) Anti-SARS-CoV-2 reactive T cells in a XLA patient after CoronaVac vaccine

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X-linked Agammaglobulinemia (XLA) is an inherited immunodeficiency disorder caused by mutation in BTK gene, which plays a key role in pro- and pre-B-cells maturation. B-cell lineage complete maturation is impaired in affected patients, resulting in absent/very low B lymphocytes in blood and tissues, inability of antibody production, but normal T cell number and function. In the context of COVID-19 pandemic, it is crucial to investigate the immune status of vaccinated immunodeficient individuals. We describe here the case of a 32-year-old XLA patient, diagnosed in the second semester of life, and since then undergoing gamma globulin replacement therapy; he presented a benign evolution without any severe infection, and is currently an engineer in normal activities. The mutation, identified as p.P203Lfs*13, results in a premature stop codon further downstream. The patient received two doses of the anti-COVID-19 inactivated whole virus vaccine CoronaVac (Sinovac) 4 weeks apart, with no significant effect reactions. Blood samples were obtained 3 weeks after

the 2nd dose and as expected, no detectable levels of serum total anti-SARS-CoV-2 neutralizing antibodies (NAbs) and IgG antibodies anti-Trimeric Spike glycoprotein of SARS-CoV-2 were found. On the other hand, IFN-gamma intracellular production by CD4+ and CD8+ T lymphocytes after stimulus with SARS-CoV-2 peptides were comparable to that from samples of 22 vaccinated health age-matched controls, who also received 2 CoronaVac doses, remaining respectively between 25–50 and 5–10 percentiles (Figure 1). This case report highlights the relevance of immunizing patients with antibody production disorders. To the best of our knowledge, this is the first description of T-cell reaction against CoronaVac vaccine, although equivalent reports against Pfizer-Biontech preparation were previously reported.

Financial support: São Paulo Research Foundation – FAPESP (2014/50489-9 and 2016/25212-9)

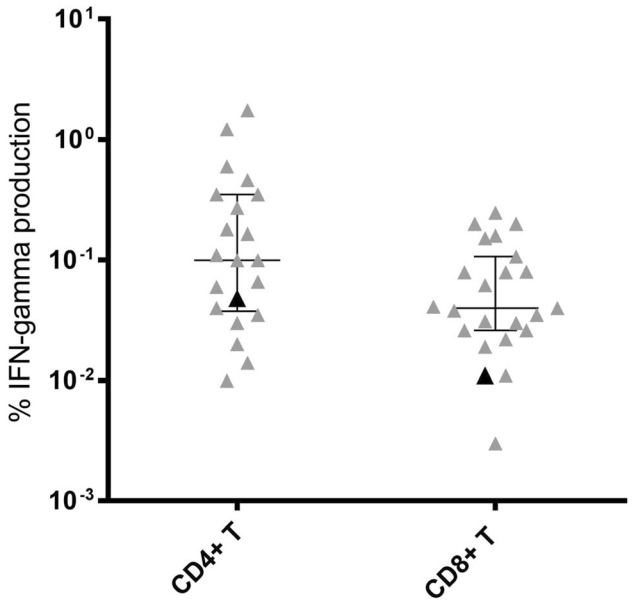

Figure. T cell responses to SARS-CoV-2 peptide pools. PBMCs from CoronaVac vaccinated healthy donors (gray triangles) (n = 22) and the XLA patient (black triangle) were incubated for 18 h with a mixture of grouped SARS-CoV-2 peptide pools (membrane, nucleocapsid and spike) at a final concentration of 1 μg/mL. The logarithmic scale represents the percentage of CD4+ and CD8+ T cells producing IFN-γ. Scatterplots show lines at the median with interquartile ranges. IFN-gamma production was analyzed by intracellular flow cytometry.

Keywords: X-linked Agammaglobulinemia, CoronaVac vaccine, cellular immune response

Disclosures: All authors indicated they had no financial relationships to disclose.

(85) Anti-IL-17 autoantibody, a contributing factor for a refractory histoplasmosis in an otherwise immunocompetent man

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Histoplasma capsulatum is a dimorphic fungus which primarily causes disease in the lungs that is self-limited in immunocompetent individuals. However, some may develop symptoms and require antifungal treatment. In addition, 10-15% of immunocompetent individuals may fail systemic antifungal treatment for unclear reason.

Here, we report a 56-year-old Caucasian Canadian man with refractory histoplasmosis. He was only known to have obstructive lung disease, gastroesophageal reflux disease and obstructive sleep apnea. He presented with several weeks of non-productive cough and constitutional symptoms following an exposure to bats while working on a chimney. Serologic, radiographic, and histopathological examinations confirmed pulmonary histoplasmosis. He was treated with Itraconazole for six months. He only responded partially, and symptoms worsened again after discontinuation of antifungal treatment. Other antifungal agents were trialed for another six months with no effect. A repeat lung biopsy was performed a year following the initial one. It showed small oval-shaped yeast cells consistent with Histoplasma spp. and significant lung inflammation.

Interestingly, he reported being sick with upper respiratory tract infections frequently. He had tonsillectomy at age 45 for pharyngitis. He has had poor wound healing with small cuts. There was no history of mucocutaneous candidiasis but recurrent herpes simplex infections and cutaneous warts. Investigation for possible underlying immunodeficiency was initiated. He had waning immunity against Measles and Rubella despite having had these infections during childhood. Nevertheless, he responded to booster vaccination. Complete blood count, B-, T-, and NK cell counts were unremarkable. Immunoglobulin profile was normal. Anti-cytokine autoantibody panel showed high level of anti-IL-17A in the patient's serum. This was confirmed by Western Blot in our laboratory. Further testing is being performed to evaluate the potential Th17 impairment in this patient.

In summary, this is the first case of a possible immunodeficiency from anti-IL-17 autoantibody and its potential predisposing factor for refractory histoplasmosis. Therapeutic intervention maybe possible with further evaluation of the role of anti-IL-17 autoantibody in the antifungal immunity.

Keywords: Anti cytokine autoantibody, IL-17A, Histoplasmosis

Disclosures: D. William Cameron has relevant financial relationships with proprietary interests with Takeda (Speaker/Honoraria includes speakers bureau, symposia, and expert witness). Juthaporn Cowan has relevant financial relationships with proprietary interests with Alexion Pharmaceuticals (Speaker/Honoraria includes speakers bureau, symposia, and expert witness), CSL Behring (Research Grant includes principal investigator, collaborator or consultant and pending grants as well as grants already received), EMD Serono (Speaker/Honoraria includes speakers bureau, symposia, and expert witness), Grifols (Research Grant includes principal investigator, collaborator or consultant and pending grants as well as grants already received), GSK (Speaker/Honoraria includes speakers bureau, symposia, and expert witness), Octapharma (Other Financial or Material Support, Research Grant includes principal investigator, collaborator or consultant and pending grants as well as grants already received, Speaker/Honoraria includes speakers bureau, symposia, and expert witness), and Takeda Development Center Americas, Inc. (Other Financial or Material Support, Educational funding). All other authors indicated they had no financial relationships to disclose.

(86) Effects of Age and Body Mass Index on the Pharmacokinetics of Immunoglobulin G in Primary Immunodeficiency Diseases Following Intravenous or Subcutaneous Dosing

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Objective: To assess the impact of age and body mass index (BMI) on immunoglobulin G (IgG) pharmacokinetics (PKs) following intravenous (IVIG) or subcutaneous (SCIG) dosing with and without hyaluronidase in primary immunodeficiency disease (PIDD) using population PK (popPK) modelling and simulations.
Design and Methods: A two-compartment popPK model, with an additional compartment for subcutaneous absorption, was developed and validated using data from 8 clinical trials (≥1-year duration) of IVIG 10%, facilitated SCIG 10% with recombinant human hyaluronidase (fSCIG), SCIG 16% or SCIG 20% in patients with PIDD (n=384). IgG dose range was 0.04–1.2g/kg, weekly to every 4 weeks (Q4W). Age, lean body mass (LBM), BMI and other demographic factors were tested as covariates in the popPK model. IgG PK profiles for a typical IVIG, SCIG or fSCIG dose (0.6g/kg Q4W) in patients with PIDD were simulated to steady state for the following age and BMI categories: ages 2 to < 6, 6 to < 12, 12 to < 18 and ≥18 years; adult BMI of >18 to < 18.5, 18.5 to < 25, 25 to < 30 and ≥30kg/m2.
Results: Covariate analysis revealed significant effects of LBM on clearance and volume of distribution parameters and was included as an allometric scaling factor on these parameters. Model-based simulations showed no substantial trends in PKs across age and BMI groups. A mean IgG trough level at steady state of ≥7g/L (putative therapeutic target in PIDD) was maintained with a dosing regimen of 0.6g/kg Q4W IVIG, SCIG or fSCIG, regardless of age or BMI. Exposure was slightly increased in adults (age ≥18 years; mean IgG trough 11.5g/L and 11.1g/L for fSCIG and SCIG, respectively) versus pediatric groups (4–19% lower). Exposure was also higher in obese patients (BMI ≥30kg/m2; mean IgG trough 12.3g/L and 11.9g/L for fSCIG and SCIG, respectively) versus other BMI groups (9–15% lower).
Conclusions: The PopPK model predicted small differences in exposure (< 20%) in the pediatric and obese patient groups; however, these differences may not warrant dose adjustment in patients with PIDD in line with dosing based on IgG trough level of individuals.
Takeda Development Center Americas, Inc. funded this study and writing support.

Keywords: Age, Biologics, Body Mass Index, Immunoglobulin Replacement Therapy, Immunology, Intravenous Immunoglobulin, Population Pharmacokinetics, Primary Immunodeficiency Disease, Subcutaneous Immunoglobulin

Disclosures: Zhaoyang Li has relevant financial relationships with proprietary interests with Takeda Development Center Americas, Inc. (Employment). Kristin Follman has relevant financial relationships with proprietary interests with Certara Strategic Consulting, Certara USA (Employment). Ed Freshwater has relevant financial relationships with proprietary interests with Certara Strategic Consulting, Certara USA (Employment). Frank Engler has relevant financial relationships with proprietary interests with Certara Strategic Consulting, Certara USA (Employment). Leman Yel has relevant financial relationships with proprietary interests with Takeda Development Center Americas, Inc. (Employment, Ownership Interest includes stock, stock options, patent or other intellectual property).

(87) Delayed Diagnosis Due To An Atypical Presentation Of Nijmegen Breakage Syndrome (NBS): Relevance Of A Rapid Clinical Flow Cytometric Assay For Evaluation Of DNA Repair Defects

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A 13-year-old male with microcephaly, hydrocephalus, expressive-receptive language disorder, chronic pansinusitis with nasal polyps, Wolff-Parkinson-White syndrome, and recurrent otitis media presented to the Immunology Clinic with three episodes of bacterial pneumonia in the preceding six months. His initial evaluation was significant for low IgG (67 mg/dL), undetectable IgA, and elevated IgM (547 mg/dL) with decreased CD19+CD20+ B cells (150 cells/μL) with normal T cells, low CH50 (33.1 U/mL), no antibody responses to tetanus and diphtheria vaccines, and bronchiectasis on chest CT. The lack of switched memory B cells, in the context of elevated serum IgM suggested CD40L deficiency. Flow cytometry revealed only 65% of T cells expressed CD40L with CD40muIg binding but normal CD4+ T cell activation (98% of T cells expressed CD69). Genetic testing with a targeted 407 commercial gene panel revealed no variants in CD40LG, but rather compound heterozygous variants in NBN, c.657_661del (p.Lys219Asnfs*16) and c.808_809del (p.Val270Cysfs*2; NM_002485.4). The c.657_661del is a well-known Slavic founder variant; however, the c.808_809del is a novel variant, and classified as PM2 (moderate evidence of pathogenicity) by ACMG (American College of Medical Genetics) criteria. This variant is in the second BRCT (BRCA1-C terminal) domain of the nibrin protein, and the two BRCT domains do not affect the interaction of the protein with the Mre11-Rad50-Nibrin complex, but affects nibrin phosphorylation after irradiation, and disrupts nuclear focus formation. The pathogenicity of these variants was confirmed by a rapid functional flow cytometry assay for assessing the DNA double-strand break (DSB) repair pathway.
Take-home points: (1) This case exemplifies an atypical presentation of NBS, which resulted in a delayed diagnosis. (2) NBS patients may present with features of CVID or X-linked Hyper IgM syndrome, and the mosaic expression of CD40L may be related to the underlying immune dysregulation associated with NBS. (3) The functional evaluation of the NBN variants, and especially the second novel variant, by a rapid clinical flow cytometric assay for DNA DSB repair defects proved to be informative in the diagnosis.

Keywords: Nijmegen Breakage Syndrome, NBS, DNA Repair Defect, c.808_809del, NBN, DNA double-strand break, flow cytometry, c.808_809del (p.Val270Cysfs*2; NM_002485.4), c.657_661del (p.Lys219Asnfs*16), nibrin

Disclosures: Hemalatha Rangarajan has relevant financial relationships with proprietary interests with Medexus (Consultant, Medexus Treosulfan (one time only)). All other authors indicated they had no financial relationships to disclose.

(88) Alterations in T cell counts and differentiation in patients with severe cutaneous viral infections post-Fontan procedure

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Introduction: Patients with single ventricle physiology who have undergone the Fontan procedure have increased risk of immunological abnormalities. Lymphopenia and hypogammaglobulinemia are commonly

observed in patients with protein losing enteropathy (PLE), but may also occur in the absence of this complication. While most post-Fontan patients do not experience severe or opportunistic infections, a subset have severe warts and/or molluscum contagiosum. We hypothesize that immune dysregulation may underlie this predisposition.

Methods: Twenty-four patients were recruited from the Children's Hospital of Philadelphia multidisciplinary Fontan FORWARD program. Table 1 demonstrates the sample source in each study population. Research peripheral blood samples were collected and peripheral blood mononuclear cells (PBMCs) were prepared and cryopreserved. High dimensional immune profiling of PBMCs was performed using spectral flow cytometry. Table 2 shows the panel of antibodies used for immune profiling.

Results: We compared the relative balance of lymphocyte subsets in post-Fontan patients with and without severe cutaneous viral infections to assess immune differences without the confounding complication of PLE. The proportion CD3+ T cells was decreased in patients with severe cutaneous viral infections versus those without ($p = 0.028$). Within the T cell population, there was an increased proportion of CD8+ central memory T cells (TCM; CD27+ CD45RA-) and CD8+ effector memory T cells (TEM; CD27- CD45RA-) ($p < 0.001$ and $p = 0.006$, respectively). There was also a trend towards higher proportion of CD4+ T cells that were TCMs ($p = 0.073$). These differences were not seen in post-Fontan patients with PLE when comparing those with and without severe cutaneous viral infections. Of note, immunophenotyping of all post-Fontan patients demonstrated decreased frequency of CD3+ T cells, with significant skewing towards a memory phenotype, when compared to healthy control patients.

Conclusion: Post-Fontan patients without PLE who develop severe cutaneous viral infections have a reduced frequency of CD3+ T cells with an increased proportion of CD8+ TCMs and CD8+ TEMs when compared to post-Fontan patients without infections and to healthy controls. These differences were present in the absence of PLE and suggest altered presence and differentiation of T cells in post-Fontan patients with severe cutaneous viral infections.

Table 1: Study populations

Population	# of Patients
Healthy Control	9
Cutaneous viral infection + No PLE	5
Cutaneous viral infection + PLE	3
No cutaneous viral infection + No PLE	12
No cutaneous viral infection + PLE	4

Table 2: General immunophenotyping panel

Marker	Type
CD45RA	Surface
Live/Dead	Live Dead
CD16	Surface
CD14	Surface
CD45	Surface
CD11c	Surface
CD56	Surface
CD26	Surface
PD-1	Surface
CD123	Surface
CD161	Surface
ICOS	Surface
Ki67	Intracellular
CD3	Surface/Intracellular
CCR4	Surface
CXCR3	Surface
CCR6	Surface
CXCR5	Surface
CD8	Surface
Foxp3	Intracellular
CD19	Surface
CD20	Surface
CD11b	Surface
TCRgd	Surface
CD4	Surface/Intracellular
Tbet	Intracellular
CD25	Surface
BCL6	Intracellular
CD27	Surface
CD33	Surface
CD127	Surface
CD38	Surface
HLA-DR	Surface

Keywords: Fontan, Lymphopenia, Warts, Molluscum contagiosum, Cutaneous viral infections

Disclosures: Jennifer Heimall has relevant financial relationships with proprietary interests with ADMA (Advisory Board), CIRM (Consultant, Other Financial or Material Support, Data Safety Monitoring Board), CSL Behring (Advisory Board, Research Grant includes principal investigator, collaborator or consultant and pending grants as well as grants already received, Speaker/Honorariaincludes speakers bureau, symposia, and expert witness), Horizon (Advisory Board), Regeneron (Contracted Research), and UpToDate (Other Financial or Material Support, Section Author). All other authors indicated they had no financial relationships to disclose.

(89) An H234Q mutation in PSTPIP1 reveals general activation of ASC-dependent inflammasomes as a cause of PAPA syndrome

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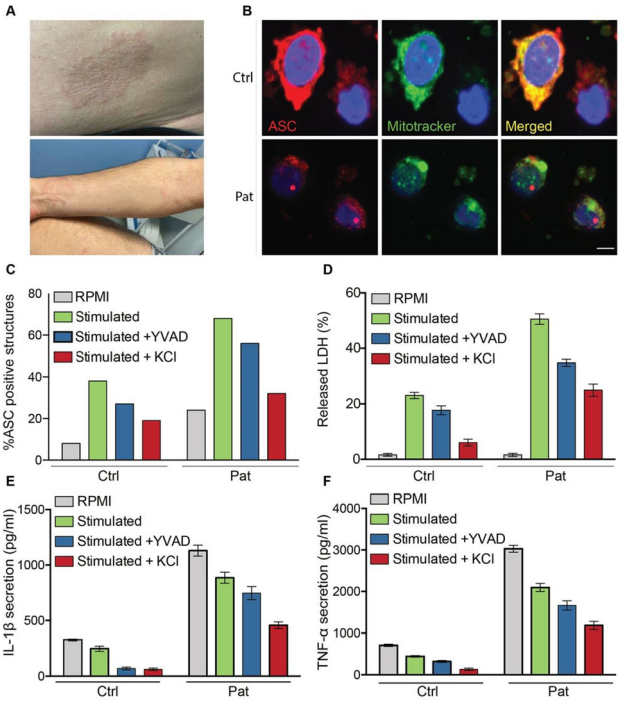
PSTPIP1(Proline-Serine-Threonine Phosphatase Interacting Protein 1) is a cytoskeleton-associated adaptor protein that regulates T lymphocyte and leukocyte activation, cytoskeletal organization, interleukin-1 release. It is recruited by pyrin to the pyroptosome, a scaffold formed by oligomerized ASC proteins. Variants of PSTPIP1 are associated with a wide range of autoinflammatory manifestations, the most representative being the PAPA syndrome which associates pyogenic arthritis, pyoderma gangrenosum, and acne. The precise mechanisms responsible for PAPA syndrome remain to be elucidated, representing a considerable challenge to developing effective therapy. To uncover the pathogenesis of PAPA syndrome, we examined the clinical status and cellular phenotypes of a patient presenting with features belonging to the PAPA syndrome spectrum. This 42-year-old male suffered from recurrent fever, chronic abdominal pain with hepatosplenomegaly, myalgia and arthralgia, annular granuloma, and acne. Laboratory tests revealed chronic hemolytic anemia and lymphopenia with low CD4 and B cells. The genetic screening revealed an H234Q variation in PSTPIP1, which was absent from the GnomAD database and affected well-conserved amino acids.

Monocytes from the patient displayed an increased secretion of IL1β and TNFα, increased Gasdermin D cleavage, and increased expression of ASC speck formation, suggesting an excessive activation of the pyroptosome. We reproduced this mutation in an immortalized monocytic cell line using as control cells infected with the wild-type gene. We confirmed the results seen in the patient's monocytes. The severity of the inflammatory phenotype was alleviated by either reducing the K+ efflux, blocking the ASC oligomerization with dimethyl fumarate, or by PSTPIP1 knock-down, suggesting that this mutation triggers ASC oligomerization, pyroptosome assembly, pore formation and K+ efflux. Moreover, we observed a similar phenotype using activators specific for the NLRC4 (flagellin) and AIM2 (poly (dA:dT)) inflammasomes, suggesting that the ASC oligomerization induced by the H234Q mutant triggers also the activation and assembly of other ASC dependent-inflammasomes.

Hence, we propose that PAPA syndrome results from a pyroptosome activation that enhances the activation of ASC-dependent inflammasomes. Our study underlines the potential efficacy of dimethyl fumarate, a chemical known to inhibit ASC oligomerization and currently used for treating multiple sclerosis, as a therapy in PSTIPI1-associated disorders.



A. Patient having annular granuloma. B. Increased oligomerization of ASC in pyroptosome in the patient's stimulated monocytes as compared to cytoplasmic distribution of ASC in the control. C, D Activation of the pyroptosome is reversed by blocking K+ (KCl), or by blocking pyroptosis (YVAD). E, F Excessive secretion of pro-inflammatory cytokines that is reversed by KCl or by YVAD.

Keywords: PSTPIP1, PAPA syndrome, ASC-dependent inflammasomes

Disclosures: All authors indicated they had no financial relationships to disclose.

(90) Final Analysis of Long-Term Safety of Facilitated Subcutaneous Immunoglobulin Across the Age Range: Results from a Post-authorization Study

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Background: Facilitated subcutaneous immunoglobulin (fSCIG) 10% is an immunoglobulin replacement therapy that utilizes recombinant human hyaluronidase (rHuPH20) to depolymerize hyaluronan in the extracellular matrix. This prospective, non-interventional, open-label, multicenter study (EUPAS5812) assessed long-term safety, immunogenicity, treatment regimens, and administration of fSCIG in routine clinical practice. Outcomes were evaluated across age groups.

Methods: The study (conducted from July 2014 to February 2020 in Europe) enrolled patients aged ≥18 years receiving or prescribed

fSCIG. Treatment regimens were planned by the attending physician in accordance with standard clinical practice. Anti-rHuPH20 antibody assessment was voluntary.
Results: Of 111 enrolled patients, 106 patients with data for ≥1 fSCIG dose were included in the safety analysis population (mean [standard deviation (SD)] age: 46.2 [14.7] years; 56.6% female; 14.2% [n=15] aged ≥65 years) and most patients received fSCIG for primary immunodeficiency (91.5%). Median (range) fSCIG exposure was 3.2 (0–5.2) years and decreased with increasing age: 3.7 (0.2–5.1) years in the 18– < 30 age group (n=13) and 1.4 (0.2–4.4) years in the ≥65 age group (n=15). Incidence of treatment-related non-serious (non-infectious) adverse events (AEs) per person-year ranged from 0.11 (18– < 30 age group) to 1.58 (40– < 50 age group; n=28). One treatment-related serious AE occurred in a single patient (50– < 60 age group) during the first year of follow-up after multiple uneventful doses of fSCIG. Three of 74 patients (4.1%; n=2 [30– < 40 age group]; n=1 [≥65 age group]) tested for anti-rHuPH20 antibodies developed positive binding antibodies (defined as titer ≥160; max titer=1280) to rHuPH20; no positive titers were reported after 3 years of fSCIG treatment. No neutralizing antibodies were detected. Mean (SD) infusion duration was 2.7 (0.7) hours. The proportion of infusions administered with an infusion rate change or infusion interruption due to AEs was 0.4%. Most infusions were administered at home (94.2%).
Conclusions: This final analysis confirms the long-term safety of fSCIG in routine clinical practice across age groups and supports home fSCIG administration.
Funding: Baxalta Innovations GmbH, a Takeda company, funded this study; Takeda Development Center Americas, Inc. provided medical writing support.

Keywords: Immunoglobulin, Facilitated subcutaneous immunoglobulin, Safety, Immunogenicity, Primary immunodeficiency diseases

Disclosures: Pauline Ellerbroek has relevant financial relationships with proprietary interests with Takeda group (Research Grant includes principal investigator, collaborator or consultant and pending grants as well as grants already received). Torsten Witte has relevant financial relationships with proprietary interests with Takeda (Speaker/Honoraria includes speakers bureau, symposia, and expert witness). Jie Chen has relevant financial relationships with proprietary interests with Takeda Development Center Americas, Inc. (Employment, Ownership Interest includes stock, stock options, patent or other intellectual property). Andras Nagy has relevant financial relationships with proprietary interests with Baxalta Innovations GmbH, a Takeda company (Ownership Interest includes stock, stock options, patent or other intellectual property). Barbara McCoy has relevant financial relationships with proprietary interests with Baxalta Innovations GmbH, a Takeda company (Employment, Ownership Interestincludes stock, stock options, patent or other intellectual property). Leman Yel has relevant financial relationships with proprietary interests with Takeda Development Center Americas, Inc. (Employment, Ownership Interest includes stock, stock options, patent or other intellectual property). All other authors indicated they had no financial relationships to disclose.

(91) Efficacy and Safety of Facilitated Subcutaneous Immunoglobulin in Pediatric Patients with Primary Immunodeficiency Disease: Interim Analysis of a Phase 3 Study in the USA

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Background: Facilitated subcutaneous immunoglobulin (fSCIG), a dual vial unit comprising immunoglobulin G (IgG) 10% and recombinant human hyaluronidase (rHuPH20), has been shown to be effective and bioequivalent to intravenous IgG, with fewer systemic adverse events (AEs), in patients with primary immunodeficiency disease (PIDD; NCT00814320). This phase 3, open-label, prospective, non-controlled study aims to acquire further data on fSCIG efficacy, safety, tolerability, immunogenicity, and pharmacokinetics in pediatric patients with PIDD (NCT03277313).
Methods: Patients aged 2–< 16 years with PIDD and prior IgG treatment were enrolled from 17 US centers. Patients ramped up fSCIG in ≤6 weeks (Epoch 1) and were then treated every 3–4 weeks for ≤3 years (Epoch 2). The primary endpoint was rate of acute serious bacterial infections (ASBIs). Anti-rHuPH20 antibody testing occurred every 3 months. Pre-planned interim analysis was performed when all patients completed 12 months in Epoch 2.
Results: Forty-four patients were enrolled (mean age, 9.0 years; 2–< 6 years, n=9; 6–< 12 years, n=23; 12–< 16 years, n=12). At interim analysis, all but one patient had completed their last visit.
Mean rate of ASBIs/patient-year was 0.04 (99% confidence interval upper limit: 0.21), significantly lower than the regulatory-defined threshold rate of 1.00 (p< 0.001). Mean rate of all infections/patient-year was 3.20. Mean serum IgG trough levels were 10.1, 9.1, and 9.2g/L at months 0, 6, and 12 (Epoch 2), with similar levels across age groups. IgG pharmacokinetic parameters were similar across age groups.
Overall, 320 treatment-related AEs (excluding infections; systemic: n=130, most commonly headache; local: n=190, most commonly infusion-site pain), mainly mild in nature, were reported in 34 patients. One serious AE (excluding infections), tonsillar hypertrophy, was not considered treatment-related. No rHuPH20-neutralizing antibodies were detected. Most patients (80.0%) expressed a preference for continuing fSCIG.
Conclusions: The study met its primary endpoint, demonstrating efficacy of fSCIG in preventing bacterial infections in children with PIDD. Stable and protective IgG levels were maintained across pediatric age groups. fSCIG was administered at the same dosing interval as intravenous IgG therapies for PIDD. The safety profile was consistent with previous clinical studies.
Study/writing support funder: Takeda Development Center Americas, Inc.

Keywords: Facilitated subcutaneous immunoglobulin, Immunoglobulin replacement therapy, Primary immunodeficiency disease, Pediatric, Efficacy, Safety

Disclosures: Niraj Patel has relevant financial relationships with proprietary interests with CSL Behring (Research Grant includes principal investigator, collaborator or consultant and pending grants as well as grants already received, Speaker/Honoraria includes speakers bureau, symposia, and expert witness), Horizon Therapeutics (Speaker/Honoraria includes speakers bureau, symposia, and expert witness), and Takeda group of companies (Research Grant includes principal investigator, collaborator or consultant and pending grants as well as grants already received, Speaker/Honorariaincludes speakers bureau, symposia, and expert witness). Richard Wasserman has relevant financial relationships with proprietary interests with ADMA Biologics (Other Financial or Material Support, Research Grant includes principal investigator, collaborator or consultant and pending grants as well as grants already received, Personal fees), CSL Behring (Other

Financial or Material Support, Research Grant includes principal investigator, collaborator or consultant and pending grants as well as grants already received, Personal fees), Evolve Biologics (Other Financial or Material Support, Research Grant includes principal investigator, collaborator or consultant and pending grants as well as grants already received, Personal fees), Grifols (Other Financial or Material Support, Research Grant includes principal investigator, collaborator or consultant and pending grants as well as grants already received, Personal fees), Kedrion Biopharma (Research Grant includes principal investigator, collaborator or consultant and pending grants as well as grants already received), Korean Green Cross (Other Financial or Material Support, Research Grant includes principal investigator, collaborator or consultant and pending grants as well as grants already received, Personal fees), Octapharma (Research Grant includes principal investigator, collaborator or consultant and pending grants as well as grants already received), and Takeda group of companies (Other Financial or Material Support, Research Grant includes principal investigator, collaborator or consultant and pending grants as well as grants already received, Personal fees). T Prescott Atkinson has relevant financial relationships with proprietary interests with CSL Behring (Advisory Board), Horizon Therapeutics (Advisory Board), and Pharming Healthcare, Inc. (Advisory Board). Erin Greco has relevant financial relationships with proprietary interests with Baxalta Innovations GmbH, a Takeda company (Employment, Ownership Interestincludes stock, stock options, patent or other intellectual property). Sara Russo-Schwarzbaum has relevant financial relationships with proprietary interests with Baxalta Innovations GmbH, a Takeda company (Employment, Ownership Interestincludes stock, stock options, patent or other intellectual property). Shumyla Saeed-Khawaja has relevant financial relationships with proprietary interests with Takeda Development Center Americas, Inc. (Employment, Ownership Interest includes stock, stock options, patent or other intellectual property). Barbara McCoy has relevant financial relationships with proprietary interests with Baxalta Innovations GmbH, a Takeda company (Employment, Ownership Interest includes stock, stock options, patent or other intellectual property). Leman Yel has relevant financial relationships with proprietary interests with Takeda Development Center Americas, Inc. (Employment, Ownership Interest includes stock, stock options, patent or other intellectual property). All other authors indicated they had no financial relationships to disclose.

(92) Common variable immunodeficiency in two families with heterogenous phenotypes caused by novel heterozygous NFKB1 mutations

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NFKB1 haploinsufficiency was first described in 2015 in three families with common variable immunodeficiency (CVID), presenting heterogeneously with symptoms of increased infectious susceptibility, skin lesions, malignant lymphoproliferation and autoimmunity. The described mutations all led to a rapid degradation of the mutant protein, resulting in a p50 haploinsufficient state. Since then, more than 50 other mutations have been reported, located throughout different domains of NFKB1 with the majority situated in the N-terminal Rel homology domain (RHD). The clinical spectrum has also expanded with possible disease manifestations in almost any organ system. In silico prediction tools are often used to estimate the pathogenicity of NFKB1 variants but to prove causality between disease and genetic findings, further downstream functional validation is required. In this report, we used immunophenotyping, functional analysis of peripheral blood mononuclear cells (PBMCs), , protein interaction analysis and RNA sequencing to validate two novel mutations in NFKB1, resulting in a phenotype of CVID with heterogenous inter- and intrafamilial presentation.

Keywords: Primary immunodeficiency, NFKB1, monogenic, Common variable immunodeficiency

Disclosures: Frederik Staels has relevant financial relationships with proprietary interests with Fonds Wetenschappelijk Onderzoek Vlaanderen (Employment, Research Grant includes principal investigator, collaborator or consultant and pending grants as well as grants already received). Mathijs Willemsen has relevant financial relationships with proprietary interests with Vlaams Instituut voor Biotechnologie (Employment). Julika Neumann has relevant financial relationships with proprietary interests with Fonds Wetenschappelijk Onderzoek Vlaanderen (Employment, Research Grant includes principal investigator, collaborator or consultant and pending grants as well as grants already received). Isabelle Meyts has relevant financial relationships with proprietary interests with Fonds Wetenschappelijk Onderzoek Vlaanderen (Research Grant includes principal investigator, collaborator or consultant and pending grants as well as grants already received). Rik Schrijvers has relevant financial relationships with proprietary interests with Fonds Wetenschappelijk Onderzoek Vlaanderen (Research Grant includes principal investigator, collaborator or consultant and pending grants as well as grants already received). All other authors indicated they had no financial relationships to disclose.

(93) A Case of Hereditary Alpha-Tryptasemia With Inflammatory Bowel Disease

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Case Report

Introduction: Hereditary alpha-tryptasemia is an autosomal dominant disease where excess copies of the TPSAB1 gene result in elevated tryptase levels and multi-system involvement. Due to the wide spectrum of presentations, it is often misdiagnosed for anxiety, reflux, inflammatory bowel syndrome among other diagnoses. We present a unique case of a patient diagnosed with hereditary alpha-tryptasemia and inflammatory bowel disease.
Case Description: A 22-year-old male with a history of IgA deficiency, chronic rhinitis and contact dermatitis presented with chronic abdominal pain and diarrhea. He further experienced fatigue, nighttime awakenings, pruritus with cold showers and was noted to be dermatographic. Differential diagnoses were broad, including reflux, IBD, food allergy and systemic mastocytosis. Initial gastrointestinal evaluation, consisting of colonoscopy and pill endoscopy, was unremarkable, with the exception of intraepithelial lymphocytes within the small intestine. Skin prick testing (SPT) was positive for coconut, egg and kidney beans. A trial of omeprazole and avoidance of positive foods on SPT was attempted without symptom improvement. Repeat colonoscopy was consistent with IBD. He was also found to have an elevated tryptase level at 11.8 mcg/L (< 11mcg/L) with repeat levels demonstrating persistent elevation between 10.3 - 11.6mcg/L. KIT D816 mutation analysis for mastocytosis was negative. Analysis of TPSAB1 gene revealed an extra allelic alpha-tryptase copy number confirming the diagnosis of hereditary alpha-tryptasemia.
Discussion: Hereditary alpha-tryptasemia is a multifaceted condition including gastrointestinal manifestations, skin involvement, joint hypermobility, dysautonomia and anaphylaxis, thus the diagnosis can be difficult to make. It is essential to consider this condition as a co-morbidity with other disorders with similar presentations, such as inflammatory bowel disease, in order to not miss an underlying concomitant illness.

Keywords: Hereditary alpha tryptasemia, Inflammatory bowel disease, Anaphylaxis, Autonomic dysfunction

Disclosures: Vivian Hernandez-Trujillo has relevant financial relationships with proprietary interests with CSL (Advisory Board), Kaleo (Advisory Board, Consultant, Speaker/Honoraria includes speakers bureau, symposia, and expert witness), Regeneron (Advisory Board), and Takeda (Advisory Board, Consultant, Speaker/Honoraria includes speakers bureau, symposia, and expert witness). All other authors indicated they had no financial relationships to disclose.

(94) A novel missense hemizygous variant in CYBB resulting in X-linked chronic granulomatous disease with chronic diffuse dermatitis, hypohidrosis and alopecia universalis.

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X-linked chronic granulomatous disease (CGD) is caused by mutations in the CYBB gene, which encodes for gp91phox, a protein in the NADPH oxidase complex. Patients with pathogenic missense variants that encode amino acids 1-309 for gp91phox are associated with residual superoxide production and reduced risk of infection, compared to more severely affected missense mutations involving amino acids 310-570 with nearly absent superoxide production. We report a 3-year-old male who initially presented to dermatology with a history of severe diaper dermatitis that appeared at 12 months of age and gradually progressed to a diffuse, erythematous, non-pruritic dermatitis accompanied by alopecia universalis by 18 months. Parents reported that he did not perspire, and his skin would become warm and red with activity, suggestive of hypohidrosis. Patient failed topical and oral antifungals therapy. Topical steroids provided some improvement, with recurrence of rash after therapy discontinuation. Due to occipital and axillary lymphadenopathy, a lymph node biopsy was obtained, which demonstrated increased interfollicular histiocytes. Skin biopsy of the scalp demonstrated inflammation around deep hair follicles and eccrine sweat glands, composed of abundant neutrophils and smaller numbers of lymphocytes and histiocytes, with neutrophilic inflammation more sparsely involving the superficial dermis and epidermis. Both biopsies were culture negative. Clinical exome sequencing identified a novel hemizygous missense variant in the CYBB gene (c.901G>T; pVal301Phe). A dihydrorhodamine (DHR) assay was performed which demonstrated reduced NADPH oxidase activity with patient stimulation index (SI) of 14.7, control SI = 124.4. He has no infectious history, likely due to presence of residual oxidative burst activity. The lymphadenopathy and diffuse dermatitis resolved with a prolonged steroid taper over 9 months. He has started to perspire with activities and has had some sparse hair growth. Due to his prolonged, severe inflammatory dermatitis, hematopoietic stem cell transplant is planned utilizing a matched sibling donor for definitive cure.
Conclusion: We present a unique case of X-linked CGD with predominant dermatologic features of hypohidrosis, inflammatory folliculitis and alopecia universalis that did not respond to standard topical treatment or antibiotics. Chronic granulomatous disease should be considered in the differential in patients who present with diffuse inflammatory skin disease.

Keywords: CYBB, chronic granulomatous disease, hypohidrosis, rash, perspire, alopecia, dermatitis, folliculitis, eccrine, lymphadenopathy

Disclosures: Maria Teresa De la Morena has relevant financial relationships with proprietary interests with Chiesi Farmaceutici S.p.A. (Contracted Research). Karin Chen has relevant financial relationships with proprietary interests with Horizon Therapeutics (Advisory Board). All other authors indicated they had no financial relationships to disclose.

(95) A 23-year-old male with lymphadenopathy and immune-mediated cytopenias

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A 23-year-old male was referred to Allergy/Immunology from Hematology/Oncology due to a history of longstanding lymphadenopathy and immune-mediated cytopenias. His history was significant for severe anemia as a neonate later requiring splenectomy. At age nine, he developed worsening lymphadenopathy; lymph node biopsy demonstrated a predominance of CD3+/CD4-/CD8- or 'double negative' T-cells (DNT), however, no changes in clinical management were made based on this finding. At age sixteen, he developed immune thrombocytopenic purpura (ITP), which was treated with steroids. At age twenty-one, he developed severe thrombocytopenia, neutropenia, and worsening diffuse lymphadenopathy. PET CT demonstrated diffuse hypermetabolic lymph nodes, and lymph node biopsy redemonstrated increased DNT cells. Bone marrow biopsy was not consistent with malignancy.

At the time of presentation to Immunology Clinic, he had not received a definitive diagnosis. Further history revealed no family members with lymphoproliferation. His labs were notable for: IL-10 of 120 pg/mL (normal2000 pg/mL. Autoimmune lymphoproliferative syndrome (ALPS) sequencing panel did not demonstrate any pathogenic abnormalities. DNT cell sorting did not reveal a Fas somatic mutation. ALPS panel to Cincinnati Children's Hospital met 4/4 ALPS criteria. An assay for Fas-mediated apoptosis demonstrated markedly decreased apoptosis, consistent with ALPS-U. He was started on sirolimus and his lymphadenopathy and ITP have significantly improved.

ALPS is a disorder of non-malignant/non-infectious lymphoproliferation, autoimmunity, and increased risk of malignancy. Most cases result from either autosomal dominant or somatic mutations, although one-third do not have an identified genetic defect. Diagnosis requires chronic lymphoproliferation >6 months, increased alpha-beta DNT's >2% of total lymphocytes, and several primary and secondary accessory criteria. Diagnostic confirmation entails either defective lymphocyte apoptosis or somatic/germline mutations in Fas, FasL, or CASP10. Treatment with immunosuppressants is necessary when both lymphoproliferation and autoimmunity are present. The only curative intervention is a bone marrow transplant.

This case highlights the importance of Immunology involvement with expertise in using immunomodulatory medications in patients with non-malignant, non-infectious lymphoproliferation. These cases are often complex with multi-system involvement and have a broad differential diagnosis.

Keywords: Chronic non-malignant lymphoproliferation, Autoimmune lymphoproliferative syndrome, Double-negative T cell, Fas-mediated apoptosis, Sirolimus

Disclosures: All authors indicated they had no financial relationships to disclose.

(96) Anti-CD20 Therapy: Underutilizing A Seed for Success?

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Anti-CD20 monoclonal antibodies have revolutionized the treatment of B-cell malignancies and antibody-mediated autoimmune disorders. The association between anti-CD20 therapy and subsequent development of prolonged hypogammaglobulinemia and severe infections in a subset of patients is well established. Furthermore, the potential for the condition warranting anti-CD20 therapy to be a presenting feature of Inborn Errors of Immunity (IEI) is increasingly recognized. We hypothesized that immunologic evaluation is underutilized in the setting of anti-CD20 therapy, both in the context of hypogammaglobulinemia and IEI evaluation.

We performed a retrospective analysis of 100 patients treated with anti-CD20 antibody therapy within the Mayo Clinic Enterprise between January 2017 and January 2020. We evaluated treatment indication, serious infection both pre- and post- therapy and frequency and type of pre- and post-treatment immunologic testing.

Fifty-six patients were treated for autoimmune disorders, 40 for hematologic malignancy and 4 for benign hematologic conditions. Thirteen patients had a history of severe infection requiring hospitalization prior to therapy. Thirty-five patients had baseline immunoglobulin levels, median IgG 881 mg/dL (range 172 – 3070 mg/dL). Three patients (8.6%, 3/35) had IgG levels less than 400 mg/dL. Eight patients had baseline lymphocyte enumeration, 7 (87.5%, 7/8) of which were abnormal. CD4+ T cell lymphopenia and CD19+ B-cell lymphopenia were the most frequent abnormalities noted. No patients had immunology consultation prior to treatment. Forty patients had post-treatment immunoglobulin levels, with 16 patients (40%, 16/40) having one IgG check only. Eleven patients (27.5%, 11/40) had a post treatment IgG level less than 400 mg/dL. Ten patients received immunoglobulin replacement therapy. Thirty patients required hospitalization due to infection, with death of seven patients owing to infectious complications. A total of 2 patients had immunology consultation following treatment. No patients had genetic testing for underlying IEI.

Most patients treated with anti-CD20 therapy do not undergo any immune evaluation prior to or following treatment. IEI with an initial presentation of autoimmunity or malignancy may be underrecognized. Sustained growth in the clinical use of anti-CD20 therapy is anticipated. A systematic approach to assessing for both underlying and acquired immunodeficiency in the context of anti-CD20 therapy is needed.

Keywords: Anti-CD20 therapy, immunodeficiency, inborn errors of immunity, acquired immunodeficiency

Disclosures: All authors indicated they had no financial relationships to disclose.

(97) A 31-month old female with streptococcus anginosus subdural empyema

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A 31-month-old, previously healthy, fully immunized female was diagnosed with fulminant meningitis complicated by subdural empyema and multifocal arteritis.

Initial symptoms included persistent cough and fever. On day 7 of symptoms, she had a new-onset seizure and was diagnosed with a simple febrile seizure in the Emergency Department. On day 9, she represented with continued fever, decreased activity and was admitted. Labs revealed neutrophilic leukocytosis and elevated inflammatory markers. Chest x-ray, abdominal ultrasound, echocardiogram, and viral respiratory panel were unrevealing. Urine culture grew 25-50,000 CFU/mL E. coli, and ceftriaxone was started. Upon admission, she developed refractory seizures. Imaging demonstrated subdural collection with mass effect, requiring emergent hemicraniectomy. Culture from the surgical site grew Streptococcus anginosus. Ultimately, the patient expired from complications of her infection.

Immunology was consulted given possible predisposing immunodeficiency. There was no family history of immunodeficiency or deep-seated, atypical or recurrent infections. She was of Indian descent, had no siblings, and there was no known consanguinity.

Functional immune testing demonstrated low complement levels, specifically undetectable AH50 with normal CH50 and mannose-binding lectin. Toll-like-receptor (TLR) testing was abnormal with decreased response to TLR2-TLR1, TLR5, and TLR4 stimuli. In contrast, CBC/differential, T cells (including naive and memory CD4+ and CD8+ subsets), B cells (including class-switched memory subset), NK cells, serum immunoglobulins and subclasses, antibody titers to T-dependent/-independent antigens, and HIV testing were normal.

Whole-exome sequencing (WES) was pursued in parallel. There were no mutations identified in complement or TLR pathways. Instead, WES demonstrated two heterozygous variants of uncertain significance (VUS) in HYOU1 at exons 7 (c.506T>c) and 9 (c.832C>T). These cause missense mutations with population frequency 0.1-0.2%, and PolyPhen-2 scores are predicted to be damaging. Limited evidence suggests HYOU1

mutations are associated with combined immunodeficiency. Genetic consultation is ongoing with plans to phase HYOU1.
Severe pyogenic bacterial infections can be seen in disorders of innate immunity, complement deficiency, and/or combined immunodeficiency. This case highlights the potential for discordant functional and genetic immune testing. As single-opportunity functional testing was performed during life-threatening acute illness, genetic and functional immunoassays are ongoing in family members to best guide future risk for recurrence.

Keywords: Immunodeficiency, Diagnostic Dilemma, HYOU1, Alternative Complement, Toll-like receptor, Meningitis

Disclosures: Jocelyn Farmer has relevant financial relationships with proprietary interests with Bristol Myers Squibb (Research Grant includes principal investigator, collaborator or consultant and pending grants as well as grants already received) and Pfizer (Research Grant includes principal investigator, collaborator or consultant and pending grants as well as grants already received). All other authors indicated they had no financial relationships to disclose.

(98) Evaluation of the effect of reproductive pathology on the TREC and KREC copy number of premature infants

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Infectious and inflammatory complications of pregnancy increase the risk of preterm birth. Premature or functionally immature babies are born, and the level of perinatal mortality increases.
The mechanisms of changes in the innate immune system and the impact of immaturity on the overall risk of developing immunological disorders associated with a high risk of early development of infectious pathology in the neonatal period are not fully understood, but preterm birth is considered the greatest risk factor for the development of infections in the neonatal period.
We examined the levels of TREC and KREC in 100 preterm infants with gestational age 36-37 weeks. To investigate the effect of maternal infectious and inflammatory complications of pregnancy on TREC and KREC copy number, the examined neonates were divided into 2 groups:
Group I (n = 35) - newborns from mothers without urinary tract infections and inflammatory diseases with at 34.0 (32.5-34.8) weeks' gestation; Group II (n = 65) - newborns from mothers with urinary tract infections and inflammatory diseases at 34.0 (32.3-35.5) weeks' gestation. Quantity of TREC and KREC were determined using RQ-PCR Children from mothers without infectious inflammatory diseases of the urogenital system the median of TREC copies was 25 313.0 (11 765.50-43 762.00), the median of KREC copies was 16 478.0 (6 351.50-27 306, 50) respectively. In children from mothers with infectious inflammatory diseases of the urogenital system the median TREC values was 25 344.0 (11 291.0-40 495.0), copies of KREC was 13 106.0 (5 323.0-22 171.0) respectively. There were no statistically significant differences in copy values. The presence of infectious and inflammatory diseases during pregnancy did not significantly affect the TREC and KREC indices in premature infants.
Thus, the infectious pathology of the mother's reproductive system does not affect the functional activity of the thymus and bone marrow of premature babies.
The use of determining the levels of TREC and KREC makes it possible to determine whether a newborn child belongs to the group of immunocompromised individuals from mothers with infectious pathology of the reproductive system.

Keywords: premature newborns, TREC, KREC, infectious pathology of the reproductive system

Disclosures: Ekaterina Polyakova:No financial relationships or conflicts of interest Tatyana Gnedko:No financial relationships or conflicts of interest Svetlana Beresten:No financial relationships or conflicts of interest Irina Guryanova:No financial relationships or conflicts of interest Mikhail Belevtsev:No financial relationships or conflicts of interest.

(99) ALPS phenotype diagnosis in a patient with a pathogenic CBL variant

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Autoimmune lymphoproliferative syndrome (ALPS) occurs secondary to a defective FAS-mediated apoptosis pathway in lymphocytes, most commonly due to a genetic defect in the genes encoding FAS, FASLG, and CASP10 [1]. As genetic testing methods continue to improve and evolve, we are identifying more genetic defects responsible for causing ALPS and ALPS-like phenotypes. One ALPS-like phenotype that has been well described is Ras-associated autoimmune leukoproliferative disorder, commonly referred to as RALD. RALD is known to be caused by defects in the RAS pathway, in particular, gain of function mutations in NRAS and KRAS [2]. Additionally, there are other genetic defects in the RAS pathway that can result in other phenotypes such as juvenile myelomonocytic leukemia (JMML), Noonan and Costello syndromes [3,4]. Casitas B lineage lymphoma (CBL) is a gene that has been implicated in different RASopathies to include JMML and Noonan syndrome. CBL is a RING-dependent E3-ubiquitin-protein-ligase that ubiquitinates receptor tyrosine kinases for endocytic internalization and has a role in regulating several cell-signaling processes [5]. Dysregulation of the Cbl protein has been shown to result in autoimmunity or increased tumor progression in murine models [6].
Our patient is a 17-year-old female who initially presented to the pediatric hematology & oncology clinic at 4 years of age after she was noted to have splenomegaly during a well-child examination. Upon further evaluation, the patient was found to have autoimmune thrombocytopenia and underwent a bone marrow biopsy and genetic testing. The bone marrow biopsy showed a genetically normal female 46,XX and a cellularity of 90% with no detectable clonal abnormalities. ALPS genetic panel testing was performed on whole blood in 2017 and repeated via a buccal swab in 2020 which identified no pathogenic variants. Subsequently in 2021, a primary immunodeficiency panel examining 407 genes revealed a heterozygous pathogenic variant in the CBL gene where tyrosine was replaced with histidine at codon 371 of the CBL protein. This case demonstrates that in patients with a long-standing diagnosis of an ALPS phenotype without a known genetic etiology, utilizing broader genetic screens should be considered.

Table 1:

Test	Result
WBC	2.4 K/mcL (N-51.5%, L-31.6%, M-12.8%, E-3.1%, B-0.9%)
Hgb	12.7 g/dL
Platelets	112 K/mcL
Fas-mediated killing assay by anti-APO-1	Normal
Fas TNFRSF6 (APO-1/CD95) sequencing	No genetic alteration detected
CD3+CD4-CD8-TCR alpha-beta cells	1.6% (2009), 0.9% (2021)
IgG	1539 mg/dL
IgA	<8 mg/dL (low)
IgM	157 mg/dL
Vitamin B12	461 pg/mL
Ferritin	5.74 ng/mL
Antibody Screen	Positive
Coomb's Direct	Negative
IL-10	25.23 pg/mL
Platelet Associated Antibodies	IgG-negative, IgM-strongly positive
CD3+ absolute	496 cells/mcL (low)
CD4+ absolute	325 cells/mcL (low)
CD8+ absolute	143 cells/mcL (low)
CD19+ absolute	78 cells/mcL (low)
CD15/56+ absolute	173 cells/mcL
4:8 Ratio	2.29
CD3+/CD4+/CD25hi/FoxP3+	8%
C3	80
C4	11.1
TSH	19.1 mcIU/mL
FT4	0.67 ng/dL
CMP	Normal
ESR	9
CRP	<0.5
CD4+/CD45RA+ (Naïve T cells)	30.1% (low)
CD4+/CD45RO+ (Memory T cells)	69.9%
CD38hi/IgMhi (Trans B cells)	4.7%
CD38hi/IgMlo (Plasma Blasts)	0.3%
CD38lo/CD21lo (Immature B Cells)	1.7%
CD27+/IgD+ (Unswitched)	14.4%
CD27+/IgD- (Switched)	3.2% (low)
CD27-/IgD+ (Naïve)	80%
CD4+CD38-/HLADR+	5%
CD4+CD38+/HLADR-	30%
CD4+CD38+/HLADR+ (Activated CD4+ T cells)	15% (high)
CD4+CD57+ (senescent CD4+ T cells)	42% (high)
CD4+PD-1+ (exhausted CD4+ T cells)	92% (high)
CD8+CD38-/HLADR+	5%
CD8+CD38+/HLADR-	50%
CD8+CD38+/HLADR+	24%
CD8+CD57+	24%
CD8+PD-1+ (exhausted CD8+ T cells)	72% (high)
T Follicular Helper Cells	57% (high)

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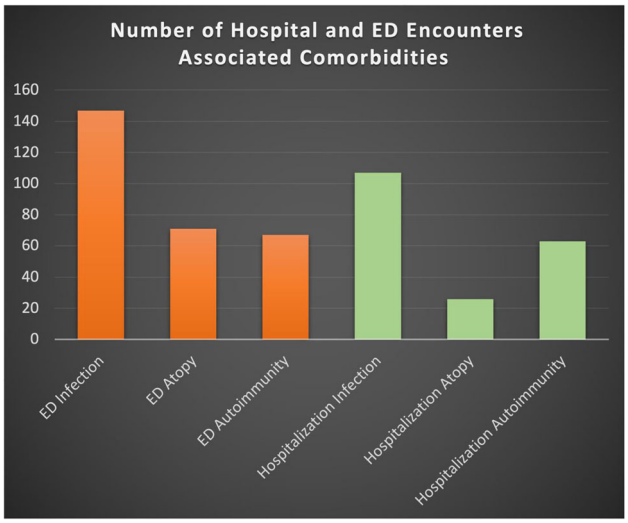

Keywords: Autoimmune lymphoproliferative syndrome, ALPS, Ras-associated autoimmune leukoproliferative disorder, RALD, RASopathies, Casitas B lineage lymphoma, CBL

Disclosures: All authors indicated they had no financial relationships to disclose.

Saturday Poster

(100) Non-infective manifestations of Severe combined Immune deficiency: Our experience from a tertiary care center in North-India

RAJNI Kumrah*[1], Gummadi Anjani[1], Murugan Sudhakar[1], Ankita Singh[1], Anit kaur[1], Jitendra Shandilya[1], Kanika Arora[1], Madhubala Sharma[1], Ankur Kumar Jindal[1], Deepti Suri[1], Anju Gupta[1], Amit Rawat[1], Vignesh Pandiarajan[1], SURJIT SINGH[1]
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Severe combined immunodeficiency (SCID) is the most severe form of PID characterized by severe, life-threatening, recurrent infections in early infancy. It is a genetically heterogeneous disorder due to mutations in >30 genes characterized by T lymphocyte dysfunction, decreased or normal numbers of B lymphocytes and NK cells. Non-infective manifestations of SCID include Omenn syndrome (OS), graft versus host disease (GVHD), autoimmunity, and hemophagocytic lymphohistiocytosis (HLH).
Methods: Retrospective case record review of patients diagnosed with SCID at Allergy Immunology Unit, Department of Pediatrics, Postgraduate Institute of Medical Education and Research, Chandigarh, North India. Various clinical, laboratory, genetic details associated with non-infective manifestations were analyzed.
Results: Eighteen (18.9%) of 95 diagnosed SCID patients were found with non-infective manifestations. Ten patients (55.5%) had omen syndrome with varied non-infective features and 2 patients had nephrotic syndrome with T-B-NK- phenotype (11.1%). Five patients (27.7%) had features of HLH. Of the patients with Omenn phenotype, 5 patients (50%) had defect in RAG1 gene; 4 (40%) had RAG2 defect and 1 (10%) had mutation in IL2RG gene. The variants found in RAG1 gene in both the patients were novel, and the parents were heterozygous carrier for the novel mutation. Clinical manifestations in children with Omenn syndrome include diarrhea (n=4); erythematous rash (n=3); alopecia (n=2); loss of eyebrows (n=1); failure to thrive (n=5); GVHD (n=1); and hepatosplenomegaly (n=1). Direct antiglobulin test positive autoimmune hemolytic anemia was found

in 2 patients [RAG1 (1), and NHEJ1 defect (1)]. Nephrotic disease (n=2) was found in 2 patients with T-B-NK- type of SCID, of which 1 patient showed a novel mutation in ADA1 gene at exon 5 c.407G>A (Homozygous). Two patients had normal lymphocytes counts, and 2 patients had eosinophilia in our cohort of patients with Omenn phenotype.
Conclusion: We report non-infective manifestations in 18.9 % of our cohort of patients with SCID. Presentation with nephrotic syndrome is rarest of these. Nephrotic syndrome could be due to extensive peritubular infiltrations of T lymphocytes and the aberrant cellular response.

Keywords: Non- infective, Omenn syndrome, Nephrotic disease

Disclosures: Vignesh Pandiarajan has relevant financial relationships with proprietary interests with Indian Council of Medical Research (Research Grant includes principal investigator, collaborator or consultant and pending grants as well as grants already received), Jeffrey Modell Foundation (Research Grant includes principal investigator, collaborator or consultant and pending grants as well as grants already received). All other authors indicated they had no financial relationships to disclose.

(101) Partial RAG Deficiency Favors Expansion of T-bet high CD21 low B Cells with Unique Repertoire and Transcriptome

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T-bethigh CD21low B cells with extrafollicular origin are frequently expanded in various form of autoimmunity implying a possible role in the pathology of these diseases. In common variable immunodeficiency (CVID), their generation was recently linked to T cell-mediated interferon gamma signature. The BCR repertoire and transcriptome of T-bethigh CD21 low B cell subsets in specific primary immune deficiencies remain elusive.
Studying a cohort of patients with partial Rag deficiency (pRD) and immune dysregulation (n=5) we found that T-bet high CD21 low CXCR5 low CD11c+ B cells (age-associated [ABC]-like) were highly abundant in their peripheral blood (20-25x) compared to healthy individuals. ABC-like cells exhibited activated phenotype (determined by the surface expression of CD25, CD69, CD80, CD86 and HLA-DR) and also expressed ABC-specific inhibitory surface markers such as CD85j, FcRL4, FcRL5. In pRD patients, ABC-like (CXCR5low CD11c+) B cells were enriched in naïve (Ig+, CD27−), memory (CD27+) and double negative (DN) B cell subsets were clonal and displayed inter-compartmental lineage connection as determined by BCR repertoire sequencing. Transcriptome studies were performed in sorted ABC-like cells from the same compartments to assess for differentially expressed genes (DEGs) and ABC-fate signature. Genes associated with inflammatory pathways; such as type-2 interferon responses were enriched and shared in ABC-like B cells both from healthy controls and pRD patients, although more expanded in the latter. In addition, the ABC-signature dominated the gene expression profile of naive, memory and DN cells of pRD patients suggestive of early polarization commitment towards ABC fate. Our findings demonstrate that T-bet high CD21low ABC-like B cells are clonally expanded lineages with a unique BCR repertoire and type-2 IFN-dominant gene expression profile. They appear early and persist in several B cell compartments in pRD patients, which points towards polarization even before cognate T cell help.

Keywords: partial RAG deficiency, B cell dysregulation, Tbet high CD21low B cells, B cell lineage connectivity, B cell transcriptome

Disclosures: Jolan Walter has relevant financial relationships with proprietary interests with Octapharma (Research Grant includes principal investigator, collaborator or consultant and pending grants as well as grants already received), Pharming (Consultant), Takeda (Consultant, Research Grant includes principal investigator, collaborator or consultant and pending grants as well as grants already received), and X4 Pharmaceuticals (Consultant). All other authors indicated they had no financial relationships to disclose.

(102) Idiopathic lymphopenia in a 40-year-old

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Introduction: The differential for T-cell lymphopenia in a previously healthy adult includes infection, drug-induced immune suppression, malignancy, immunodeficiency, and autoimmune disease. Idiopathic CD4+ T-cell lymphocytopenia is defined as persistent CD4+ T-cell lymphopenia (< 300 cells/microL or < 20% of total lymphocytes on 2 separate occasions) in the absence of HIV infection or other cause of immunodeficiency.
Case: We present a previously healthy 40-year-old male referred for occasional sinusitis. He had warts on his neck and developed shingles 2 years prior but was otherwise well. He did not have detectable HIV by PCR. Past history included joint infection that progressed to sepsis and sinus infections requiring antibiotics.
Labs: He had low lymphocyte counts since at least 1998. Most recently, his CD4+ T cell count was 30/microL, with CD8 104/microL. His TREC count was 654 per 10^6 T cells, indicating normal T-cell production. B-cell counts were low, with CD19+ counts at 13 cells/microL. IgG was 606 and IgM was < 8. He had low pneumococcal titers even after vaccination. TLR and NK cell function were normal, and proliferation in response to mitogens and tetanus antigen was normal. Spleen and liver were not enlarged. Invitae SCID panel did not reveal any useful and pathogenic variants.
Discussion: Patient is mostly healthy and his lymphopenia has no known cause. Conditions known to contribute to lymphocyte losses were excluded. Proposed mechanisms for idiopathic CD4+ T-cell lymphopenia include autoantibody-mediated destruction, increased apoptosis, insufficient production, poor proliferation, and sequestration. Hypomorphic variants in RAG1, as well as mutations in UNC119 and MAGT1 can cause lymphopenia. Standard treatment includes anti-microbial prophylaxis and immunoglobulin replacement if appropriate.
Idiopathic CD4+ T-cell lymphocytopenia can be considered in patients with a negative work-up for other causes of immunodeficiency; additional work-up may include evaluating for presence of anti-lymphocyte antibodies, especially anti-CD4 antibodies. Therapies to increase CD4 counts

include IL-2 and bone marrow transplantation. IL-7 administration has also been shown to increase absolute lymphocyte counts.
Conclusion: Patients who present with persistent T-cell lymphopenia should be evaluated for causes of immunodeficiency. Additional work-up may include evaluating for presence of anti-lymphocyte antibodies.

Keywords: Lymphopenia, T-cell, Autoantibodies

Disclosures: Roger Kobayashi has relevant financial relationships with proprietary interests with IDF (Other Financial or Material Support, Travel support), IgNS (Other Financial or Material Support, Travel support), Octopharma (Research Grant includes principal investigator, collaborator or consultant and pending grants as well as grants already received), Vietnamese Respiratory Society (Speaker/Honoraria includes speakers bureau, symposia, and expert witness). All other authors indicated they had no financial relationships to disclose.

(103) Inborn errors of Th17 immunity predisposing to fungal infections: An experience from a Tertiary Care Centre in North India

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Background: Inborn errors affecting Th17 immunity result in a predisposition to fungal infections. Both superficial and invasive forms of fungal infections have been described with these disorders. There is a paucity of data on the clinical and immunological spectrum of inborn errors of human Th17 immunity from India.
Methods: Case records of patients diagnosed with chronic mucocutaneous candidiasis and invasive fungal infections (without underlying secondary immunodeficiency) at Pediatric Immunodeficiency Clinic, Advanced Pediatrics Centre were analyzed. Children, less than 12 years of age with chronic, persistent or recurrent non-invasive mucocutaneous or invasive fungal infections were included. Patients with severe combined immunodeficiency were excluded. Blood counts, immunoglobulin profile, lymphocyte subsets, and Th17 assay by flow cytometry was performed in all cases. Phospho-STAT1 and phospho-STAT3 assays by flow cytometry were performed in selected cases.
Results: We identified 13 patients with IEI who had reduced Th17 and had developed a fungal infection (4 STAT1 gain of function, 4 STAT3 loss of function, 3 AIRE defects, 1 CARD9, 1 unidentified). A clinical phenotype of chronic mucocutaneous candidiasis was identified in 9 patients (4 STAT1 gain of function, 3 AIRE, and 2 STAT3 loss of function). Recurrent verrucous tinea was identified in a patient with STAT1 GOF. Pulmonary aspergillosis was identified in 2 patients with STAT3 loss of function. Features of ectodermal dystrophy, alopecia, and hypoparathyroidism were identified in 1 patient who was subsequently found to have a novel defect in AIRE (c.1032 IVS2-1G>C). A novel variant in STAT1 (c.1032 G>T) was identified in 2 patients who were not related to each other and were from different geographical regions. Autoimmune hemolytic anaemia (n=2) and autoimmune thyroiditis (n=2) was also identified in patients with STAT1 GOF defect. Invasive mucormycosis was identified in a patient with a homozygous novel intronic defect in CARD9.
Conclusion: Flow cytometry-based analysis of Th17 cells helps in the identification of patients to be screened for molecular defects. STAT1 gain of function is the commonest genetic cause for chronic mucocutaneous candidiasis in our cohort. Apart from recurrent infections due to Candida spp., autoimmunity and bacterial infections are also noted in STAT1 GOF.

Keywords: Th17 immunity, Fungal infections, India

Disclosures: Vignesh Pandiarajan has relevant financial relationships with proprietary interests with Indian Council of Medical Research (Research Grant includes principal investigator, collaborator or consultant and pending grants as well as grants already received), and Jeffrey Modell Foundation (Research Grant includes principal investigator, collaborator or consultant and pending grants as well as grants already received). Jhumki Das has relevant financial relationships with proprietary interests with Indian Council of Medical Research (Research Grant includes principal investigator, collaborator or consultant and pending grants as well as grants already received). All other authors indicated they had no financial relationships to disclose.

(104) STAT1 Gain-of-Function Variant as a Cause of Chronic Mucocutaneous Candidiasis and Steatorrhea

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An 11-year-old male, previously diagnosed with chronic mucocutaneous candidiasis (CMCC), with unknown genetic variant, presented with hypokalemia in the setting of steatorrhea. CMCC is a heterogenous syndrome, caused by various genetic defects, with common features of chronic noninvasive Candida infections affecting the skin, nails, and mucous membranes.
At 6-months-old, the patient began having gastrointestinal complaints with solid foods. At 18-months-old, he became jaundiced and was diagnosed with autoimmune hepatitis. At 3-years-old, he began having thrush and oral ulcers, prompting esophagogastroduodenoscopy (EGD), which noted Candida esophagitis and villous blunting. He was diagnosed with CMCC based upon very low proliferative response to Candida. Additionally, he developed frequent skin abscesses and pneumonias. At 6-years-old, genetic testing was negative for the AIRE variant. At 9-years-old, he developed steatorrhea with low fecal elastase and high fecal fat and was started on pancrelipase with no improvement.
At 11-years-old, he presented to an outside hospital with hypokalemia in the setting of high-volume steatorrhea and was transferred to our children's hospital. EGD noted esophageal candidiasis, villous blunting of the duodenum, multiple disaccharidase deficiencies, and chronic gastritis. He was started on an amino-acid-based formula with some improvement. IgG was noted to be around 400 mg/dL. Immunology was consulted and recommended whole genome sequencing, significant for two heterozygous-gain-of-function (GOF) variants in STAT1 (Arg241Gln and Met390Val), the latter thought to be pathogenic. Immunology recommended MRA brain, immunoglobulin replacement, prophylactic acyclovir, and initiation of the JAK1/JAK2 inhibitor ruxolitinib at 0.4 mg/kg/day with plans to increase while monitoring for cytopenias, elevated transaminases, and viral infections, side-effects described in STAT1-GOF patients on ruxolitinib. The patient's diarrhea improved with his elemental diet and improved further with ruxolitinib. MRA noted a small cerebral aneurysm.
Heterozygous STAT1-GOF variants can lead to autosomal-dominant CMCC due to impaired STAT1 dephosphorylation. These variants can lead to a wide range of clinical features, including infectious, autoimmune, cerebral aneurysms, carcinomas, and steatorrhea. The JAK-inhibitor ruxolitinib can be used to treat STAT-1-related CMCC. This case highlights the importance of being cognizant of the systemic manifestations of

STAT1-GOF-related disease and the importance of determining the genetic variant(s) underlying CMCC to better guide therapy.

Keywords: chronic mucocutaneous candidiasis, CMCC, STAT1, ruxolitinib, JAK, jakinib, steatorrhea, candida

Disclosures: Cathleen Collins has relevant financial relationships with proprietary interests Enzyvant Therapeutics (Consultant). Michael Land has relevant financial relationships with proprietary interests with Quest Diagnostics (Research Grant includes principal investigator, collaborator or consultant and pending grants as well as grants already received). All other authors indicated they had no financial relationships to disclose.

(105) Identification of inborn errors of immunity in children with autoimmune cytopenia: An experience from India

Vignesh Pandiarajan*[1], Murugan Sudhakar[1], Kaushal Sharma[1], Sumit Goel[1], Ankur Kumar Jindal[1], Deepti Suri[1], Amit Rawat[1], Jaikumar Ramamoorthy[2], Ankit Mehta[3], Surjit Singh[1]
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Objective: Autoimmune hemolytic anaemia (AIHA) is the most common form of autoimmune manifestation reported in patients with inborn errors of immunity (IEI). Herein, we report our experience with 17 patients with monogenic AIHA.
Methods: We performed a retrospective review of case records of children diagnosed with AIHA and proven IEI. We also prospectively studied (2018-2021) infants and children with early-onset autoimmune cytopenia to identify possible underlying IEI.
Results: We identified 17 patients of AIHA with an underlying PID. The diagnosed PID include Wiskott-Aldrich syndrome (WAS) (n=4, 23.5%); Autoimmune lymphoproliferative syndrome (ALPS) (n=4, 23.5%); Lipopolysaccharide-responsive and beige-like anchor protein (LRBA) deficiency (n=2, 12%); Severe combined immunodeficiency [SCID, n=2 (12%); STK defect (1), and NHEJ1 defect (1)]; STIM1 defect (n=1, 5.8%); STAT3 defect (n=1, 5.8%); CD40L defect (n=1, 5.8%); and ACP5 defect (n=2, 12%). AIHA was seen as initial presentation of the disease in patients with CD40L defect, LRBA defect (n=3), ALPS (n=4), ACP5 defect, STIM1 defect, and in 1 patient with WAS. Corticosteroid was the first-line agent used (n=12/ 17, 70.5%), whereas 3 patients were managed without corticosteroid [17.6%, SCID (2), and CD40L defect (1)]. Other agents utilised include Mycophenolate mofetil (MMF) (n=7, 41.1%); Azathioprine (n=3, 17.6%); Sirolimus [n=7, 41.1%; ALPS (3); LRBA (2); STAT3 defect (1); STIM1 defect (1)]; and Rituximab [n=2, 11.7%; ALPS (1); STIM1 defect (1)]. Complete remission of AIHA was achieved with Corticosteroid alone (n=1, 5.8%); IVIg with corticosteroids (n=3, 17.6%); and MMF (n=2, 11.7%). All patients administered with Sirolimus had achieved either partial or complete remission without further blood product transfusions or additional immunosuppressants. Of the 4 patients with ALPS, the newly diagnosed patient was considered for Sirolimus with corticosteroids upfront as a first-line agent due to the published evidence for Sirolimus. AIHA in patients with WAS and SCID were corticosteroid responsive and did not require further immunosuppressive therapy for AIHA.
Conclusion: Experience gained from our cohort reiterates the fact that AIHA can be an important presenting manifestation of IEI. This study also shows clinical improvement with targeted therapy which implies the need to elucidate underlying genetic causes in patients with secondary AIHA.

Keywords: Autoimmune hemolytic anaemia, Evans Syndrome, Inborn errors of immunity

Disclosures: Vignesh Pandiarajan has relevant financial relationships with proprietary interests Indian Council of Medical Research (Research Grant includes principal investigator, collaborator or consultant and pending grants as well as grants already received) and Jeffrey Modell Foundation (Research Grant includes principal investigator, collaborator or consultant and pending grants as well as grants already received). All other authors indicated they had no financial relationships to disclose.

(106) Prolonged High Dose Subcutaneous Immunoglobulin Therapy for Chronic Immune Thrombocytopenia Purpura in A Cohort of Pediatric Patients

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Introduction: Chronic immune thrombocytopenic purpura (ITP) is a condition that involves the destruction of platelets in the body's circulation by autoantibodies persisting for over 12 months. Standard first-line therapies for the acute phase of chronic ITP include corticosteroids and high dose intravenous immunoglobulin (HDIVIG). HDIVIG infusions can have systemic side effects and the benefits are temporary. The use of HDIG either intravenous or subcutaneous route for the chronic phase of ITP has not been fully established. In our cohort of pediatric patients, we report the feasibility and effectiveness of high dose subcutaneous Ig (HDScIg) for the control of chronic ITP.
Methods: A retrospective medical chart review.
Results: We present a cohort of four pediatric patients who were treated with intermittent HDIVIG for flares of thrombocytopenia with bleeding. Immune evaluation in all four patients revealed a specific antibody deficiency syndrome (SAD). Two patients had an additional diagnosis of partial DiGeorge Syndrome (pDGS) and the other two patients had unspecified SAD. All four patients qualified for subcutaneous immunoglobulin (ScIg) based on their antibody deficiency syndrome and were started on a standard replacement dose of (0.5g/kilogram/4 weeks). However, due to the nature of their chronically low platelet levels and history of bleeding, all four patients elected to proceed with high dose subcutaneous immunoglobulin (0.5g/kilogram/2 weeks). The average length of HDScIg treatment for the cohort was 8 months (range: 4 to 14 months). All four patients tolerated HDScIg well with no history of nausea, headaches, and pain at the injection site. The patients' platelet counts were stabilized on extended HDScIg treatment and remained clinically asymptomatic.
Discussion: While HDScIg has not been established as a treatment for pediatric chronic ITP, we report four patients who benefitted from the platelet-stabilizing effect. There have only been two other reports of the use of HDScIg in 3 pediatric patients with ITP. On a small scale, we show the feasibility, safety, and efficacy of HDScIg for the treatment of

pediatric patients with SAD and chronic ITP with bleeding. In conclusion, we propose that HDScIg may be considered as a viable and practical treatment option.

Keywords: Subcutaneous Immunoglobulin Therapy, Chronic Immune Thrombocytopenic Purpura, Pediatric

Disclosures: Jolan Walter has relevant financial relationships with proprietary interests with Octapharma (Research Grant includes principal investigator, collaborator or consultant and pending grants as well as grants already received), Pharming (Consultant), Takeda (Consultant, Research Grant includes principal investigator, collaborator or consultant and pending grants as well as grants already received), and X4 Pharmaceuticals (Consultant). All other authors indicated they had no financial relationships to disclose.

(107) Late-onset X-linked Chronic Granulomatous Disease: Identification of A Novel Variant in the CYBB Gene

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BACKGROUND: Chronic granulomatous disease (CGD) is a primary immunodeficiency characterized by severe and recurrent infections due to defective nicotinamide adenine dinucleotide phosphate (NADPH) oxidase activity. Disease-causing variants in CYBB, an X-linked gene, are responsible for 70% of cases of CGD. X-linked CGD typically presents within the first 2 years of life. We report a novel variant in the CYBB gene in a patient presenting with a late-onset phenotype.
CLINICAL PRESENTATION: A 13-year-old white male with no significant past medical history presented with community-acquired pneumonia refractory to outpatient therapy. Chest CT showed bilateral necrotizing pneumonia and he received treatment with multiple IV antibiotics without clinical improvement.
RESULTS: Following a month of hospitalization, a bronchoscopy and bronchoalveolar lavage was performed. Respiratory cultures grew Burkholderia multivorans which prompted an evaluation of the patient's immune system. NADPH oxidase activity after neutrophil stimulation to PMA for dihydrorhodamine fluorescence was diminished with two peaks of distinct intensity; one peak showed no response, and one peak showed a moderately decreased response (50% PMA ox-DHR+; normal: > or =95%). Genetic testing revealed a hemizygous likely pathogenic variant in the CYBB gene (c.1712 A>C; p.*571Serext*8). This variant substitutes a stop codon with a serine codon leading to an 8 amino acid extension of the protein at the C-terminus. Familial genetic testing revealed this variant was maternally inherited.
CONCLUSIONS: We identified a novel variant in the CYBB gene that manifested as a delayed presentation of X-linked CGD. The CYBB c.1712A>C variant leads to an intact, though extended, protein product. We theorize that it is a hypomorphic variant and explains the patient's later presentation. Thus, while X-linked CGD is more commonly diagnosed in younger children, clinicians should remain vigilant when considering X-linked CGD for patients presenting with severe or unusual infections regardless of age.

Keywords: Chronic granulomatous disease (CGD), Novel variant, CYBB gene

Disclosures: All authors indicated they had no financial relationships to disclose.

(108) Identifying Comorbidities in Adult Patients with Primary Immunodeficiency Diseases Presenting to the Emergency Department and/or Hospital

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Introduction: Current literature regarding comorbidities in patients with primary immunodeficiency diseases (PIDD) is sparse. We investigated the comorbidities and mortality in adult patients with PIDD presenting to the emergency department (ED) and/or hospital.
Methods: A retrospective chart review was performed on adult patients with PIDD from 2012 to 2019 within a single quaternary medical center. Patients were identified using ICD-9 and ICD-10 codes for PIDD. Patients with a previous diagnosis of PIDD with associated ED and/or hospital encounters were included in the analysis. This study was approved by and conducted in accordance with the institutional review board.
Results: There were 704 patient charts identified and 163 met study criteria. Of the 163 charts, there were a total of 274 ED and hospital encounters reviewed. Twelve patients died during chart review years. Of the ED encounters, 147 had infection, 71 had atopic disease and 67 had autoimmune disease (Figure 1). Regarding hospitalization encounters, 107 had infection, 26 had atopic disease, and 63 had autoimmune disease (Figure 1). For ED encounters, the most common infections, atopic diseases, and autoimmune diseases were the following: 17% skin and soft tissue infections, 53% asthma, and 29% hypothyroidism, respectively. For hospital encounters, the most common infections, atopic diseases, and autoimmune diseases were the following: 37% sepsis, 69% asthma, and 19% systemic lupus erythematosus, respectively. Patients with a higher average number of ED and hospital encounters also had increased risk of mortality (Figure 2).
Conclusion: Our results demonstrate the prevalence of associated comorbidities in patients with PIDD who presented to the ED and/or hospital. An increase in mortality related to average number of ED visits and hospitalizations was also noted. These data can be used to raise awareness of PIDD related comorbidities, which will enable appropriate management in the delivery of care. Furthermore, this increased level of awareness will hopefully reduce the number of ED and hospital visits and may potentially improve mortality rates.

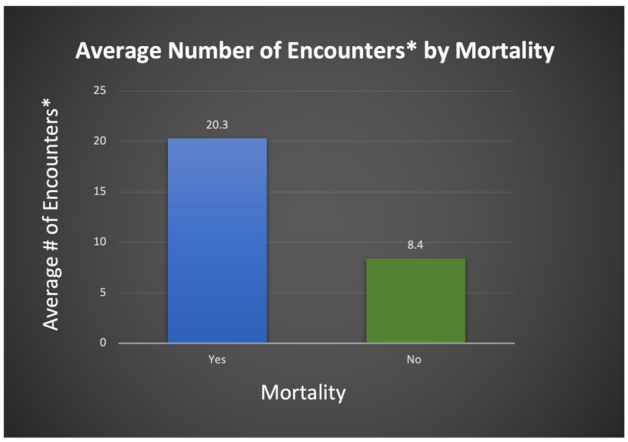

Figure 1: Number of comorbidities (infection, atopy, autoimmunity) in the ED vs. hospital in adult patients with PIDD.

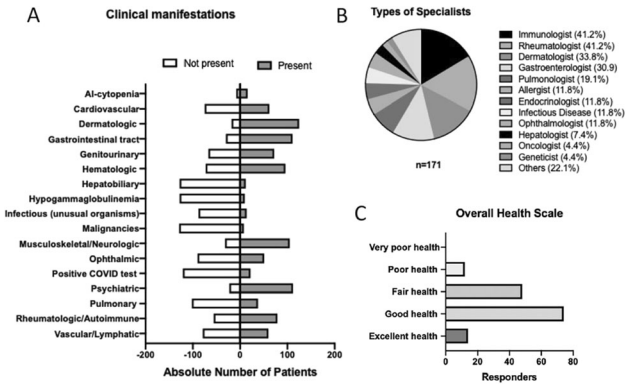

Figure 2: *Includes hospitalizations and ED visits. Average number of ED and hospital encounters in relation to mortality outcome.

Keywords: PIDD, Comorbidities, Infection, Autoimmunity, Atopy, Mortality

Disclosures: All authors indicated they had no financial relationships to disclose.

(109) Psychosocial Concerns among Patients Diagnosed with Primary Immunodeficiency and their Caregivers

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Background: Children with chronic diseases and their caregivers may be at increased risk for psychological distress and decreased quality of life, which may impact medical outcomes. Little is known about psychosocial risks among patients with rare chronic diseases such as primary immunodeficiency disorders (PID) or their caregivers.
Aims: This study's goal was to better understand the unique psychosocial needs of PID patients and families by conducting a preliminary assessment of the psychosocial functioning of patients with PID and their caregivers and their relationship with child age, time since PID diagnosis, disease severity, and medical experiences.
Methods: Caregivers of children with PID ages 0-17 years, and children with PID ages 8-17 years were recruited from a pediatric immunology clinic at a mid-Atlantic pediatric hospital to complete online surveys about their mental health. Caregivers and patients over 8 years completed self-report measures regarding their own mental health using the PROMIS scales regarding anxiety, depressive symptoms, fatigue, sleep disturbance, emotional support, and informational support. Caregivers of children ages 5-17 years also completed parent-proxy surveys.
Results: Forty-four caregivers of 42 children with PID completed the survey, as did 13 patients. Among caregivers, 25% reported clinically elevated fatigue scores and 29% reported clinically elevated anxiety scores. Child self-reported data revealed clinically elevated scores for 46% of children on the depressive symptoms subscale, 38% on the fatigue and anxiety subscales, 30% on the peer relationships and pain interference subscales, and 23% on the physical functioning subscale. Results indicated that greater time since diagnosis was associated with caregivers' self-report of less emotional support and information support ($r = -.45$ and $r = -.42$, respectively; $p < 0.01$). Child self-report of their mental health indicated that greater time since diagnosis was associated with higher fatigue scores ($r = .63$, $p < 0.05$), and there was a trend for an association with greater depressive symptoms ($r = .51$, $p = 0.09$).
Conclusions: Preliminary study indicates that psychosocial concerns are prevalent among children with PID and their caregivers. Screening should be considered for all patients and families with PID, and future studies may determine if interventions may improve patient health outcomes.

Keywords: Primary Immunodeficiency, Mental Health, Depression, Anxiety

Disclosures: Michael Keller has relevant financial relationships with proprietary interests with Enzyvant (Advisory Board). All other authors indicated they had no financial relationships to disclose.

(110) Self-Reported Symptom Burden of Female X-linked Chronic Granulomatous Disease Carriers – a PIDTC Report

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Background: CYBB variants of NADPH oxidase leads to X-linked (XL) chronic granulomatous disease (CGD), the most common form. Through Lyonization, female XL-CGD carriers express a normal (Dihydrorhodamine [DHR]+) population of phagocytes and an abnormal (DHR-) population. Increased risk of autoimmunity and infections in some cases have been reported in female XL-CGD carriers.
Methods: An IRB approved 57 question survey administered through the CGD Association of America was completed by female XL-CGD carriers. Data gathered included demographics, method of diagnosis, medical history, utilization of medical care and treatments.

Results: The survey was completed by 171 subjects having mean age 45 (range 15-85) years. Most respondents were family members of CGD patients (93%). Nearly half (45%) were followed by specialists including immunologists, rheumatologists and dermatologists (Figure 1). Over half of respondents (59%) reported good or excellent health (Figure 2). However, 25% indicated impairment in daily activities, most commonly secondary to chronic fatigue or arthralgias. Affected organ systems and symptoms included dermatologic (87%), psychiatric (83%), gastrointestinal (79%), musculoskeletal (77%), rheumatologic (59%) and hematologic (57%) (Figures 3 and 4). Anxiety, depression, panic attacks, and post-traumatic stress disorder were reported mental health problems. Half of respondents (50%) worked less than full time and 10% had restrictions in work hours. Twenty-five percent felt they had impairment in daily activities; fatigue was the most common (42%) cited reason. Infections were common among respondents (66%) including: skin abscesses (36%), cellulitis, (23%), pneumonia (27.5%), and lymphadenitis (10%). Pneumonia causing organisms were reported in 6 (Figure 5). Importantly, 7 (5.3%) respondents reported deep-tissue infections. Of note, 33% of respondents (n=44) reported infection with a CGD-related organism: Staphylococcus aureus (n=31), Aspergillus (n=6), Salmonella (n=5), Burkholderia (n=1), Serratia (n=1) and Mycobacteria (n=1). Antibacterial and/or antifungal prophylaxis was administered in 36% (n=51).

Conclusions X-linked CGD female carriers have a variety of symptoms that affect their overall health including auto-inflammation and infections. There is an increased incidence of self-reported psychiatric symptoms amongst respondents. Many carriers would benefit from close monitoring and in some cases, anti-microbial prophylaxis. Careful studies of carriers to define best approaches are warranted.

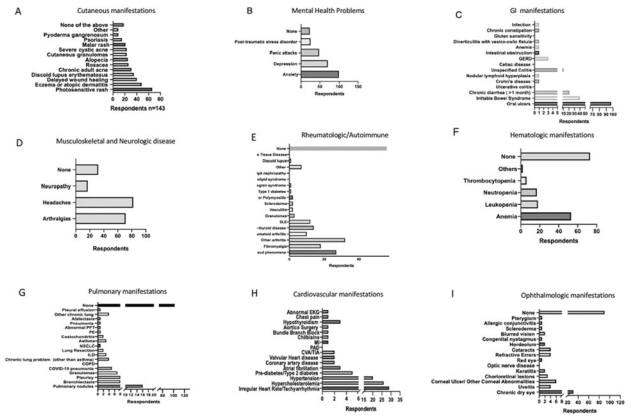

Figure1: Clinical manifestations, types of specialists providing care, and overall health scale of X-linked CGD Female carriers

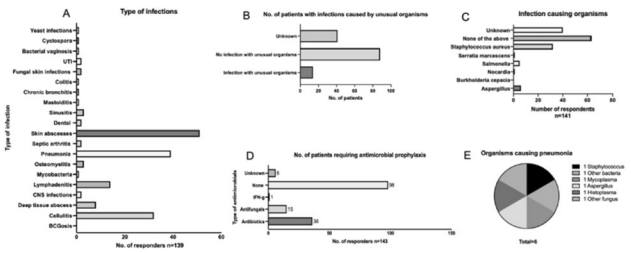

Figure 2: Clinical Manifestations by Organ System in X-linked CGD Female Carriers

Understanding attitudes and obstacles to vaccination against COVID-19 in patients with primary immunodeficiency

Tables

Table 1 Primary immunodeficiencies among 101 COVID-19 survey respondents

Type of primary immunodeficiency disorder	Percentage	Responses
Common variable immunodeficiency (CVID)	72.3%	73
Hypogammaglobulinemia	10.9%	11
Immunoglobulin deficiency (IgA, IgA1, IgG, IgG2, IgG3, IgM)	6.9%	7
STAT1 deficiency	2.0%	2
B cell dysfunction	1.0%	1
Chronic lymphocytic leukemia (CLL)	1.0%	1
IPEX syndrome	1.0%	1
Severe combined immunodeficiency disease (SCID) Omenn Syndrome *RAG1*	1.0%	1
Secondary hypoglobulinemia	1.0%	1
Secondary immunodeficiency	1.0%	1
HLA-B27 autoimmune disease	1.0%	1
Dysgammaglobulinemia	1.0%	1

Data from COVID-19 Vaccine Hesitancy Survey in Primary Immunodeficiency Patients, March 24 to April 7, 2021

CLL chronic lymphocytic leukemia, *CVID* common variable immunodeficiency, *HLA-B27* human leukocyte antigen B27, *Ig* immunoglobulin, *IPEX* immunodysregulation polyendocrinopathy enteropathy X-linked, *RAG1* recombination activating 1 gene, *SCID* severe combined immunodeficiency disease, *STAT1* signal transducer and activator of transcription 1

Table 2 COVID-19 vaccine hesitancy among 121 primary immunodeficiency patients in Canada

Reason for COVID-19 vaccine hesitancy	Percentage	Responses
Not sure of benefit and immune response given underlying immunodeficiency	56.2%	68
Concerned about long-term side-effects that are yet to be uncovered	50.4%	61
History of allergies and afraid of reacting to the vaccine	32.2%	39
Not confident in the vaccine as it is too new and the process feels rushed	30.6%	37
Plan to wait for more data being available on effectiveness and side-effects	22.3%	27
Skeptical of the science behind the COVID-19 vaccine	16.5%	20
Skeptical of the medical system and the data regarding these vaccines	14.9%	18
Already have or think I have contracted COVID-19	5.0%	6
Do not want to get vaccinated	2.5%	3
Do not believe in vaccination	1.7%	2
Other (please specify)	31.4%	38

Data from COVID-19 Vaccine Hesitancy Survey in Primary Immunodeficiency Patients, March 24 to April 7, 2021

Table 3 Racial/ethnic background of COVID-19 survey respondents

Racial/ethnic heritage	Percentage	Responses
Caucasian	92.4%	329
Non-Hispanic White or Euro-Canadian	6.5%	23
French Canadian	2.8%	10
Métis	1.1%	4
Hispanic/Latino	0.8%	3
First Nations	0.3%	1
Middle Eastern or Arab Canadian	0.3%	1
Pacific Islander	0.3%	1
South Asian	0.3%	1
Inuit	0.0%	0

Data from COVID-19 Vaccine Hesitancy Survey in Primary Immunodeficiency Patients, March 24 to April 7, 2021

Figure 3: Infections in XL-CGD Female Carriers

Keywords: CGD, X linked female carrier, Symptomatology in carriers

Disclosures: Jennifer Leiding has relevant financial relationships with proprietary interests with bluebird bio (Employment, Ownership Interest includes stock, stock options, patent or other intellectual property), Horizon Therapeutics (Consultant, Speaker/Honoraria includes speakers bureau, symposia, and expert witness), Pharming (Advisory Board, Consultant, Speaker/Honoraria includes speakers bureau, symposia, and expert witness), Sobi (Consultant, Speaker/Honoraria includes speakers bureau, symposia, and expert witness), and Takeda (Consultant, Speaker/Honoraria includes speakers bureau, symposia, and expert witness). Christopher Dvorak has relevant financial relationships with proprietary interests with Alexion Inc (Advisory Board, Consultant), Jazz Pharma (Consultant), and Omeros Corp (Consultant). Jennifer Puck has relevant financial relationships with proprietary interests with Invitae (Employment, Ownership Interest includes stock, stock options, patent or other intellectual property) and UpToDate (Other Financial or Material Support, Royalties). Michael Pulsipher has relevant financial relationships with proprietary interests with Adaptive (Research Grant includes principal investigator, collaborator or consultant and pending grants as well as grants already received), Equillium (Advisory Board), Medexus (Advisory Board), Mesoblast (Advisory Board), Miltenyi (Research Grant includes principal investigator, collaborator or consultant and pending grants as well as grants already received), and Novartis (Advisory Board, Speaker/Honoraria includes speakers bureau, symposia, and expert witness). Troy Torgerson has relevant financial relationships with proprietary interests with Horizon Pharma (Consultant), Pharming Healthcare (Consultant) , Takeda (Consultant), UCB Pharma (Consultant), and X4 Pharma (Consultant). Felicia Morton has relevant financial relationships with proprietary interests with Horizon Therapeutics (Research Grant includes principal

investigator, collaborator or consultant and pending grants as well as grants already received) Horizon Therapeutics (Other Financial or Material Support, Horizon Therapeutics is a sponsor of the CGD Association of America). Peter Newburger has relevant financial relationships with proprietary interests with X4 Pharmaceuticals (Consultant). All other authors indicated they had no financial relationships to disclose.

(111) The IDDA2.1 'kaleidoscope' score: Phenotype expression profiling in inborn errors of immunity with immune dysregulation

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Background: Clinical scores (measures, indices, scales, or similar) may be used in inborn errors of immunity (IEI) to support making a diagnosis or to classify an IEI, to assess and monitor the disease severity over time, and to guide treatment decisions. Especially in IEI with immune dysregulation and/or risk of malignancy, making the correct diagnosis early and assessing the existing and expectable phenotypical features prospectively is vital. In cases without a genetic diagnosis or with variable penetrance, key determinants are the clinical and immune laboratory features. Many of the existing tools are highly disease- and context-specific and complex.
Methods: We developed a user-friendly 22-parameter score for evaluating the immune deficiency and dysregulation activity (IDDA version 2.1) that includes graded organ involvement and disease burden, intended for prospective monitoring of all IEI with immune dysregulation.
Results: To extend the utility from one IEI (LRBA deficiency), where we evaluated the longitudinal course of patients or compared treatment responses cross-sectionally, to all IEI with immune dysregulation, we included hemophagocytic lymphohistiocytosis into the parameter list; and we modified the calculation of the numerical score to correct for very low performance scales. A new accompanying feature, the kaleidoscope function, is enabled by plotting the IDDA2.1 parameters as radar chart or heatmap which illustrates phenotypical similarities and variances between different patients or conditions. The discriminative power of this method was confirmed by unsupervised hierarchical clustering of 18 representative IEI according to their phenotype expression profiles in analogy to genotype expression arrays.
Conclusions and perspectives: The IDDA2.1 kaleidoscope score may be used for prospective monitoring of patients with IEI with immune dysregulation, e.g., in patient registries or clinical trials. A recently launched ESID registry study will collect data and apply unsupervised machine learning algorithms to detect similarities of patterns in training cohorts consisting of patients with known monogenic IEI to assess potentially predictive values in diagnosis finding, complication monitoring, and to suggest phenotype-driven, "semi-targeted" therapy options for undiagnosed patients.

Keywords: primary immune regulatory disorders (PIRD), registry, clinical score, phenotype, inborn error of immunity (IEI), hierarchical clustering

Disclosures: Markus Seidel has relevant financial relationships with proprietary interests with Amgen (Research Grant includes principal investigator, collaborator or consultant and pending grants as well as grants already received, Speaker/Honoraria includes speakers bureau, symposia, and expert witness), CSL Behring (Other Financial or Material Support, travel grant), Novartis (Research Grant includes principal investigator, collaborator or consultant and pending grants as well as grants already received), and Takeda (Research Grant includes principal investigator, collaborator or consultant and pending grants as well as grants already received). All other authors indicated they had no financial relationships to disclose.

(112) Rubella Virus Infected Macrophages and Neutrophils Define Patterns of Granulomatous Inflammation in Inborn and Acquired Errors of Immunity

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Both wild type and the vaccine strain of rubella virus (RuV) have been found associated with chronic inflammatory lesions in people with and without an inborn error of immunity (IEI). Infectious immunodeficiency-

related vaccine-derived rubella viruses (iVDRV) with multiple mutations and altered biological properties were recovered from cutaneous granuloma biopsies years after vaccination. RuV was most frequently found in M2 macrophages at the core of cutaneous granulomas. There is a key knowledge gap in understanding where iVDRV asymptomatically persists prior to emerging in granulomas, how the virus spreads to the affected tissues, and understanding the characteristic features of the granulomas. In this study, we investigated the tissue distribution of RuV-associated granulomas and characterized their spatial and cellular organization. We collected clinical and immunological data from 28 granuloma patients with a broad spectrum of IEI and RuV-associated granulomas in various body sites. The cellular organization of granulomas was analyzed by using double fluorescent immunohistochemical staining of granuloma biopsies (27 skin lesions and 33 biopsies from 9 different extracutaneous sites) for rubella capsid protein and each of the cell-type specific markers. RuV-associated granulomas were found in all tissue types tested including three newly recognized sites, bone marrow (BM), brain, and gastrointestinal tract. In addition to M2 macrophages, neutrophils were identified as a novel cell type infected with RuV. Four patterns of RuV-associated granulomatous inflammation were classified based on their cellular composition. Non-necrotizing M-type and necrotizing M(n)-type with RuV-positive macrophages at the granuloma cores and necrotizing N-type with RuV-positive neutrophils at the granuloma core were typically observed in cutaneous lesions. A disorganized aggregation of abundant RuV-positive neutrophils intermixed with RuV-positive macrophages were typically observed in extracutaneous sites and designated DNI-type granulomas. RuV-positive neutrophils were also found in BM biopsies without pathological changes. This suggests that BM could be a site where RuV persists subclinically in neutrophil precursor cells and subsequently emerges in the skin and other body sites with diminution of immune control. Characterization of granuloma structures may lead to a better understanding of the role of macrophages and neutrophils in RuV-associated granuloma pathologies and facilitate targeting of future interventions.

Keywords: granulomatous inflammation, vaccine-derived rubella viruses, skin lesion

Disclosures: Joud Hajjar has relevant financial relationships with proprietary interests with The Texas Medical center Digestive Diseases Center (Research Grant includes principal investigator, collaborator or consultant and pending grants as well as grants already received), Jeffrey Modell Foundation (Research Grant includes principal investigator, collaborator or consultant and pending grants as well as grants already received), Immune Deficiency Foundation (Research Grant includes principal investigator, collaborator or consultant and pending grants as well as grants already received) Baxalta (Research Grant includes principal investigator, collaborator or consultant and pending grants as well as grants already received), Chao Physician-Scientist Foundation (Research Grant includes principal investigator, collaborator or consultant and pending grants as well as grants already received), Takeda (Consultant/Advisory Board Member), Pharming (Consultant/Advisory Board Member), Horizon: Consultant/Advisory Board Member, and Alfaisal University (ad hoc consultancy/speaker). Koen Vanden Driessche has relevant financial relationships with proprietary interests with Curevac (Ownership Interest includes stock, stock options, patent or other intellectual property), Merck (Ownership Interest includes stock, stock options, patent or other intellectual property), Pfizer (Ownership Interest includes stock, stock options, patent or other intellectual property), Sanofi-Pasteur (Advisory Board), Misha Rosenbach has relevant financial relationships with proprietary interests with Eli Lilly (Consultant), Janssen (Consultant), Merck (Consultant), Novartis (Consultant), Processa (Consultant, Research Grant includes principal investigator, collaborator or consultant and pending grants as well as grants already received). Hemalatha Rangarajan has relevant financial relationships with proprietary interests with Medexus (Consultant, Medexus Treosulfan (one time only)). T Prescott Atkinson has relevant financial relationships with proprietary interests with CSL Behring (Advisory Board), Horizon Therapeutics (Advisory Board), and Pharming Healthcare, Inc. (Advisory Board). All other authors indicated they had no financial relationships to disclose.

(113) PATH4WARD: A Genetic Testing Program to Aid in Molecular Diagnosis of Congenital Neutropenia and Other Primary Immunodeficiencies Including WHIM Syndrome

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Patients with suspected congenital neutropenia (CN) present with heterogenous symptoms, making early diagnosis challenging. X4 Pharmaceuticals and Invitae are partnering on PATH4WARD, a sponsored genetic testing program utilizing a targeted next-generation sequencing panel. The goal of the program is to provide early and accurate molecular diagnosis for patients suspected of having primary immunodeficiencies (PIDs) characterized by neutropenia, such as WHIM (Warts, Hypogammaglobulinemia, Infections, Myelokathexis) syndrome.
Initially, PATH4WARD utilized a 23-gene CN panel including the CXCR4 gene, with optional reflex to a 207-gene PID panel. In September 2020, inclusion criteria were broadened to include patients with an absolute neutrophil count (ANC) ≤750 cells/μL (previous cutoff, ≤500 cells/μL), and the panel was expanded to 407 genes to identify the molecular etiology for more patients with CN and other PIDs. Sequencing of exons and flanking splice regions was performed by Invitae at ≥50X depth (average 350X), and variants were classified using Sherloc, a semiquantitative, evidence-based classification framework. We report findings from utilization of PATH4WARD from July 2019 through September 2021.
PATH4WARD was utilized by 319 health care professionals (HCPs). Of these, 175 HCPs reported specialties, with >50% specializing in pediatric hematology/oncology. Of the 592 patients (median age, 5 years) who underwent genetic testing through the reported period, 56 tested positive for any PID gene, and 30 tested positive for genes associated with CN. PATH4WARD identified 234 CN gene variants—43 pathogenic, 11 likely pathogenic, and 180 variants of unknown significance.
Based on variant diagnoses achieved through PATH4WARD, 26 of 56 (46%) patients with CN were identified for consideration of approved treatments, 23 (41%) for eligibility in clinical trials, and 14 (25%) for both. Genetic testing for PIDs, including neutropenia, can aid in the molecular diagnosis of specific clinical disorders (eg, WHIM syndrome). Their identification may enable opportunities for early treatment with approved therapy or participation in interventional trials. Future expansion of PATH4WARD will include a modification of the ANC eligibility criteria to ≤1000 cells/μL to allow for broader assessment of patients with neutropenia and a patient-initiated testing option to further increase accessibility to genetic testing and treatment options for patients with PIDs.

Keywords: primary immunodeficiency, congenital neutropenia, PATH4WARD, genetic testing

Disclosures: Heather McLaughlin has relevant financial relationships with proprietary interests with Invitae (Employment, Ownership Interest includes stock, stock options, patent or other intellectual property). James Connelly has relevant financial relationships with

proprietary interests with Horizon Therapeutics (Advisory Board), Sobi (Advisory Board), and X4 Pharmaceuticals (Advisory Board). Lori Neri has relevant financial relationships with proprietary interests with X4 Pharmaceuticals (Employment). Jan Seng has relevant financial relationships with proprietary interests with X4 Pharmaceuticals (Employment). Hoda Saedi has relevant financial relationships with proprietary interests with Color Genomics (Employment, Ownership Interest includes stock, stock options, patent or other intellectual property) and X4 Pharmaceuticals (Employment). Sumit Pawar has relevant financial relationships with proprietary interests with X4 Pharmaceuticals (Employment). Katarina Zmajkovicova has relevant financial relationships with proprietary interests with X4 Pharmaceuticals (Employment, Ownership Interest includes stock, stock options, patent or other intellectual property). Peter Newburger has relevant financial relationships with proprietary interests with X4 Pharmaceuticals (Consultant). All other authors indicated they had no financial relationships to disclose.

(114) Secondary T cell immunodeficiency in a patient with primary B cell immunodeficiency.

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Introduction: Screening algorithm for diagnosis of Human Immunodeficiency Virus (HIV) released by Centers for Disease Control and Prevention (CDC) includes initial antigen-antibody immunoassay, then HIV-1/HIV-2 antibody differentiation immunoassay if the initial test is reactive. Only when the screening test and antibody differentiation assay are divergent, is when RNA nucleic acid test (NAT) is performed. However, a patient with B cell immunodeficiency likely will have a false negative result if the patient was screened with a third-generation antibody-based point-of-care test, or when HIV replicative capacity is low, and antigen is below the level of detection. We describe a unique case of a patient with primary B cell immunodeficiency and secondary T cell immunodeficiency with HIV.
Case Description: 31-year-old male with idiopathic B cell lymphopenia and hypogammaglobulinemia was seen for initial consultation. His history included negative genetic testing (GeneDx) for pathogenic mutations in BTK, BLNK, CD79A, CD79B, IGLL1, LRRC8A, PIK3R1, TCF3, and immunoglobulin replacement therapy since childhood for hypogammaglobulinemia. He presented with chronic urethral discharge for more than one year. Given his high-risk sexual behavior and immunocompromised state, he was screened for sexually transmitted diseases, including HIV. His initial antigen-antibody screening test was noted to be positive prior to the initial visit. His HIV-1/HIV-2 antibody differentiation immunoassay was negative, as expected. Reflex testing to confirmatory qualitative HIV RNA NAT was positive. Screening tests were repeated during the initial consultation, one week after the initial positive screen. He again had negative HIV-1/HIV-2 antibody differentiation immunoassay but had positive antigen-antibody immunoassay and confirmatory HIV RNA NAT. He is currently receiving highly active antiretroviral therapy, including bictegravir, emtricitabine, and tenofovir alafenamide, and has an undetectable HIV-1 viral load.
Conclusion: Early detection of HIV is critical in reducing patient mortality and transmission. However, use of third generation antibody-based point-of-care tests, often performed in emergency room or clinics with low likelihood of follow-up, may result in false negative results, especially with patients with a pre-existing B cell immunodeficiency because they cannot make appropriate antibodies against infections. Use of fourth generation HIV screening assays, and NAT testing is essential to diagnose HIV-1 in these patients.

Keywords: Secondary T cell immunodeficiency, primary B cell immunodeficiency, Human Immunodeficiency Virus, HIV, hypogammaglobulinemia, third generation antibody-based point-of-care tests, fourth generation HIV screening

Disclosures: All authors indicated they had no financial relationships to disclose.

(115) Understanding attitudes and obstacles to vaccination against COVID-19 in patients with primary immunodeficiency

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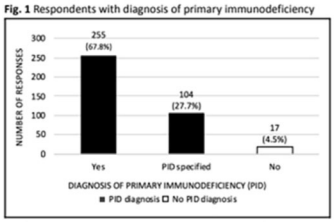
Background: Patients with primary immunodeficiency (PID) are at increased risk for infections such as SARS-CoV-2 (COVID-19), due to the nature of their diseases. At this time, four vaccines against COVID-19 (Pfizer-BioNtech's Comirnaty ®, Moderna's Spikevax ®, AstraZeneca's Vaxzevria®, Johnson & Johnson's Janssen ®) have been approved for use by Health Canada. Due to the novelty of these vaccines, clinical studies in patients with PID are ongoing. Despite limited evidence, Canada's National Advisory Committee on Immunization (NACI) recommend that patients with PID without any contraindications should be vaccinated with any of the approved vaccines as the potential benefits of being immunized against the virus likely outweigh the risks of contracting a severe infection. The aim of this study was to understand the perceptions regarding COVID-19 vaccination among patients with PID and to identify specific factors related to vaccine hesitancy.
Methods: The Canadian Immunodeficiencies Patient Organization (CIPO) conducted an online survey of its members to evaluate uptake of the COVID-19 vaccines by patients with PID. Data was collected using a self-administered online questionnaire. The survey was conducted between March and April 2021.
Results: At the time of survey, among 370 respondents who had not received the COVID-19 vaccine, 302 respondents (81.6%) indicated they were very or somewhat likely to get vaccinated against COVID-19; and 68 respondents (18.4%) indicated they were somewhat or very unlikely, undecided, or not planning to get vaccinated. A large majority of respondents indicated they had a diagnosis of PID (67.8%) and/or specified their type of PID (27.7%). The most common reason for vaccine hesitancy was due to uncertainty about immune response given an underlying immunodeficiency. Other concerns included unknown long-term side effects of COVID-19 vaccination, pre-existing history of allergic reactions, limited amount of data, lack of investigation of safety and effectiveness of COVID-19 vaccines in those with medical conditions, and skepticism of the underlying science and/or the medical system.
Conclusions: The results point to the importance of ongoing patient outreach, education, and up-to-date information on the rapidly evolving scientific knowledge and evidence on COVID-19 relevant to the PID community, from clinical trials to real-world evidence and observational studies.

Understanding attitudes and obstacles to vaccination against COVID-19 in patients with primary immunodeficiency

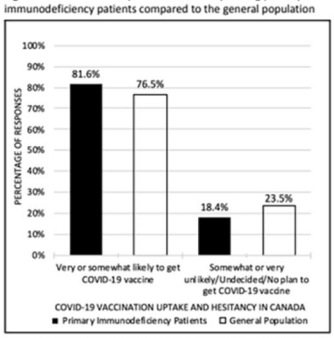
Figures

Fig. 1 Respondents with diagnosis of primary immunodeficiency



Data from COVID-19 Vaccine Hesitancy Survey in Primary Immunodeficiency Patients, March 24 to April 7, 2021

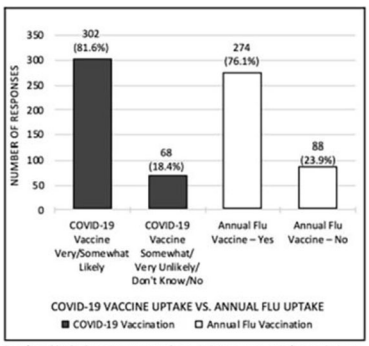
Fig. 2 COVID-19 vaccine uptake and hesitancy among primary immunodeficiency patients compared to the general population



Data from COVID-19 Vaccine Hesitancy Survey in Primary Immunodeficiency Patients, March 24 to April 7, 2021

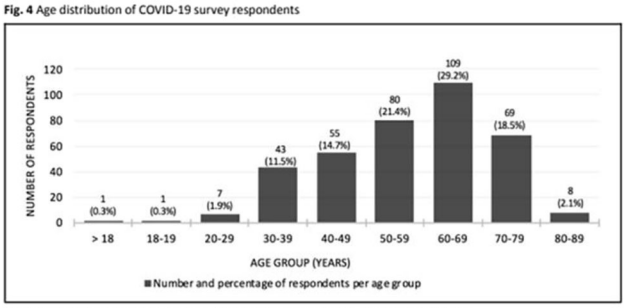
Fig. 3 COVID-19 vaccine uptake vs. annual flu vaccine uptake

Tables illustrating Understanding attitudes and obstacles in COVID-19 vaccination in PI patients



Data from COVID-19 Vaccine Hesitancy Survey in Primary Immunodeficiency Patients, March 24 to April 7, 2021

Fig. 4 Age distribution of COVID-19 survey respondents



Data from COVID-19 Vaccine Hesitancy Survey in Primary Immunodeficiency Patients, March 24 to April 7, 2021
One respondent also provided their child's age, therefore, while there were 372 respondents, age group calculations are based on 373 responses.
One respondent gave a non-specific age (>18).

Chart 1 illustrating Understanding attitudes and obstacles to COVID-19 vaccine in PI patients

Table 1:

Timeline of COVID vaccination, IV IgG infusion and COVID-19 serology in an immunosuppressed patient

Timeline of events	Date of 1st BNT162b2 vaccine	Date of 2nd BNT162b2 vaccine	Labs	Date of 3rd BNT162b2 vaccine	IV IgG	Labs	Repeat labs	IV IgG	Repeat labs
	3/16	4/6	5/4 & 6/1	8/18	8/26	9/8	9/21	9/23	10/19
Anti-NC[1]			Negative			Positive	Negative		Positive
Anti-Spike			Negative			Positive	Positive		Positive
Anti-spike Quant U/ml			<0.40			5.5	3.7		4.6
PCR test		Negative							
Neutralizing antibodies									Negative

[1] Nucleocapsid antigen

Chart 2 illustrating Understanding attitudes and obstacles to COVID-19 vaccination in PI patients

Keywords: COVID-19, SARS-CoV-2, immune response, immunocompromised, immunosuppressed, primary immunodeficiency, vaccination, vaccine hesitancy

Disclosures: All authors indicated they had no financial relationships to disclose.

(116) Limitations of COVID vaccine serology testing in patients receiving supplemental IgG therapy

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Introduction: Immunosuppression, either with primary or secondary immunodeficiency states is a high-risk category for COVID-19 infection and its complications. Two doses of COVID-19 mRNA vaccine may not able to produce and sustain desired humoral response to in many of these patients. Booster or 3rd dose of vaccine is approved for immunosuppressed patients which can be given after 28 days of 2nd dose. Preliminary data is supportive of increased humoral response after 3rd dose of COVID-19 mRNA vaccine in immunosuppressed patients. However, it is unclear if supplemental IgG therapy affects humoral immune responses to COVID-19 vaccination either due to pre-existing or cross reaction antibodies against SARS-CoV-2. Methodology: We present a case study of 65yr of immunosuppressed female who was on Mycophenolate, Belatacept and Prednisone after 2nd renal transplant in 2016 in setting of chronic kidney disease. She had secondary hypogammaglobinemia and was receiving IV IgG at the dose of 25 grams every 4 weeks. She had no evidence of seroconversion following the two doses of BNT162b2 vaccine. After her 3rd dose of BNT162b2 vaccine, we tested serial titers of COVID spike and nucleocapsid antibodies. Results: She received her booster of BNT162b2 vaccine on August 18th 2021 and 2 weeks later, antibodies to both SARS -CoV-2 Nucleocapsid and spike proteins antigen were detected. COVID Serology was repeated after 2 weeks and interestingly, antibodies to nucleocapsid antigen disappeared and antibodies to Spike protein started trending down. COVID serology was again repeated after her next IV IgG and she was again tested positive for both nucleocapsid and spike proteins. So, we hypothesized that these inconsistent results were likely due to passive transfer of antibodies from seropositive IV IgG sample. In order to decipher if these antibodies were protective vs cross reaction antibodies, we proceeded with neutralizing antibodies testing. Neutralizing antibodies came back negative which suggests the passive

transfer of cross reacting antibodies rather than active antibody production in immunosuppressed patients secondary to COVID booster. Conclusions: Interpretation of humoral response to the COVID vaccine in the immunosuppressed patients on supplemental IgG therapy is challenging and interference of passive antibodies from IgG therapy cannot be ignored.

patient ID number	clinical phenotype	mutation	inheritance	functional prediction	reported pathology associated with mutation
94	athritits, fever, hemolytic anemia, myositis, and encephalitis, diagnosed with lupus	**TNFAIP3,** (464C>T, Thr155Met)	heterozygous, autosomal dominant	VUCS	haploinsufficiency of A20: can cause inflammatory phenotypes such as Behcets and lupus
98	progressive neurologic decline with demyelination and elevated inflammatory markers	ACOX1 (detected on prior testing)		dominant gain of function	adrenoleukodystrophy, demyelination
144	periodic fever, joint swelling, rash, poor weight gain	**MEFV** (1337A>C, Glu446Ala)	heterozygous, autosomal dominant	VUCS, not reported before	Familial Mediterranean Fever
146	unexplained fever, inflammatory bowel disease, autoimmune hypothyroidism, arthritis, rash, and mouth sores	**MVK** (c.417dup)	heterozygous, autosomal dominant	frame shift, predicted pathogenic	Hyper IgD Syndrome
194	periodic fever, joint pain, lymphadenopathy, mouth ulcers, and GI bleeding	**MVK** (1129G>A, Val377Ile)	heterozygous, autosomal dominant	pathogenic--most frequent variant noted in patients with Hyper IgD Syndrome	Hyper IgD Syndrome
219	periodic fever, joint pain, multiple episodes of MAS and HLH	**PRF1** (272C>T, Ala91Val) **STX11** (650T>A, Leu217Gln)	PRF1- heterozygous, autosomal recessive; STX11- heterozygous, autosomal recessive	PRF1- VUCS, likely disease modifier; STX11- likely pathogenic	PRF1 and STX11 are both linked to familial HLH
1084	periodic fever, hip pain, abdominal pain, and elevated inflammatory markers	**NOD2** (2722G>C, Gly908Arg)	heterozygous, autosomal dominant	risk factor, suggested pathogenic	Blau syndrome-granulomatous arthritis, uveitis, and early onset sarcoidosis
1089	periodic fever, rash, oral ulcers, and CNS involvement	**COPA** (2537_2542 del, Ile846_Asp 847del) **PRF1** (272C>T, Ala91Val)	COPA- heterozygous, autosomal dominant; PRF1- heterozygous, autsomal recessive	COPA- VUCS, not reported before; PRF1- Risk factor	COPA- mutations associated with autoinflammatory disease associated with type I interferon signaling; PRF1- associated with familial HLH
1086	periodic fever, vasculopathic skin rash, digital necrosis, periodic MAS episodes	**TMEM173/ STING1** (439G>C, Val147Leu)	heterozygous, autosomal dominant	likely pathogenic, this variant reported in STING vasculopathy	infantile-onset STING vasculopathy: affects type I interferon signaling and affected patients develop interstitial lung disease and cutaneous vasculopathy
1649	recurrent fever, lymphadenopathy, mouth sores, leg pain, and history of recurrent otitis and sinusitis	**TRNT1** (668T>C, Ile223Thr)	heterozygous, autosomal recesseive	reported pathogenic variant	obesrved in patients with sideroblastic anemia, B-cell immunodeficiency, and periodic fever
1654	recurrent fever, rash, and leg pain, elevated inflammatory markers	**CFI** (658+1G>A)	heterozygous, autosomal dominant, autosomal receeive	pathogenic--this mutation disrupts the splice site of intron 4	mutations associated with atypical HUS, glomerulonephritis, autoimmune disease, and recurrent bacterial infections
1085	systemic JIA with history of macrophage activation syndrome	**STXBP2** (1089G>C, Lys363Asn)	heterozygous, autosomal recesseive	not reported, conflicting functional predictions	associated with familial HLH

Keywords: Immunosuppressed patients, IgG Therapy, COVID vaccine booster, BNT162b2 vaccine, Anti spike antibodies, Anti nucleocapsid antigen (NC) antibodies, COVID serology

Disclosures: All authors indicated they had no financial relationships to disclose.

(117) Investigating the Genetic Basis of SURFS and MAS Using An Exome Slice Approach

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Objective: Children with autoinflammatory disorders including systemic undefined recurrent fever syndrome (SURFS) and macrophage activation syndrome (MAS) often lack a genetic diagnosis. We sought to define the utility of an "exome slice" approach to examine the genetic basis of patients with SURFS and/or MAS.
Methods: 37 patients less than 18 years of age with the diagnoses listed above were enrolled in this IRB-approved study and genetic samples were obtained after an informed consent process. Targeted exome sequencing was performed for 394 genes implicated in known inflammatory disorders as well as primary immunodeficiency syndromes. Variants within exons and the flanking sequences were evaluated using an in-house bioinformatics pipeline including GATK3.5 and Alamut Batch 1.4.4 software.
Results: This exome slice approach detected likely diagnostic variants in 8/33 patients with SURFS and/or MAS. We assessed these variants as likely diagnostic based on functional predictions or significant overlap between the patient's clinical phenotype and reported cases in the literature (Figure 1). Variants in this cohort involved known monogenic causes of periodic fever syndromes (MEFV, MVK), genes implicated in cases of familial HLH (PRF1, STX11, and STXBP2), and mediators of interferon signaling (COPA, STING1). We also identified and characterized a list of variants of uncertain significance which were never reported in the Human Gene Mutation Database (HGMD) or had conflicting in silico functional predictions (Figure 2). Variants in this cohort again involved known autoinflammatory genes (MEFV (2) and NOD2), as well as genes associated with familial HLH (PRF1, STXBP2, and AP3B1). Notably, however, numerous patients in this cohort carried variants in genes implicated in autoimmunity and immunodeficiency (BACH2 (2), IL2RA (2), CD3E, TPP2, CIITA, TNFRSF13B, DOCK2). Finally, as validation, we found that this approach identified and confirmed known mutations (MVK (2), MEFV, and STING1) in four patients with defined autoinflammatory disorders.
Significance: This report demonstrates the ability of an "exome slice" approach to identify potentially significant genetic variants in a cohort of children with SURFS and/or MAS. The genetic landscape of these autoinflammatory patients includes genetic variants in known periodic fever genes, genes associated with familial HLH, and variants involved with immunodeficiency.

patient ID number	clinical phenotype	mutation	inheritance	functional prediction	reported pathology associated with mutation
90	rash and recurring fever, elevated LFTs, diarrhea, leukocytoclastic vasculitis, response to canakinumab	**TTC7A** (1583C>T, Ala528Val)	heterozygous	never reported, predicted benign	associated with very early onset IBD and combined immunodeficiency
92	systemic JIA and episodes of MAS	**PRF1** (A91V), **MEFV** (P369S and R408Q)	heterozygous	predicted benign	PRF1: mutations in this gene associated with familial HLH; MEFV: associated with familial mediterranean fever
93	periodic fever, ankle pain and swelling, rash, and seizure	**IRF2BP2** (392C>G, Ser131Cys)	heterozygous, autosomal dominant	conflicting predictions	this gene is involved in IFN signaling through JAK-STAT pathway, mutation in this gene reportedly linked to inflammatory conditions in one family
193	systemic JIA with episodes of MAS	**CD3E** (103+ 1 G>A)	heterozygous, autosomal recessive	predicted to destroy splice site of intron 5	CD3E encodes component of T cell receptor, associated with severe combined immunodeficiency
195	periodic fever, joint pain, lymphadenopathy, mouth ulcers, and GI bleeding, clinical response to canakinumab	**BACH2** (92G>A, Arg31Gln)	heterozygous, autosomal dominant	high amino acid conservation, conflicting functional predictions	encodes a transciption factor in T cells and B cells; mutations linked to immunodeficiency and defective Tregs
220	periodic fevers, mouth ulcers and rash, clinical response to colchicine	**TPP2** (124G>C, Val42Leu)	heterozygous, autosomal recessive	never reported; prediced benign	gene involved in HLA/antigen complex processing; mutations in this gene linked to autoimmunity and immunodeficiency
222	periodic fever and hemolytic anemia	**IL2RA** (83C>T, Pro28Leu)	heterozygous, autosomal recessive	never reported; conflicting predictions	forms part of the IL-2 receptor; mutations in this gene linked to autoimmunity and lymphoproliferation, affects on Treg function
1083	clinical phenotype of Behcet's disease with mouth and genital ulcers, leukocytoclastic vasculitis	**PEPD** (388G>T, Asp130Tyr); **CF1** (37T>G, Phe13Val)	PEPD: heterozygous, autosomal recessive; CF1: heterozygous, autosomal recessive	PEPD: not reported, conflicting predictions; CF1: suggested benign	PEPD (prolidase) deficiency linked to recurrent skin ulcers and CF1 mutations associated with leukocytoclastic vasculitis
1087	recurrent fever, joint pain, abdominal pain, clinical improvement with colchicine	**CIITA** (1310G>C, Trp437Ser)	heterozygous, autosomal recessive	never reported; predicted deleterious	encodes transcriptional regulatory factor for MHC class II, mutations linked to bare lymphocyte syndrome
1090	periodic fever with lip and tongue swelling, clinical improvement with anakinra	**AP3B1** (1651C>T); **IL2RA:** (484G>A, Gly162Ser)	AP3B1: heterozygous, autosomsal recessive; IL2RA: heterozygous, autosomal recessive	AP3B1: not reported, conflicting predictions; IL2RA: not reported, suggested benign	AP3B1: associated with HLH, also involved in pulmonary fibrosis; IL2RA: forms one of the components of the IL-2 receptor, mutations linked to autoimmunity and immunodeficiency
1393	ITP, neutropenia, autoimmune hepatitis, and interstitial lung disease	**COPA** (2602G>T, Val868Leu	heterozygous, autosomal dominant	not reported, suggested benign	COPA syndrome associated with autoinflammatory interstitial lung disease and arthritis; associated with STING pathway interferon signaling
1394	periodic fever, sore throat, tonsilitis, developed oral and genital ulcers and diagnosed with incomplete Behcet's	**BACH2** (332G>A, Arg111His)	heterozygous, autosomal dominant	not reported, uncertain predictions	transcription factor in T cells and B cells, causes immunodeficiency with defects in Tregs
1395	recurrent fever episodes and associated abdominal pain	**MEFV** (1382G>A, Arg461Gln)	heterozygous, autosomal dominant or recessive	not reported, suggested benign	mutations in this gene linked to Familial Mediterranean Fever
1396	recurrent fever begininning in infancy, joint pain, abdominal pain, and rash, clinical improvement with colchicine	**TNFRSF13B** (310T>C, Cys104Arg), **STXBP2** (1586G>C, Arg529Pro)	TNFRSF13B: heterozygous, autosomal dominant or recessive; STXBP2: heterozygous, autosomal recessive	TNFRSF13B: this variant reported in patients with CVID, suggested pathogenic; STXBP2: reported along with variant in PRF1 in patient with HLH, predictions uncertain	TNFRSF13B: involved in plasma cell differentiation, mutations reported in CVID and IgA deficiency; STXBP2: associated with HLH
1651	periodic fevers, arthralgia, headache, abdominal pain, elevated inflammatory markers, clinical repsonse to colchicine	**CASP8** (151+3G>A); **DOCK2** (2680G>A, Glu894Lys)	CASP8: heterozygous, autosomal recessive; DOCK2: heterozygous, autosomal recessive	CASP8: not reported, suggested benign; DOCK2: not reported, uncertain prediction	CASP8: mutations linked to ALPS with lymphadenopathy and immunodeficiency; DOCK2: associated with combined immunodeficiency and severe viral infections
1652	periodic fever, poor appetite, lymph node enlargement	**NOD2** (1190C>T, Pro397Leu)	heterozygous, autosomal dominant	not reported, uncertain predictions	associated with Blau syndrome, granulomatous arthritis, Crohns disease
1675	CRMO and psoriasis, clinical improvement with NSAIDS	**LYST** (1829A>T, His610Leu)	heterozygous, autosomal recessive	not reported, uncertain predictions	associated with Chediak-Higashi syndrome, disrupted lysosomal trafficking, immunodeficiency and HLH

Figure 1: Likely diagnostic mutations were detected in 8/33 patients. Mutations were determined to be likely diagnostic based on functional predictions or overlap between the patient's phenotype and reported cases in the literature.

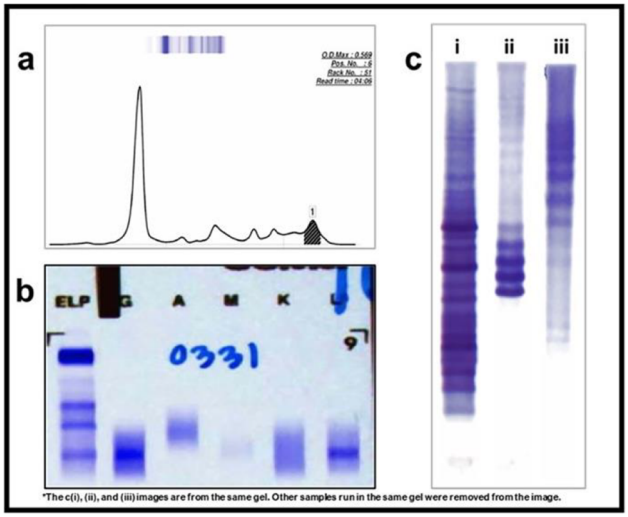

Figure 2: Variants of uncertain significance in genes implicated in autoimmunity and immunodeficiency, known autoinflammatory syndromes, and familial HLH.

Keywords: systemic undefined recurrent fever syndrome (SURFS), macrophage activation syndrome, autoinflammation, genetic testing

Disclosures: Alexei Grom has relevant financial relationships with proprietary interests with Novartis (Advisory Board, Contracted Research) and Sobi (Consultant, Contracted Research). Grant Schulert has relevant financial relationships with proprietary interests with Novartis (Consultant, Speaker/Honoraria includes speakers bureau, symposia, and expert witness). All other authors indicated they had no financial relationships to disclose.

(118) T-cell Lymphopenia in a Patient with a Heterozygous Deletion of CORO1A

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Introduction: Coronin 1A is an actin regulatory protein encoded by coronin 1A gene (CORO1A) on chromosome 16p11.2. It is involved in T-cell homeostasis, natural-killer cells cytotoxicity and calcium-calcineurin signaling. Coronin 1A deficiency is a rare autosomal recessive primary immunodeficiency. Complete absence of the proteins causes T-B+NK+ severe combined immunodeficiency (SCID) while hypomorphic variants result in extensive naïve T cells defect and susceptibility to EBV-associated B cell lymphoproliferation. Deletion of chromosome 16p11.2 was reported to cause SCID in one patient with a concomitant truncated variant in CORO1A. Literature on carriers of these variants is scarce with few reports identifying CD4 T-cell lymphopenia. We report an infant with heterozygous deletion of COROA1 and significant CD3, CD4 and CD8 lymphopenia.
Case: A 1-year-old female was referred at 12 days of age for abnormal T-cell Receptor Excision Circle (TREC) screen. She was born full term after

an uncomplicated pregnancy to non-consanguineous parents, and noted to be small for gestational age (SGA). Newborn screen showed abnormal TREC values 81,128,45,0,80,116, average 75/μl. Patient has dysmorphic facies and was SGA, but growing well. History, review of systems, and exam were otherwise unremarkable. Lymphocyte subsets showed low CD3(1170 cell/uL), CD4(823 cells/uL) and CD8(326 cells/uL). CD19, NK cell count, CD45RA, CD45RO, alpha fetoprotein levels, mitogens and antigens testing were normal. Chromosomal microarray detected a 727 kb deletion of 16p11.2. Invitae's primary immunodeficiency panel revealed a heterozygous pathogenic gross deletion encompassing exons 1 to 10 of the COROA1 gene, and 11 variants of uncertain significance not thought to be correlated. The patient was monitored closely and remained asymptomatic with no major infections or recurrent fevers. Immunological work up repeated every 2-3 months showed persistent but stable CD3, CD4 and CD8 lymphopenia, with low normal immunoglobulins but protective antibody titers. Parents deferred whole exome sequencing.
Conclusion: To our knowledge, this is the first case reported in literature with heterozygous deletion of CORO1A and significant T-cell lymphopenia. Our case suggests that carriers of COROA1 deletion may have objective clinical findings, albeit unknown risk of infections or long-term prognosis.

Keywords: T-cell lymphopenia, CORO1A, Chromosome 16 microdeletion, Immune deficiency, Coronin, SCID, TREC

Disclosures: All authors indicated they had no financial relationships to disclose.

(119) T-cell Functions are impaired in NDUFS4-related Leigh syndrome: Revisiting Primary Mitochondrial as Primary Immune Deficiency Disorders

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Purpose: High rates of infections are seen in patients with primary mitochondrial disorders (MD) and attributed to their neurological disabilities. Since mitochondria play a central role in T-cell immunity, we hypothesized that these patients might also be immunodeficient. Herein, we aimed to explore the development and function of T cells from patients with primary MD.
Methods: Peripheral blood mononuclear cells of 3 patients with MD were immunophenotyped using flow cytometry. Functional T-cell properties were evaluated following an in vitro activation with α-CD3/CD28 by measuring interferon γ (IFNγ) production, elevation of CD25 surface expression, and proliferation. Mitochondrial integrity and functions were evaluated in effector T cells by measuring their oxygen consumption rate (OCR) using Seahorse analysis, mitochondrial DNA content using semi-quantitative (sq) RT-PCR, and mitochondrial membrane potential by tetramethylrhodamine methyl ester (TMRM) staining.
Results: One patient, a 10-year-old male with NADH:ubiquinone oxidoreductase iron-sulfur protein 4 (NDUFS4)-related Leigh syndrome, presented with recurrent infections and was found to have reduced effector memory CD4+ and CD8+ T cells, as well as impaired T-cell activation and proliferation. sqRT-PCR revealed high mitochondrial DNA content, suggesting increased mitobiogenesis. OCR and TMRM staining were not reduced, indicating a metabolic bypass to complex I. In contrast, in 2 patients with variants in mitochondrially encoded tRNA leucine 1 (MT-TL1; ages 65 and 39 years), T-cell activation and proliferation were comparable to those of healthy controls.
Conclusion: T-cell–mediated immunity can be impaired in NDUFS4-related Leigh syndrome. Therefore, an immune workup should be considered when treating these patients.

Keywords: Immunometabolism, Leigh syndrome, NDUFS4, T cells, Mitochondria, Electron transfer chain.

Disclosures: All authors indicated they had no financial relationships to disclose.

(120) Resolving the Dilemma of Monoclonality in IgG4-Related Disease using Isoelectric Focusing

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Elevated IgG4 can be seen in both IgG4-related disease (IgG4-RD) and in monoclonal gammopathies (MG). While IgG4-RD is polyclonal, MG is defined by the presence of a monoclonal immunoglobulin (M-protein/M-spike) detected by serum capillary protein electrophoresis (SPEP) and immunofixation electrophoresis (IFE). In rare instances, IgG4-RD may have an apparent M-spike by SPEP; however, the increased staining in the gamma region could be attributed to polyclonal increase in IgG4 and skewed light chain ratios. Therefore, further laboratory testing is required to resolve this diagnostic dilemma.
Here, we discuss a case of a 27-year-old male who presented with periorbital inflammation and edema of the left eyelid, cheek, and face. Fine needle aspiration cytology showed lymphoplasmacytic infiltrates with no signs of malignancy, and lab results demonstrated a skewed IgG4/IgG ratio (>40%) with elevated IgG4 (231mg/dL; Ref Interval 1-123mg/dL), suggesting IgG4-RD. Strikingly, the patient showed M-protein (0.62 g/dL) on SPEP, characterized as IgG-lambda isotype by IFE, indicating monoclonal gammopathy of unknown significance (MGUS). Considering a significant difference in management of two

diseases, it was important to rule out a rare overlap of the IgG4-RD and MGUS in this patient.

To further characterize the M-spike protein, the sample was analysed by isoelectric focusing electrophoresis followed by staining for IgG (IEF). IEF of the IgG proteins is a high resolution, inexpensive, commonly available method in clinical laboratories and routinely used to screen for unique bands of IgG in the CSF in patients suspected to have multiple sclerosis. For our patient, the IEF assay of the serum sample showed multiple bands present, a pattern not consistent with M-protein and hence excluded MGUS. (Figure 1) Given these findings, the patient was treated with prednisolone, since glucocorticoids are used to treat IgG4-RD, and that essentially resolved his clinical symptoms and returned IgG4 levels to normal within two months.

Overall, our study indicates the effectiveness of the IEF assay in resolving the ambiguous result of SPEP and IFE assays. This case report suggests that IEF assay can be used as a complementary investigation tool in patients with IgG4-RD if a monoclonal protein is suspected.

Table. Infusion and dosing parameters at 12 months post-initiation

Parameter[a] *Median (IQR) unless otherwise stated*	Infusion pump (n=65)	Manual administration (n=42)
Infusion volume/infusion, mL	43 (40–60)	30 (20–40)
Infusion duration, minutes	60 (45–73)	24 (10–40)
Number of infusion sites/infusion, n (%)		
1 site	1 (1.7)	9 (33.3)
2 sites	32 (53.3)	17 (63.0)
3 sites	16 (26.7)	0 (0)
>3 sites	11 (18.3)	1 (3.7)
Maximal infusion rate/site, mL/h	40.0 (34.0–59.0)	–
Weekly dose, g	8.0 (6.0–10.0)	8.0 (6.0–8.0)
Dosing interval, n (%)		
Daily	0	0
2–6 times/week	2 (3.1)	17 (40.5)
Once weekly	56 (87.5)	25 (59.5)
Every 2 weeks	4 (6.3)	–
Other	2 (3.1)	–

[a]n value for each parameter is presented based on available data and percentages are calculated as a proportion of those values.
IQR, interquartile range.

Figure-1 Results of different assays run for patient with IgG4-RD a. Serum capillary electrophoresis (SPEP), b. Immunofixation electrophoresis, and c. Isoelectric focusing (IEF) showing banding pattern of c(i). polyclonal control sample, c(ii). a patient with known M-Protein, c(iii). the current patient with IgG4-Related disease (IgG4-RD).

Keywords: Immunoglobulin G4-related disease (IgG4-RD), Isoelectric focusing electrophoresis (IEF), monoclocnal protein (M protein), M-Spike, Serum protein electrophoresis (SPEP), Immunofixation electrophoresis (IFE)

Disclosures: All authors indicated they had no financial relationships to disclose.

(121) 4WHIM: Evaluating the Oral CXCR4 Antagonist Mavorixafor in Patients With WHIM Syndrome via a Global Phase 3, Randomized, Placebo-Controlled Trial With Open-label Extension

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Warts, Hypogammaglobulinemia, Infections, Myelokathexis (WHIM) syndrome is a primary immunodeficiency classically caused by gain-of-function mutations in CXCR4, leading to dysregulated immune cell maturation and trafficking. This causes retention of leukocytes in the bone marrow (myelokathexis), resulting in neutropenia, leukopenia, and sometimes, hypogammaglobulinemia. Patients with WHIM syndrome experience recurrent sinopulmonary infections and unusual susceptibility to human papillomavirus (HPV), causing predisposition to warts and malignancy. All management strategies are symptomatic only, do not address the underlying mechanism of WHIM syndrome, and are not effective for HPV infections. Mavorixafor is an investigational, oral CXCR4 antagonist that directly inhibits CXCR4-enhanced signaling in WHIM disease pathogenesis. It has been shown to increase white blood cell counts, decrease annualized infection rate, and reduce cutaneous warts in patients with WHIM syndrome in an open-label phase 2 clinical trial (NCT03005327). Here, we describe the design and current status of 4WHIM, a global, phase 3, double-blind, placebo-controlled, randomized trial (NCT03995108) with open-label extension evaluating the safety and efficacy of mavorixafor in patients with WHIM syndrome.

Patients aged ≥12 years with WHIM, a confirmed CXCR4 mutation, and absolute neutrophil count (ANC) ≤400 cells/μL without clinical evidence of active systemic infection were eligible for enrollment. Patients were randomly assigned in a 1:1 ratio to receive mavorixafor or placebo once daily. The primary endpoint is number of hours above ANC threshold (500 cells/μL) over a 24-hour period, assessed every 3 months for 52 weeks. Secondary endpoints include composite endpoint of infection and warts, infection rates and severity, change from baseline in cutaneous warts, number of hours above absolute lymphocyte count of 1000 cells/μL over a 24-hour period, and patient-reported quality of life assessment using age-appropriate questionnaires.

Trial enrollment is complete with 31 patients from 12 countries; 48% of participants are adolescents, 42% are male, 71% have warts, 81% have nonsense CXCR4 mutations, while 19% have frameshift CXCR4 mutations.
This is the first double-blind, placebo-controlled, randomized trial in patients with WHIM syndrome. It represents an important next step in the development of mavorixafor, an orally bioavailable targeted therapy. Top-line clinical results are expected in Q4 2022.

Keywords: primary immunodeficiency, clinical trial, WHIM syndrome, randomized, myelokathexis, neutropenia, CXCR4

Disclosures: David Dale has relevant financial relationships with proprietary interests with X4 Pharmaceuticals (Consultant, Research Grant includes principal investigator, collaborator or consultant and pending grants as well as grants already received, Speaker/Honoraria includes speakers bureau, symposia, and expert witness). Antoine Azar has relevant financial relationships with proprietary interests with ArgenX (Advisory Board), Grifols (Speaker/Honoraria includes speakers bureau, symposia, and expert witness), Optinose (Advisory Board), Regeneron (Consultant), and X4 (Consultant, Contracted Research). Raffaele Badolato has relevant financial relationships with proprietary interests with Angelini (Consultant), Janssen (Consultant), and X4 Pharmaceuticals (Consultant). Yves Bertrand has relevant financial relationships with proprietary interests with Jazz Pharmaceuticals (Advisory Board), Novartis (Advisory Board), Sanofi Genzyme (Speaker/Honoraria includes speakers bureau, symposia, and expert witness), and Servier (symposium) (Speaker/Honoraria includes speakers bureau, symposia, and expert witness), Hyoung Jin Kang has relevant financial relationships with proprietary interests with Amgen (Advisory Board, Research Grant includes principal investigator, collaborator or consultant and pending grants as well as grants already received, Speaker/Honorariaincludes speakers bureau, symposia, and expert witness), Cartexell (Consultant), and Novartis (Advisory Board). Sorena Kiani-Alikhan has relevant financial relationships with proprietary interests with BioCryst (Advisory Board, Speaker/Honoraria includes speakers bureau, symposia, and expert witness), CSL Behring (Advisory Board, Speaker/Honoraria includes speakers bureau, symposia, and expert witness), KalVista (Advisory Board, Speaker/Honoraria includes speakers bureau, symposia, and expert witness), and Takeda (Advisory Board, Speaker/Honoraria includes speakers bureau, symposia, and expert witness). Alexander Kulagin has relevant financial relationships with proprietary interests with X4 Pharmaceuticals (Research Grant includes principal investigator, collaborator or consultant and pending grants as well as grants already received, To Pavlov University). Carina Levin has relevant financial relationships with proprietary interests with Emek Medical Center Pediatric Hematology (Research Grant includes principal investigator, collaborator or consultant and pending grants as well as grants already received). Olaf Neth has relevant financial relationships with proprietary interests with Carlos III (Research Grant includes principal investigator, collaborator or consultant and pending grants as well as grants already received). Anna Shcherbina has relevant financial relationships with proprietary interests with Novartis (Speaker/Honoraria includes speakers bureau, symposia, and expert witness), Octapharma (Speaker/Honoraria includes speakers bureau, symposia, and expert witness), Sobi (Speaker/Honoraria includes speakers bureau, symposia, and expert witness). Teresa Tarrant has relevant financial relationships with proprietary interests with Abbvie (Research Grant includes principal investigator, collaborator or consultant and pending grants as well as grants already received), ThermoFisher Scientific (Consultant), Viela Bio (Research Grant includes principal investigator, collaborator or consultant and pending grants as well as grants already received), and X4 Pharmaceuticals (Advisory Board, Consultant, Research Grant includes principal investigator, collaborator or consultant and pending grants as well as grants already received). Andrea Belschner has relevant financial relationships with proprietary interests with X4 Pharmaceuticals (Employment). Diego Cadavid has relevant financial relationships with proprietary interests with X4 Pharmaceuticals (Employment, Ownership Interest includes stock, stock options, patent or other intellectual property). Honghua Jiang has relevant financial relationships with proprietary interests with X4 Pharmaceuticals (Employment, Ownership Interest includes stock, stock options, patent or other intellectual property). Richard MacLeod has relevant financial relationships with proprietary interests with X4 Pharmaceuticals (Employment, Ownership Interest includes stock, stock options, patent or other intellectual property). Weihua Tang has relevant financial relationships with proprietary interests with X4 Pharmaceuticals (Employment, Ownership Interest includes stock, stock options, patent or other intellectual property). All authors indicated they had no financial relationships to disclose.

(122) Transitioning Subcutaneous Immunoglobulin 20% Therapies in Patients with Primary and Secondary Immunodeficiencies: a Canadian Real-World Study

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Objective: Real-world data on transitioning to Immune Globulin Subcutaneous (Human) 20% Solution (Ig20Gly) are limited. This study assessed infusion parameters and experience of patients with primary immunodeficiencies (PID) or secondary immunodeficiencies (SID) transitioning to Ig20Gly in clinical practice in Canada.
Design and Methods: Patients with PID or SID who received subcutaneous immunoglobulin (SCIG) for ≥3 months before transitioning to Ig20Gly were eligible for this multicenter (n=6), phase 4, noninterventional, prospective, single-arm study (NCT03716700). Ig20Gly infusion parameters, dosing and adverse events (AEs) were collected from patient medical records at Ig20Gly initiation and 3, 6 and 12 months post-initiation. Patient satisfaction and quality of life (QoL) were assessed 12 months post-initiation using validated questionnaires.
Results: The study included 125 patients (PID, n=60; SID, n=64; PID+SID, n=1) with a mean age of 62 years (range: 19–83 years). Median volume per infusion was 30 mL at initiation and 40 mL at 6 and 12 months post-initiation. Most patients administered Ig20Gly weekly (≥70%) and used two infusion sites, primarily the upper and lower abdomen. At each time point, median infusion duration was ≤1 hour, and interrupted or slowed infusions were rare (1.3%). Infusion parameters were generally similar between the PID and SID cohorts, although median infusion duration tended to be slightly longer among those with SID (60 vs 43 minutes at 12 months).
Headache and infusion site reactions were the most frequently reported AEs of interest* (4.8% and 4.0% of patients, respectively). Patients expressed overall satisfaction with Ig20Gly at 12 months post-initiation, with all respondents indicating they would like to continue Ig20Gly.
Conclusions: This study provides a detailed description of Ig20Gly infusion parameters, tolerability and QoL in clinical practice among patients with PID or SID switching to Ig20Gly from another SCIG, which are broadly consistent with previous findings from the Ig20Gly PID pivotal trials.
*Included AEs described as warnings and precautions in the product monograph, and those reported in previous trials and observed in post-marketing surveillance.

Baxalta US Inc. and Baxalta Innovations GmbH, a Takeda company, funded this study. Takeda Development Center Americas, Inc., funded writing support.

Keywords: Ig20Gly, immunoglobulin G, immunoglobulin replacement therapy, Primary immunodeficiency diseases, Quality of life, Real-world study, Secondary immunodeficiency diseases, Subcutaneous immunoglobulin

Disclosures: Paul Keith has relevant financial relationships with proprietary interests with ALK (Consultant), Aralez Pharmaceuticals (Consultant), AstraZeneca (Consultant, Research Grant includes principal investigator, collaborator or consultant and pending grants as well as grants already received), CSL Behring (Consultant, Research Grant includes principal investigator, collaborator or consultant and pending grants as well as grants already received), Genentech (Research Grant includes principal investigator, collaborator or consultant and pending grants as well as grants already received), GlaxoSmithKline (Consultant), Kaleo (Consultant), Merck (Consultant), Mylan (Consultant), Novartis (Consultant), Pediapharm (Consultant), Sanofi (Consultant), Shire (Consultant, Research Grant includes principal investigator, collaborator or consultant and pending grants as well as grants already received), and Stallergenes (Consultant). 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Amin Kanani has relevant financial relationships with proprietary interests with, Aralez Pharmaceuticals (Consultant), CSL Behring (Consultant), Genentech (Research Grant includes principal investigator, collaborator or consultant and pending grants as well as grants already received), Mylan (Consultant), Novartis (Consultant), Pediapharm (Consultant), Takeda Development Center Americas, Inc. (Consultant, Research Grant includes principal investigator, collaborator or consultant and pending grants as well as grants already received). 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(123) Manual Administration of Subcutaneous Immunoglobulin 20% in Clinical Practice in Patients with Immunodeficiencies

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Objective: Although subcutaneous immunoglobulin (SCIG) is typically administered via an infusion pump, manual administration using a syringe and butterfly needle has emerged as an alternative technique that may be preferred by some patients. This analysis of the CANCUN study (NCT03716700) evaluated manual administration of Immune Globulin Subcutaneous (Human) 20% Solution (Ig20Gly) in clinical practice in Canada.
Design and Methods: CANCUN was a noninterventional, multicenter (n=6), prospective study that enrolled patients with primary immunodeficiencies (PID) or secondary immunodeficiencies (SID) who had transitioned to Ig20Gly from another SCIG. Data on Ig20Gly infusion parameters, dosing and adverse events (AEs) were collected from patient medical records at Ig20Gly initiation and 3, 6 and 12 months post-initiation; patient satisfaction and quality of life (QoL) were assessed 12 months post-initiation. Data were analyzed according to whether patients infused Ig20Gly manually or using a pump.
Results: Of 125 patients enrolled, 61 had PID (mean age 55 years; includes 1 patient with PID and SID) and 64 had SID (mean age 69 years). Of these, 43% (n=54) infused Ig20Gly manually. Compared with patients using an infusion pump, patients infusing Ig20Gly manually did so at lower median infusion volume per infusion and shorter infusion duration, were more likely to use two or fewer infusion sites, and typically infused more frequently (Table). In both groups, the abdomen was the most common infusion site and the median weekly dose was 8 g. Manual administration tended to be used more frequently by patients with PID than those with SID (43% vs 35%). Most AEs were mild or moderate in severity. Patients in both groups expressed overall satisfaction with Ig20Gly at 12 months post-initiation, with all respondents indicating they would like to continue Ig20Gly. Patient-reported QoL outcomes were comparable between the two groups.
Conclusions: This real-world study confirms the feasibility and tolerability of infusing Ig20Gly manually or via a pump in patients with PID or SID.
Baxalta US Inc. and Baxalta Innovations GmbH, a Takeda company, funded this study. Takeda Development Center Americas, Inc., funded writing support.

Laboratory Evaluation of patient with MGUS following hospitalization for Severe COVID-19

Investigation	Result	Reference
White blood count	5.9 K/µl	4.0-10.5 K/µl
Hemoglobin	11.3 g/dL	12.5-16.0 g/dL
Platelets	473 K/µl	150-500 K/µl
Absolute neutrophil count	2.7 K/µl	2.3-6.7 K/µl
Absolute lymphocyte count	2.4 K/µl	0.8-3.2 K/µl
Absolute monocyte count	0.7 K/µl	0.4-0.9 K/µl
Absolute eosinophil count	0.2 K/µl	0.0-0.2 K/µl
Calcium	10.1 mg/dL	8.1-11.3 mg/dL
Alkaline phosphatase	135 U/L	32-92
Aspartate transaminase	28 U/L	10-40 U/L
Alanine transaminase	37 U/L	10-40 U/L
Creatinine	0.6 mg/dL	0.5-1.3 mg/dL
Total Protein	7.6 g/dL	6.5-8.1 g/dL
Albumin	4.5 g/dL	3.5-5.0 g/dL
High sensitivity C-reactive protein	0.76 mg/dL	0.0-0.4 mg/dL
Sedimentation rate	26 mm/hr	0-30 mm/hr
C3	74 mg/dL	66-162 mg/dL
C4	10.2 mg/dL	19.0-52.0 mg/dL
Alternative pathway (AH50)	104 U/mL	77-159 U/mL
Classical pathway (CH50)	101 U/mL	176-382 U/mL
IgG	1352 mg/dL	700-1620 mg/dL
IgA	43 mg/dL	50-462 mg/dL
IgM	80 mg/dL	44-266 mg/dL
IgE	2.27 kU/L	0-100 kU/L
IL-6	2.9 pg/mL	<2.0 pg/mL
IL-12	<3.20 pg/mL	0.00-8.40 pg/mL
TNFα	12.93 pg/mL	0.00-22.30 pg/mL
IL-2	<3.20 pg/mL	0.00-60.80 pg/mL
IFNγ	<3.20 pg/mL	0.00-24.10
Tetanus antitoxoid	1.06 IU/mL	>0.10 IU/mL
Varicella Zoster IgM	0.45 ISR	<0.90 ISR
CMV PCR	Not Detected	Not Detected
HIV-1 NAAT	Not Detected	Not Detected
EBV VCA Ab (IgM) EBV VCA Ab (IgG) EBV EBNA Ab (IgG)	<36.00 U/mL 375.00 U/mL 118.00 U/mL	<36.00 U/mL <36.00 U/mL <36.00 U/mL
Streptococcus pneumonia IgG 23 serotypes	3/23 protective	>1.3 µg/mL
Haemophilus influenza type b IgG	0.53 µg/mL	>1.00 µg/mL
Semi-quant spike COVID 19 IgG	47.8 RU/mL; 153.0 BAU/mL	Positive >11 RU/mL; >35.2 BAU/mL
DHR oxidative burst	68.2	>30
B lymphocyte quantification		
CD19 %	4.9%	6.3-20.0%
CD19 Absolute	116 cells/µl	96-515 cells/µl
CD27+/IgD+ (unswitched)	0.7%	3.8-52.7%
CD27+/IgD- (switched)	1.1%	1.9-30.4%
CD27-/IgD+ (naïve)	97.2%	24.4-90.6%
CD38hi/IgMhi (transitional)	19.2%	0.3-9.2%
CD38hi/IgMlo (plasmablasts)	0.2%	0.1-4.7%
CD38lo/CD21lo (immature)	2.7%	0.5-8.0%
T lymphocyte quantification		
CD3%	86.5%	62.0-88.0%
CD3 Absolute	2052 cells/µl	678-2504 cells/µl
CD4%	65.3%	35.3-61.1%
CD4 Absolute	1549 cells/µl	414-1679 cells/µl
CD8%	21.9%	11.2-37.3%
CD8 Absolute	519 cells/µl	162-1038 cells/µl
CD4+/CD45RA+ (naïve)	22.4%	32-73%
CD4+/CD45RO+ (memory)	77.4%	29-63%
NK cell quantification		
CD16/56%	7.6%	3.2-23.7%
CD16/56 Absolute	180 cells/µl	45-523 cells/µl
Functional testing		
Lymphocyte stimulation	Normal response to Candida Low response to Tetanus	
CD40 Ligand assay	Normal expression	
Th1 (IFNγ)	20.4%	>5.3%
Th17 (IL-17+)	0.5%	>0.3%

Keywords: Ig20Gly, immunoglobulin G, immunoglobulin replacement therapy, infusion pump, Manual administration, Primary immunodeficiency disease, Quality of life, Real-world study, Secondary immunodeficiency disease, Subcutaneous immunoglobulin

Disclosures:Paul Keith has relevant financial relationships with proprietary interests with ALK (Consultant), Aralez Pharmaceuticals (Consultant), AstraZeneca (Consultant, Research Grant includes principal investigator, collaborator or consultant and pending grants as well as grants already received), CSL Behring (Consultant, Research Grant includes principal investigator, collaborator or consultant and pending grants as well as grants already received), Genentech (Research Grant includes principal investigator, collaborator or consultant and pending grants as well as grants already received), GlaxoSmithKline (Consultant), Kaleo (Consultant), Merck (Consultant), Mylan (Consultant), Novartis (Consultant), Pediapharm (Consultant), Sanofi (Consultant), Shire (Consultant, Research Grant includes principal investigator, collaborator or consultant and pending grants as well as grants already received), Stallergenes (Consultant). 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(124) The Significance of MGUS: Severe Capillary Leak Syndrome Secondary to COVID-19 in a patient with Monoclonal Gammopathy of Uncertain Significance

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Monoclonal gammopathy of uncertain significance (MGUS) is a premalignant clonal plasma cell dyscrasia which is thought to be asymptomatic, however is associated with an increased risk of infections with reduced immune responses to vaccinations. It is currently unknown whether MGUS poses a greater risk for developing severe COVID-19. We present a case of severe capillary leak syndrome in a patient with MGUS due to COVID-19.

A 62-year-old woman with IgG kappa MGUS, posterior scleritis on rituximab, and necrobiotic xanthogranulomas presented for immunologic evaluation following a prolonged hospitalization with COVID-19 complicated by life-threatening capillary leak syndrome requiring intubation and 8 fasciotomies. She had received her second dose of Pfizer/BioNTech vaccination 6 months prior. She also had a history of pneumococcal septic shock and refractory shingles. Her most recent cycle of rituximab had been 5 months prior. Bone marrow biopsy had demonstrated normocellular marrow with < 3% kappa restricted plasma cells. There was no evidence of progression to smoldering or true multiple myeloma. Following hospitalization, her total IgG level was 1,352 mg/dL, IgA 43 mg/dL, and IgM 80mg/dL. SARS-COV-2 spike protein IgG was positive. T, B, and NK cell quantification were normal. Low lymphocyte proliferation to tetanus antigen was observed, though tetanus antitoxoid antibody was protective. Low CD27+IgD- switched memory B cells and expanded CD38hiIgMhi transitional B cells were found. Decision was made to pursue alternative treatments to rituximab for her eye condition and to hold on mRNA vaccine booster given reports of flares of capillary leak syndrome with both.

We report a case of MGUS contributing to the risk of severe COVID-19 disease, we speculate, through ineffective vaccine responses and poor viral clearance. Monoclonal gammopathy of clinical significance (MGCS) requires demonstration of monoclonal immunoglobulin deposits in the setting of end organ dysfunction. This was not examined during her hospitalization and may have occurred here. Many questions are raised by this case including whether to more aggressively screen for MGUS, evaluating vaccination efficacy and the role of early SARS-COV-2 monoclonal antibody therapy in these patients, and considering a new definition MGCS to include life-threatening infection.

Hospital Course of COVID-19 in patient with MGUS
1. Systemic capillary leak syndrome Patient was significantly hypotensive requiring triple vasopressor therapy and ICU level of care. She received stress dose steroids and intravenous immune globulin replacement (IVIG). Lab values of note were low complement C3 and C4. Cryoglobulins were negative. C1q and C1 esterase inhibitor were within normal limits. She recovered from this with aggressive volume resuscitation.
2. Distributive shock Broad-spectrum antibiotics were started on arrival with meropenem, vancomycin, and azithromycin. Shock was attributed to systemic capillary leak syndrome with fluid extravasation causing compartment syndrome with hypovolemia, hypotension, and hypoalbuminemia. No infectious etiology was identified.
3. Compartment syndrome of bilateral lower extremity with fasciotomy In the setting of systemic capillary leak syndrome. Patient underwent a total of 8 fasciotomies in the bilateral upper and lower extremities as well as right forearm status post a skin graft.
4. DIC syndrome due to hemorrhagic shock Attributed to severe critical illness and lower extremity hemorrhage. INR plateaued at 2. Patient received 4 units of packed red blood cells and 2 units of FFP.
5. Acute respiratory failure with hypoxia Patient was intubated for airway protection given declining mental status and reduced level of consciousness. She was extubated several days later to nasal cannula and supplemental oxygen requirements resolved prior to discharge.
6. COVID-19 Patient was fully vaccinated prior to admission. She received stress dosing of steroids in relation to shock. She then completed a course of dexamethasone and remdesivir. No monoclonal antibody therapy was given.
7. Acute kidney injury In the setting of shock and capillary leak syndrome. This resolved with resuscitation. She did not require continuous renal replacement therapy or dialysis.

Table 1. Demographics of Conventionally Treated and Transplanted CGD Patients

Genotype	Conventionally Treated n (%)	HCT N (%)
CYBB (gp91^{phox})	94 (62.3)	176 (73.3)
CYBA (p22^{phox})	9 (6)	11 (4.6)
NCF1 (p47^{phox})	24 (22.5)	25 (10.4)
NCF2 (p67^{phox})	5 (3.3)	12 (5)
NCF4 (p40^{phox})	0	2 (0.8)

Keywords: MGUS, COVID-19, Capillary Leak Syndrome, Secondary Immunodeficiency, Vaccination

Disclosures: All authors indicated they had no financial relationships to disclose.

(125) Patient with combined complement C6 and C7 deficiency, a case report

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There are few reported cases of combined complement C6 and C7 deficiency. We report the case of an 11-year-old French Canadian male with total C6 deficiency and subtotal C7 deficiency diagnosed in the context of recurrent infections. Patient was referred to our center for multiple episodes of angioedema and urticaria, mostly secondary to infections. Medical history was remarkable for chronic spontaneous urticaria, recurrent otitis media, pharyngitis, bronchitis and one episode of impetigo. The patient required several courses of antibiotics every year. He never had pneumonia, meningitidis or bacteriemia. His vaccination schedule was up to date. Family history is negative for consanguinity, recurrent infections or autoimmunity. Extensive immunologic investigation revealed undetectable CH50, near absent AH50, undetectable hemolytic C6, very low hemolytic C7 and normal C5, C8 and C9. Interestingly, Neisseria was never identified as a cause of the infections he suffered. Genetic analysis showed that the patient was homozygous for 2 mutations that have already been described and are known to be pathogenic. The first, C6 c.2381+2T>C, is a splice donor mutation that results in a premature stop codon and in the production of a truncated protein that can be built into the membrane attack complex. This mutation is mostly found in a non-Finnish European population, with a frequency of 0,003814 according to gnomAD. The second, C7 c.1561C>A, is a missense mutation that produces a protein that is retained in the endoplasmic reticulum due to misfolding, with less than 1% of the secretion of a wild-type C7. The prevalence of this mutation is not reported in gnomAD. C6 and C7 genes are both located on the same chromosomal region, 5p13.1, along with C9 gene. We found one case report of a patient with combined C6 and C7 deficiency who was homozygous for the same two mutations. Genetic analysis for the parents has been sent and results are pending. Curiously, we found the same two mutations in a heterozygous state in a completely unrelated patient followed for another immunodeficiency, which raises the question of prevalence of these two mutations in the French Canadian population.

Keywords: Complement deficiency, C6 complement deficiency, C7 complement deficiency, terminal complement pathway deficiency

Disclosures: Aubert Lavoie has relevant financial relationships with proprietary interests with Novartis (Consultant). All other authors indicated they had no financial relationships to disclose.

(126) Neurological Involvement in Primary Immunodeficiencies

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Primary immunodeficiency diseases (PID) are a heterogeneous group of inherited disorders of the immune system characterized by recurrent infections, allergies, autoimmunity, and malignancies. Neurologic manifestations are one of the main features of some immunodeficiency syndromes, such as Ataxia-Telangiectasia (AT) and Purine Nucleoside Phosphorylase Deficiency (PNP) as considered primary involvement.
Diverse pathological mechanisms including DNA repair disorders, metabolic errors, and autoimmune phenomena have been associated with neurologic abnormalities as considered secondary involvement. In this study, we retrospectively evaluated the neurological involvement of 105 patients with PID. The female/male ratio was 48/57, the median age: 13 years (min=1 max=60), the median follow-up time was 72 months (min=7, max=240). Diagnostic distribution and neurological findings of the patients was listed in Table 1. The most common findings were; cognitive delay (n=62, 59%), epilepsy (n=23, 24.8%) and ataxia (n=18, 17%) respectively. More than one neurologic finding was founded in 47.6% (n=50) of the patients. Cranial MRI was abnormal in 80.4% (n=78) of the patients. Primary involvement was detected in 50% (n=48), secondary involvement was found in 20.8% (n=20), and structural or anatomical variants were founded in 16.7% (n=16) of the patients. Intracranial pathologies were grouped based on the anatomical location of MRI findings in the gray matter (n=6, 6.3%), the white matter (n=27, 28.4%), the pituitary gland (n=3, 3.2%), hydrocephalus (n=5, 5,3%), cerebral atrophy (n=21, 22.3%), cerebellar atrophy (n=31, 33.3%), and intracranial hemorrhage findings (n=3, 3%).The most common clinical findings were; cognitive delay (n=62, 59%), epilepsy (n=23, 22%) and ataxia (n=18, 17%) respectively. The neurologic presentation may constitute the initial manifestation in certain types of PID.
Early recognition and treatment is important to prevent or reduce future irreversible neurological damage. Therefore, physicians should be aware of the neurological manifestations accompanying PID.

Keywords: pid, neurology, primary immunodeficiency, Ataxia-Telangiectasia (AT), Purine Nucleoside Phosphorylase Deficiency (PNP)

Disclosures: All authors indicated they had no financial relationships to disclose.

(127) Neutrophilic Panniculitis and Subdural Hematoma as Presentation of NEMO Deleted Exon 5 Autoinflammatory Syndrome (NEMO-NDAS)

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Introduction: Patients with disorders involving NF- B Essential Modulator (NEMO) may present with a variety of clinical phenotypes including autoinflammatory manifestations.
Case Report: A 7-month-old female presented for evaluation of macrocephaly and indurated skin lesions on the trunk and extremities. Past medical history was notable for pulmonary artery stenosis and gross motor developmental regression. Skin biopsy demonstrated neutrophilic-rich panniculitis with associated histiocytes. CT imaging revealed acute on chronic subdural hematomas.
Initial complete blood count demonstrated a normal white blood cell count (WBC) of 12.37 103/μL [reference range (RR): 9.4-34.4 103/μL] and microcytic anemia with hemoglobin of 7.6 g/dL (RR: 10.5 - 13.5 g/dL) and MCV of 64.1 fL (RR: 70.0 - 86.0 fL). The patient developed fevers and an extensive infectious work-up was negative. Inflammatory markers including CRP (6.4 mg/dL, RR 0-0.8 mg/dL), soluble-IL2 receptor/CD25 (2158.5 pg/mL, RR 175.3 to 858.2 pg/mL) and neopterin (22.4 nmol/L, RR < 10 nmol/L) were elevated. Quantitative immunoglobulins were within normal limits for age. The infant had protective antibody titers to tetanus and partial responses to Haemophilus influenzae B and Streptococcus pneumoniae. The infant also had a coagulopathy with PT of 19.2 seconds (RR: 9.3 - 12.0 seconds) and an INR of 2.0. Fat-soluble vitamin levels were low, and coagulopathy improved following Vitamin K administration.
Whole exome sequencing revealed pathogenic variants in both maternal and parental copies of the FLG gene (c.5840 G>A, p.W1947* and c.1708

C>T. p.Q570*, respectively) associated with ichthyosis vulgaris but not consistent with the patient's phenotype. Directed long-range sequencing of IKBKG identified a de novo heterozygous variant (c.671+5, G>A) in a splice site of exon 5. Additional testing revealed an elevated interferon gene signature consistent with a diagnosis of NEMO-deleted exon 5 autoinflammatory syndrome (NDAS).
Corticosteroid treatment improved fevers, skin lesions, and inflammatory markers. Adalimumab was started as a steroid sparing agent with improvement in interferon gene signature score.
Conclusion: We present a case of NEMO-NDAS initially missed on whole exome sequencing. This case highlights the need for high clinical suspicion for disorders involving NFKB pathway. Dedicated sequencing of IKBKG can identify variants in later exons by masking the IKBKG pseudogene IKBKGP1.

Keywords: NEMO Deleted Exon 5 Autoinflammatory Syndrome (NDAS), NEMO, Pseudogenes, Interferon

Disclosures: All authors indicated they had no financial relationships to disclose.

(128) Transplanted CGD Patients have Higher Burden of Disease than Conventionally Treated Patients that Resolve with Transplantation – A PIDTC Report

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Background: Chronic Granulomatous Disease (CGD) is a primary immunodeficiency caused by NADPH oxidase defects that lead to reduced or absent reactive oxygen species. Patients are susceptible to severe invasive infections and autoinflammatory disorders that reduce life expectancy and cause significant morbidity. Allogeneic hematopoietic cell transplant (HCT) can resolve infections and inflammatory disease.
Methods: Three hundred ninety-one CGD patients treated at Primary Immune Deficiency Treatment Consortium (PIDTC) centers between 1996 and 2018 enrolled on the PIDTC 6903 natural history study were included. Conventionally treated patients (n=151) and HCT patients (n=240) were treated per site standard of care. Burden of disease defined as frequency of autoinflammation manifestations, infection density (infections per person years), need for medications, nutrition, and growth were compared between conventionally treated, transplanted patients at pre-HCT baseline, and surviving patients 3-5 years following HCT.

Results: The median age of patients who underwent HCT was lower than conventionally treated patients (5.0vs.15.5 years,p< 0.001). More than 50% of patients had X-linked CGD in both cohorts (Table1). At pre-HCT baseline, patients undergoing HCT had more frequent non-infectious pulmonary disease (18.9%vs.11.4%,p=0.050), non-infectious liver disease (7.9%vs2.6%,p=0.031); total, bacterial, fungal, and CGD-related infection density (all p< 0.001); need for enteral or parenteral nutrition (16.2% vs. 4.3%, p< 0.001), and low albumin (25.3% vs. 13.4%, p=0.007)(Table2). Patients undergoing HCT were more likely to be treated with systemic steroids (32.3%vs.20.8%,p=0.014). Both groups received anti-bacterial and anti-fungal prophylaxis. Post-HCT patients at 3-5 years had significantly lower rates of IBD (1.8%vs.29.8%,p< 0.001) and non-infectious pulmonary disease (4.4%vs.11.4%,p=0.041) compared to conventionally treated patients(Table3). Total, bacterial, fungal, and CGD-related infection densities were also significantly lower (all p< 0.001). By 3-5 years post-HCT, patients were less likely to receive systemic steroids (4.5%vs.20.8%,p< 0.001), anti-bacterial prophylaxis (9.9%vs.91%,p< 0.001), and anti-fungal prophylaxis (7.3%vs.96.6%,p< 0.001) than conventionally treated patients. Height z-score (p=0.006) and albumin levels (p=0.017) improved or normalized.

Conclusion: HCT patients have higher baseline burden of CGD manifestations prior to HCT than conventionally treated patients, including frequency of auto-inflammation and infections. Despite starting with worse disease, infections and inflammatory disease frequency reduce significantly post–HCT. Following HCT patients have improved growth and are less likely to require medications used to manage CGD.

Table 2. Burden of Disease in Conventionally Treated and Pre-HCT CGD Patients at Baseline

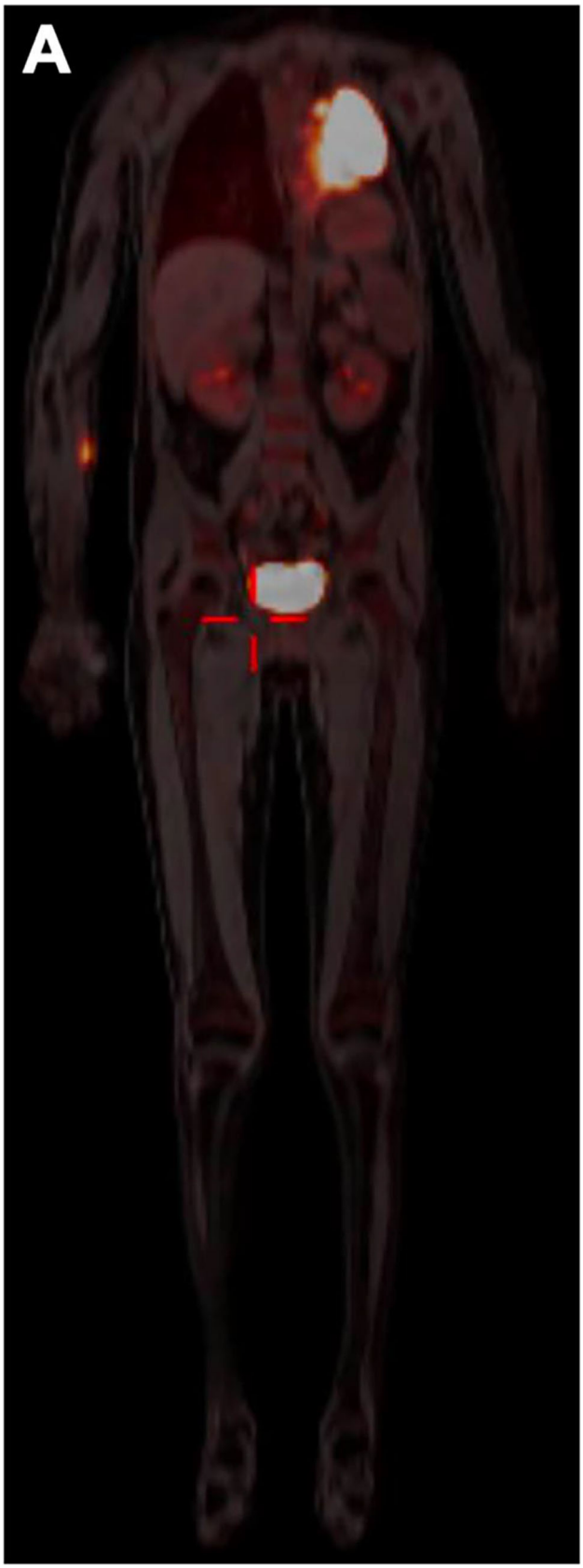
Symptom	Conventionally Treated (n=151)	Baseline HCT (n=240)	P value
Inflammatory Disease, n (%)			
Inflammatory bowel disease	45 (29.8)	71 (29.6)	0.893
Noninfectious pulmonary disease	17 (11.4)	45 (18.9)	0.050
Noninfectious liver disease	4 (2.6)	19 (7.9)	0.031
Total Inflammatory Disease	54 (37.5)	92 (40.2)	0.623
Infection Density (per person years)			
Total Infections	0.649	1.322	<0.001
CGD related	0.172	0.473	<0.001
Bacterial	0.371	0.615	<0.001
Fungal	0.106	0.364	<0.001
Need for Medications, n (%)			
Systemic steroids	31 (20.8)	76 (32.3)	0.014
Steroid sparing agents	16 (10.6)	23 (9.6)	0.745
Biologics	5 (3.4)	10 (4.3)	0.657
Antibacterial prophylaxis	132 (91)	219 (94.0)	0.387
Antifungal prophylaxis	143 (96.6)	226 (97.0)	1.000
Subcutaneous IFN-γ injections	60 (51.3)	97 (44.1)	0.208
Nutrition, n (%)			
Low albumin	18 (13.4)	59 (25.3)	0.007
Need for supplemental nutrition*	6 (4.1)	39 (16.3)	<0.001
Growth, mean Mean (SD)			
Weight Z score	-0.7 (1.8)	-0.7 (1.4)	0.022
Height Z score	-1.6 (2.6)	-1.2 (2.1)	0.873
Performance Status			
Lansky/ Karnofsky <90	11 (11.1)	25 (11.4)	0.938

*Requiring nutrition per gastric or nasogastric tube, or via total parenteral nutrition

Table 3. Burden of Disease in Conventionally Treated and Transplanted CGD Patients Over Time

Symptom	Conventionally Treated (n=151)	Baseline HCT (n=240)	1 year post HCT (n=187)	2 years post HCT (n=150)	3-5 years post HCT (n=114)	P value (conventionally treated vs. 3-5 years post-HCT)
Inflammatory Disease, n (%)						
Inflammatory bowel disease	45 (29.8)	70 (29.6)	8 (4.3)	1 (0.7)	2 (1.8)	<0.001
Non-infectious pulmonary disease	17 (11.4)	45 (18.9)	21 (11.3)	13 (8.7)	5 (4.4)	0.041
Non-infectious liver disease	4 (2.6)	19 (7.9)	17 (9.2)	7 (4.7)	1 (0.9)	0.394
Any inflammatory disease	54 (37.5)	92 (40.2)	30 (16.1)	11 (7.5)	6 (5.3)	<0.001
Infection Density (per person years)						
Total Infections	0.649	1.322	2.218	0.337	0.136	<0.001
CGD related	0.172	0.473	0.366	0.027	0.009	<0.001
Bacterial	0.371	0.615	0.921	0.142	0.064	<0.001
Fungal	0.106	0.364	0.225	0.020	0.009	<0.001
Need for Medications, n (%)						
Systemic steroids	31 (20.8)	76 (32.3)	25 (13.4)	9 (6.1)	5 (4.5)	<0.001
Steroid sparing agents	16 (10.6)	23 (9.6)	21 (11.2)	3 (2.0)	2 (1.8)	0.005
Biologics	5 (3.4)	10 (4.3)	6 (3.2)	3 (2.0)	1 (0.9)	0.243
Antibacterial prophylaxis	132 (91.0)	219 (94.0)	75 (40.5)	22 (15.1)	11 (9.9)	<0.001
Antifungal prophylaxis	143 (96.6)	226 (97.0)	71 (38.8)	16 (11.0)	8 (7.3)	<0.001
Subcutaneous IFN-γ injections	60 (51.3)	97 (44.1)	9 (4.9)	3 (2.1)	2 (1.8)	<0.001
Nutrition, n (%)						
Low albumin	18 (13.4)	59 (25.3)	24 (13.7)	16 (11.4)	4 (4.1)	0.017
Need for supplemental nutrition*	6 (4.1)	39 (16.3)	32 (17.2)	16 (10.7)	4 (3.5)	1.000
Growth, mean Mean (SD)						
Weight Z-score	-0.7 (1.8)	-0.7 (1.4)	-0.6 (1.5)	-0.4 (1.5)	-0.4 (1.5)	0.133
Height Z-score	-1.6 (2.6)	-1.2 (2.1)	-1.4 (2.6)	-1.0 (1.3)	-0.8 (1.4)	0.006
Performance Status n (%)						
Lansky/ Karnofsky <90	11 (11.1)	25(11.4)	16 (6.4)	6 (4.6)	6 (6.3)	0.229

*Requiring nutrition per gastric or nasogastric tube, or via total parenteral nutrition



Keywords: Chronic granulomatous disease, infections, hematopoietic cell transplant, autoinflammation, inflammatory bowel disease

Disclosures: Jennifer Leiding has relevant financial relationships with proprietary interests with bluebird bio (Employment, Ownership Interest includes stock, stock options, patent or other intellectual property), Horizon Therapeutics (Consultant, Speaker/Honoraria includes speakers bureau, symposia, and expert witness), Pharming (Advisory Board, Consultant, Speaker/Honoraria includes speakers bureau, symposia, and expert witness), Sobi (Consultant, Speaker/Honoraria includes speakers bureau, symposia, and expert witness), Takeda (Consultant, Speaker/Honoraria includes speakers bureau, symposia, and expert witness). Jennifer Heimall has relevant financial relationships with proprietary interests with ADMA (Advisory Board), CIRM (Consultant, Other Financial or Material Support, Data Safety Monitoring Board), CSL Behring (Advisory Board, Consultant, Research Grant includes principal investigator, collaborator or consultant and pending grants as well as grants already received), Horizon (Advisory Board), Regeneron (Contracted Research), UpToDate (Other Financial or Material Support, Section Author). Jeffrey Bednarski has relevant financial relationships with proprietary interests with Horizon Pharmaceuticals (Advisory Board) and Sobi (Advisory Board). Karin Chen has relevant financial relationships with proprietary interests with Horizon Therapeutics (Advisory Board). Hey Chong has relevant financial relationships with proprietary interests with Horizon (Advisory Board). Geoffrey Cuvelier has relevant financial relationships with proprietary interests with Miltenyi Biotech (Consultant). Lisa Forbes-Satter has relevant financial relationships with proprietary interests with csl behring (Consultant), enzyvant (Advisory Board), Grifols (Consultant), and Takeda (Consultant). Susan Prockop has relevant financial relationships with proprietary interests with ADMA (Advisory Board), Atara Biotherapeutics (Intellectual Property / Patents, Research Grant includes principal investigator, collaborator or consultant and pending grants as well as grants already received, IP with all rights assigned to MSKCC), Jasper Therapeutics (Other Financial or Material Support, Support for the conduct of sponsored trials), and Neovii (Advisory Board). Blachy Dávila Saldaña has relevant financial relationships with proprietary interests with Sobi (Consultant). Hemalatha Rangarajan has relevant financial relationships with proprietary interests with Medexus (Consultant, Medexus Treosulfan (one time only)). All other authors indicated they had no financial relationships to disclose.

(129) Loss of Treg identity in IPEX patients is associated with increase autoreactivity in Teff cells

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Peripheral self-tolerance is an active process established by different mechanisms and maintained by regulatory cells, which prevents or ameliorate undesirable and excessive immune responses. Among the regulatory cells, CD4+CD25+CD127-/lowFOXP3+ regulatory T cells (Treg) are the best recognized players. Inborn errors in the FOXP3 gene cause loss of Treg cell function and consequently development of multiorgan autoimmunity, named Immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome (IPEX). In murine model of IPEX, the key drivers of the autoimmune damage are autoreactive T cells. However, in patients with IPEX, the origin, phenotype, numbers and localization of

autoreactive T cells have never been analyzed. Given the critical role of Tregs in self-tolerance, the knowledge gained from IPEX study has been extended to more common autoimmune diseases and thus the lack of knowledge about autoreactive T cells in IPEX represents a crucial gap in the global understanding of autoimmunity. Here, we analyzed T cell specific receptor repertoire of patients with IPEX combined with phenotypic and epigenetic analysis of their mutated Treg cells. We found that IPEX Tregs, detected by demethylation of their specific region (TSDR), are expanded but a fraction of them lost the Treg phenotype (hereafter called loss of Treg identity) and are detectable in the non-Treg compartment. In addition, data from a transplanted patient with only partial chimerism suggest that the expansion of loss of Treg identity cells could be controlled by presence of healthy Treg cells. Moreover, expansion of these loss of Treg identity cells correlates with increased autoreactivity of bona fide T effector cells (Teff) suggesting that 1) loss of Treg phenotype is accompanied by loss of their ability to control expansion of autoreactive T cells, and/or 2) these altered Tregs might be actively participating in the autoimmune reaction, expanding the autoreactive T cell compartment. Collectively, we have for the first time detected autoreactive T cells in patients with IPEX and showed that their expansion is associated with expansion of loss of identify Treg cells, which might represent a new source of autoreactive T cells in autoimmunity of different origin.

Keywords: IPEX, FOXP3, Treg, TSDR, Autoreactive T cells, Loss of Treg identity, TCR, APECED, Self-tolerance

Disclosures: All authors indicated they had no financial relationships to disclose.

(130) Profile of Inborn Errors of Immunity (IEI) In Nepal- Everest Ahead Yet to Be Scaled

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Background: Inborn errors of immunity (IEIs) are increasingly being diagnosed in various regions of the world. With increasing awareness, and diagnostics, IEIs are diagnosed with increasing frequency and accuracy in Nepal. Besides, IEIs are also being evaluated in children presenting with autoimmune manifestations. We describe the profile of patients diagnosed with IEIs in Nepal during 2020-2021.
Methods: Records of all patients with IEIs who were diagnosed and treated at our tertiary care centre in Nepal from August 2020 to October 2021 were analysed. Lead author (DB) has examined and diagnosed all cases. IEIs were diagnosed as per European Society for Immunodeficiencies (ESID) diagnostic criteria based on clinical and laboratory evidence including flow-cytometric and genetic analysis.
Results: Twenty-four patients with IEI (14 boys; 10 girls) and 171 children with autoimmune disorders were diagnosed during the study period. Genetic analysis was done in 10 patients. The profile includes patient with chronic granulomatous disease (12.5%), X-linked agammaglobulinemia (12.5%), severe combined immunodeficiency (RAG and IL2RG gene defects) (8.3%), Common variable immunodeficiency (8.3%), Job syndrome (8.3%), Selective IgA deficiency (8.3%), Wiskott-Aldrich Syndrome (4%), IFN-IL12 pathway defect (4.1%), MonoMac syndrome (4.1%), Leukocyte adhesion defect (4.1%), hereditary angioneurotic edema (4.1%), early-complement deficiency lupus (4.1%), autoimmune lymphoproliferative syndrome (4.1%) and unclassified IEI (12.5%). Both patients of SCID succumbed to their illness before exploring the scope of hematopoietic stem cell transplantation (HSCT). In addition, 171 cases of autoimmune disorders were diagnosed. It included connective tissue disorders (Childhood lupus (n=23), dermatomyositis (n=4), and scleroderma n=2)), autoinflammatory disorders (3%), juvenile idiopathic arthritis (53%), interferonopathy (0.58%), multisystemic inflammatory syndrome in children (10%) and autoimmune vasculitis (7%). All patients with IEIs are on antimicrobial prophylaxis. All children with humoral immunodeficiencies are commenced on regular intravenous immunoglobulin replacement. Two patients with IEIs are planned for HSCT.
Conclusion: We present our experience of IEIs in resource-limited settings. Socio-economic status and limited resources coupled with lack of awareness of IEIs among laity and pediatrician accounted for a missed diagnosis, late diagnosis, and poor outcome in Nepal. Antimicrobial prophylaxis reduced the incidence of breakthrough infections.

Keywords: Inborn Errors of Immunity, Nepal, Immunodeficiencies, Hematopoietic stem cell transplantation, Immunedysregulations, Autoimmunity

Disclosures: All authors indicated they had no financial relationships to disclose.

(131) Inflammatory Myofibroblastic Tumor Masquerading as IgG4-Related Disease

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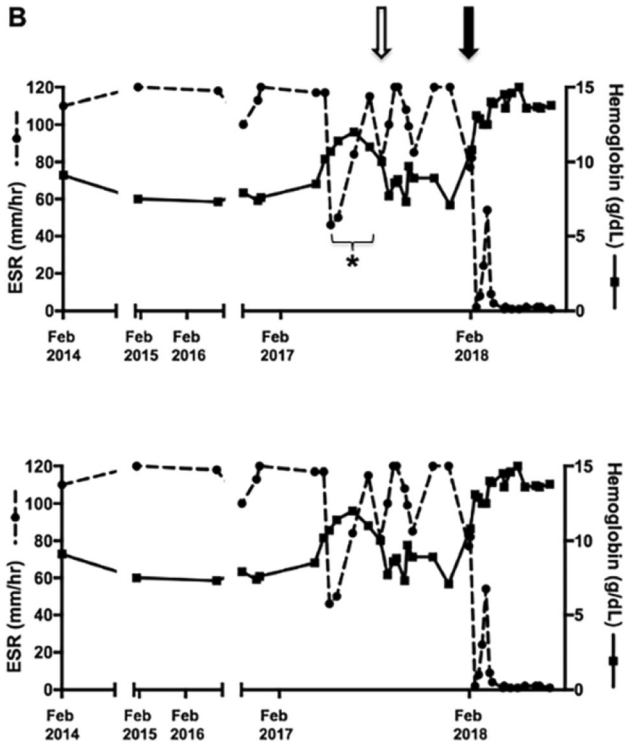
There is growing recognition that IgG4-positive cells are a non-specific immunohistochemical finding shared among multiple inflammatory disorders.
We evaluated a teenage male with an intrathoracic mass. He had undergone left pneumonectomy at age 6 for “recurrent pneumonia”. He represented age 11 with a partially calcified 8.4x6.4x9.7 centimeter mass occupying the left hemithorax, extending into the left thoracic neuroforamina, and encasing the left mainstem bronchus and pulmonary artery. Core biopsy demonstrated a lymphoplasmacytic infiltrate with IgG4/IgG ratio >0.41, >51 IgG4-positive cells/HPF, and confluent storiform fibrosis. Elastin stain highlighted a fibrosed, obliterated vein and ALK-1 was negative. Serum IgG4 was 588mg/dL (< 143). He was diagnosed with the immune-mediated, fibroinflammatory condition IgG4-related disease (IgG4-RD). Treatment with glucocorticoids and rituximab did not reduce the mass or improve his fatigue, anemia, or systemic inflammation.
Upon our evaluation at age 13, he was < 1st percentile for height and weight. In the preceding 2.5 years, he had grown only 1 centimeter. External records revealed >4 years of anemia (7.3-9.7g/dL) and ESRs >100 mm/hr. Serum IL-6 was 92pg/mL (< 15.5). PET-MRI showed an FDG-avid mass (SUV 14.4) without other locations of disease. We initiated tocilizumab, IL-6 receptor antagonist, for refractory IgG4-RD. His hemoglobin normalized promptly. Six weeks after starting therapy, the mass was almost completely surgically resected.
After starting tocilizumab, the patient grew 4 centimeters in 6 months, serum IL-6 was 10pg/mL and IgG4 was 97mg/dL. However, the residual mass did not decrease on serial imaging after one year. Genetic analysis of the resected tumor was pursued and revealed a TGF-ROS1 fusion present in some inflammatory myofibroblastic tumors (IMT), rare mesenchymal neoplasms. Fusions involving ALK-1 are common in IMTs, but a range of other fusions have been reported in ALK-1 negative cases. IMT management involves resection with systemic therapy for residual or recurrent

disease. Our patient was started on the kinase inhibitor crizotinib; tocilizumab was weaned off. He was well at most recent evaluation, with continued growth and normal inflammatory markers.

This case highlights the overlapping pathologic and laboratory findings between IgG4-RD and IMTs, and the importance of reevaluation of atypical disease to avoid diagnostic momentum.



A. PET MRI revealed the patient's left hemithorax was occupied by a metabolically active inflammatory mass; there were no additional sites of disease (there is physiologic uptake in the kidneys and bladder and a focal area of extravasation at the iv insertion in the right forearm). The leftward mediastinal shift and right lung hyperexpansion are sequelae of prior pneumonectomy.

Table 1: NK, dendritic cell, and perforin/granzyme studies

	Reference Range	Patient's Result
NK cell function	7-125	6 (L); on repeat, 2 (L)
Quantitative NK/NKT subsets		
CD45+ Abs	940-2673 cells/mcL	388 (L)
CD45+CD3- Abs	232-813 cells/mcL	75 (L)
CD45+CD3- %	17.4-40.93	19.3
Total NK cells Abs	103-498 cells/mcL	72 (L)
Total NK cells %	7.2-30.5	18.5
Cytotoxic NK (CD16++CD56+) Abs	47-395 cells/mcL	63
Cytotoxic NK (CD16++CD56+) %	51.6-88.1	87.8
Cytokine-producing NK (CD56++) Abs	3-21 cells/mcL	3
Cytokine-producing NK (CD56++) %	1.3-14.6	4.2
CD45+CD3+ Abs	610-1880 cells/mcL	313 (L)
CD45+CD3+ %	57.3-81.5	80.5
NKT (CD3+CD56+) Abs	15-335 cells/mcL	107
NKT (CD3+CD56+) %	1.2-18.4	34.3 (H)
DC and Monocyte enumeration		
Monocytes (CD14+)	173-637 cells/mcL	288
pDC (CD123+)	3-17 cells/mcL	0 (L)
mDC (CD11c+)	14-84 cells/mcL	2 (L)
Perforin/Granzyme B		
Perforin+, %NK	79-94	25 (L)
Perforin MCF, NK	98-181	36 (L)
Perforin+, %CD8	2-15	0 (L)
Granzyme B+, %NK	80-98	98
Granzyme B MCF, NK	152-825	891 (H)
Granzyme B+, %CD8	0-61	90 (H)

MCF = mean channel fluorescence

B. The initiation of tocilizumab (black arrow) resulted in prompt control of the patient's systemic inflammation, as reflected in normalization of the hemoglobin for the first time in more than 4 years. The asterisk indicates a brief period of partial response to oral glucocorticoids. Administration of rituximab (white arrow) had no clinical or laboratory impact; B cell depletion was confirmed.

Keywords: IgG4-related disease, inflammatory myofibroblastic tumor, fusion protein

Disclosures: John Stone has relevant financial relationships with proprietary interests with Abbott (Speaker/Honoraria includes speakers bureau, symposia, and expert witness), Principia Biopharma (Consultant, Research Grant includes principal investigator, collaborator or consultant and pending grants as well as grants already received), Roche (Consultant, Research Grant includes principal investigator, collaborator or consultant and pending grants as well as grants already received), and Viela Bio (Consultant, Research Grant includes principal investigator, collaborator or consultant and pending grants as well as grants already received). All other authors indicated they had no financial relationships to disclose.

(132) Late-Onset Hemophagocytic Lymphohistiocytosis with Perforin Defect

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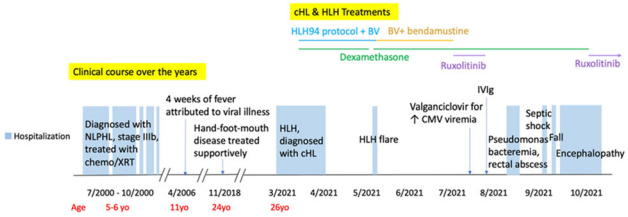
A 26-year-old Vietnamese male with a history of EBV-related nodular lymphocyte predominant Hodgkin lymphoma (NLPHL), successfully treated at age 6, presented with fever, night sweats, and weight loss. He met all eight of the 2004 diagnostic criteria for hemophagocytic lymphohistiocytosis (HLH). An infectious work-up was negative other than EBV viral load < 1000. Lymph node biopsies revealed a CD30- and EBV-positive lymphoma that was thought to be consistent with classical Hodgkin lymphoma (cHL), though with an atypical mixed T-cell infiltrate. The patient was treated with HLH-94 protocol (etoposide and dexamethasone) plus brentuximab vedotin (BV), followed by BV-bendamustine for cHL. Despite complete metabolic response of cHL based on PET-CT, he had persistently elevated inflammatory markers possibly related to CMV viremia.

Development of a second EBV-associated lymphoproliferative disease raised concern for an immunodeficiency. NK cell subsets, dendritic cell (DC) enumeration, and perforin/granzyme levels showed markedly decreased perforin expression in NK and CD8 cells and low numbers of dendritic cells (Table 1), in addition to decreased NK cell function. Primary immunodeficiency genetic panel testing (Invitae) revealed one pathogenic variant [c.133G>A (p.Gly45Arg)] and one variant of uncertain significance (VUS) [c.112G>A (p.Val38Met)] in PRF1, without deletions or duplications and on opposite chromosomes (trans). PRF1 is associated with autosomal recessive familial HLH. The same VUS in PRF1 has been previously reported in two patients with suspected genetic HLH who were of Native American and Moroccan ancestry, respectively. Our patient also had a pathogenic variant in CFI and a VUS in IRF8 [c.1261A>G (p.Asn421Asp)]. These findings suggest a rare dysfunctional NK-DC phenotype with perforin defect, which may explain the development of HLH in the setting of cHL, an atypical trigger.

Given ongoing evidence of HLH, the patient received ruxolitinib with plan for allogeneic stem cell transplant. His sister was a fully matched donor; however, she had identical genetic variants in PRF1 and low perforin expression despite having no personal history of recurrent infections or malignancy, suggesting varying gene expression or exposures.

His sister has received vaccination against HPV and varicella. The patient has had multiple infectious complications and is awaiting transplant with an unrelated donor.



Patient's immune studies showed decreased NK cell function, low numbers of dendritic cells, and decreased perforin expression in NK and CD8 cells.

Age	TCR V-beta	Recent thymic emigrants (X 10^9/L)	Total Lymphocyte Count (X10^9/L)	CD3+ (X 10^9/L)	CD4+ (X 10^9/L)	CD8+ (X 10^9/L)	Double Negative T cells (X 10^9/L)	B cells (X 10^9/L)	NK (X 10^9/L)
1 week	Polyclonal, all families represented	0.1	7.3	1.390	1.110	0.240	0.030	4.630	1.23
2 months		0.3	9.8	1.190	0.960	0.180	0.040	5.160	0.390
9 months	Polyclonal, all families represented	0.1	20.9	1.590	1.210	0.260	0.120	13.310	2.00
12 months	Polyclonal, all families represented	0.3	15.1						
17 months	Polyclonal, all families represented	0.3	15.8						

Table 1. Immunologic parameters over the first two years of life

Figure 1. Patient's clinical course and hospitalizations over the years. NLPHL = nodular lymphocyte predominant Hodgkin lymphoma, cHL = classical Hodgkin lymphoma, BV = brentuximab vedotin.

Keywords: perforin, hemophagocytic lymphohistiocytosis, EBV-associated lymphoproliferation

Disclosures: All authors indicated they had no financial relationships to disclose.

(133) Hyperactive mTOR in PIRD

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Primary immunoregulatory disorders (PIRD) are group of disorders associated with autoimmunity, autoinflammation and dysregulation of lymphocyte homeostasis. The functional significance of mTOR molecules can be determined by analyzing the phosphorylation status of ribosomal protein S6 (at Ser 235/236) and Akt (at Ser473) which is routinely used as readout of mTORC1 and mTORC2 activity respectively.Since defects in genes encoding for different members of PI3K/AKT/mTOR/S6K cascade or for the molecules interacting with this pathway are associated with immune dysfunction, we evaluated patients with clinical suspicion of PIRDs to identify possible hyperactive mTOR signalling on different lymphocyte subsets :T, B and DNTs.
13 patients with mutations in different PIRDs namely FADD (n=2), FASLG (n=1), LRBA (n=3), CTLA4 haploinsufficiency (n=2), PIK3D-GOF (n=1), no variant identified (n=4) along with healthy controls were analysed. Interestingly, we found that patient with mutations affecting the Fas apoptotic pathway (FADD and FASLG), had nearly three fold elevated basal level of pAkt/ pS6 on DNTs, as compared to DNTs of healthy controls. We observed a two fold increase in basal level of pAkt on B cells in LRBA deficient patients whereas in CTLA4 patients the basal level of pS6 was elevated on both T and B cells. PIK3CD-GOF had three fold increase in pAkt levels on both T and B cells. We also identified a 4 fold increase in basal level of pS6 on T and B cell in 4 patients with high clinical suspicion and immunological findings consistent with PIRD with no molecular defects.
Hyperactive mTOR in these deficiencies and a particular lymphocyte subset can be due to mutations in functional domains (p110δ in PIK3CD,WD40 in LRBA) or due to protein interaction with key mTOR signalling cascade (PI3K with CTLA4) or the maintenance and lymphoproliferation of DNTs as observed in ALPS. Therefore, mTOR inhibitors can be used as a targeted therapy in these PIRDs. This is first study which shows the discordant pattern on different lymphocyte population which might give clues to underlying PIRD, which need to be validated on larger numbers.

Keywords: mTOR, PIRDs, pAKT, pS6, FADD, FASLG, CTLA4, LRBA, PI3KCD-GOF

Disclosures: All authors indicated they had no financial relationships to disclose.

(134) Single cell RNAseq analysis reveals profound abnormalities in thymic epithelial cells in Rag1 mutant mice: implications for immune reconstitution after stem cell transplantation

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The thymus contains a heterogeneous population of stromal cells which orchestrate T cell development and selection. Although recent reports highlighted the complexity of thymic epithelial cells (TEC), their developmental origin, hierarchy, and function remain ill-defined. We compared TEC distribution and gene expression in wild-type (WT) mice and in mice carrying Rag1 hypomorphic mutations observed in patients with immunedeficiency and immune dysregulation. Single cell RNA-seq analysis of TECs isolated from adult Rag1 mutant mice revealed an excess of cortical TECs (cTECs), segregating in different clusters. The medullary TEC (mTEC) compartment was reduced in size, but showed a largely preserved distribution of previously described subsets (Ccl21a+ mTEClow, Aire+ mTEChigh, post- AIRE/Krt10+ mTEC and Tuft-like mTEC), suggesting perturbation of mTEC development rather than defective differentiation into distinct functional subsets. To address whether TEC abnormalities in Rag1 mutant mice might reflect defects in TEC development, we compared distribution of TECs from 8-12-week-old Rag1 mutant mice to what observed in neonate WT mice. Although the distribution of TECs from adult Rag1 mutant mice was similar to that of newborn WT mice, we identified novel cTEC subsets with different gene expression profiles in adult Rag1 mutant mice. This defect in adult Rag1 mutant mice correlates with a total decreased number of thymocytes, in particular double-positive thymocytes, suggesting that impaired lymphostromal cross-talk in the thymus of Rag1 mutant mice is associated with abnormalities of TEC composition. Transplantation of WT hematopoietic stem cells (HSCs) into Rag1 mutant mice was able not only to correct thymocyte development, but also to revert TEC phenotype to normalcy. However, in a competitive transplantation setting where 10% of WT and 90% mutant HSCs were used, only partial restoration

of number and distribution of thymocyte subsets was observed associates with incomplete rescue of TEC phenotype. In conclusion, we show that abnormalities of TEC composition in Rag1 hypomorphic mice correlate with impaired development of thymocytes, highlighting the role of lymphostromal cross-talk in TEC maturation. These data have implications on the need to achieve full donor chimerism after HSC transplantation in order to rescue the thymic compartment and prevent defects of immune tolerance.

Keywords: Thymus, Thymic epithelial cells, Rag1, Immune dysregulation, Stem cell transplantation

Disclosures: All authors indicated they had no financial relationships to disclose.

(135) Somatic NRAS mutation identified by absent T cell receptor excision circles on newborn screen

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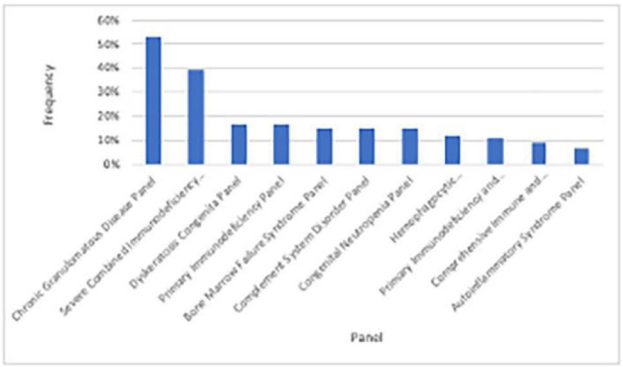
Background:
Ras-associated autoimmune lymphoproliferative disease (RALD) is a rare condition leading to early childhood cytopenias, splenomegaly and lymphoproliferation. RALD is caused by heterozygous somatic mutations in RAS proto-oncogenes, NRAS and KRAS, and may reflect a pre-malignant state given a shared pathogenesis with juvenile myelomonocytic leukemia (JMML). Abnormal lymphocyte production, measured by T-cell and B-cell receptor excision circles (TREC and KREC respectively), has been reported. We describe the case of a now 22-month-old patient with a somatic NRAS mutation identified following a positive SCID (severe combined immunodeficiency) newborn metabolic screen (NMS).
Case:
A one-week-old girl was referred for a positive NMS for SCID with absent TREC. She was born at 35-weeks following an uncomplicated pregnancy to non-consanguineous parents with noncontributory family history. She was admitted to the NICU for respiratory distress and was found to have congenital CMV. Initial management included valganciclovir, isolation precautions and PJP prophylaxis.
Immunophenotyping showed markedly low thymic output and T cell lymphopenia with normal mitogen proliferation. TCR V beta repertoire and gamma-delta T cell enumeration revealed no clonal T-cell clonal expansion. Genetic testing for a presumed primary immunodeficiency revealed a pathogenic heterozygous mutation in NRAS c.34G>A, p(Gly12Ser). Genetic evaluation confirmed no clinical features consistent with Noonan syndrome, and skin biopsy was negative for NRAS mutation, supporting the diagnosis of RALD secondary to somatic NRAS mutation.
At 2 months, she was admitted with acute splenomegaly and pancytopenia. Bone marrow analysis revealed no excess blasts, but mild non-diagnostic dysplasia and immunophenotypic aberrancy. She did not meet criteria for JMML. In follow up, she continues to have leukocytosis, lymphadenopathy and hepatosplenomegaly but these have improved over time. Serial immunologic investigations show a stable pattern of lymphocyte subsets, low thymic output, and polyclonal T-cell repertoires (Table 1). She is otherwise well with normal growth and development, and no recurrent or opportunistic infections or CMV reactivation.
Conclusions:
To our knowledge this is the first case of RALD secondary to somatic NRAS mutation identified because of absent TRECs on newborn screen for SCID. Ongoing monitoring will determine if decreased thymic output represents a phenotype that will progress to malignancy or autoimmunity.



Keywords: Somatic NRAS mutation, RALD, low TREC

Disclosures: All authors indicated they had no financial relationships to disclose.

(136) Primary Immunodeficiencies: The Diagnostic Yield Diagnostic Yield of Next-Generation Sequencing Panels Including Noncoding Variants and High-Resolution CNV Analysis

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Introduction: Primary immunodeficiencies, or inborn errors of immunity (IEIs), are a group of inherited disorders affecting the immune system development or function. Historically, diagnosis was based on clinical features and laboratory studies. The clinical presentations of IEIs are diverse but they also overlap. Identifying the genetic etiology of an IEI can impact patient management. Given the challenges of clinical diagnosis and the value of a molecular diagnosis, genetic testing is essential for these patients. Here, we report results from over 4,800 patients who underwent multigene panel testing with 1 of 11 immunology-related panels (Table 1) including high-resolution copy number variant detection (CNV) and clinically relevant noncoding variants for the indication of IEI.
Methods: We retrospectively examined deidentified genetic test results from consecutive patients tested for the indication of IEI. Panel target regions generally included all coding exons, 20 base pairs at intron-exon boundaries, and select regions containing clinically relevant non-coding variants. Copy number variant (CNV) analysis was performed bioinformatically with 2 pipelines, including a proprietary pipeline specifically designed for the detection of small (4 or less), exon-level CNVs. Variant interpretation was performed using a point-based modification of the ACMG guidelines.
Results: Median age at testing of the 4,894 patients was 16 years (range 0-90). Pediatric patients (< 19 years) accounted for 62% of the cohort. Median coverage was 99.91% while median sequencing depth was 206X. Overall, a diagnosis was achieved in 547 patients (11.2%); however, the diagnostic rate varied by panel and age at testing (Figures 1 and 2). Diagnostic variants in 158 genes were reported. CNVs contributed to the diagnosis in 56 patients (10%), with 18 (32%) being 4 exons or smaller. Non-coding variants contributed to the diagnosis in 21 patients (4%).
Conclusion: The use of comprehensive panels including detection of small CNVs and non-coding variants are key in the IEI population as they account for over 10% of the diagnostic yield in this large, unselected IEI cohort.

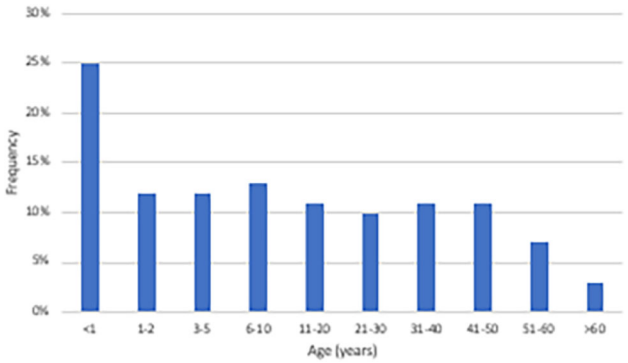

Figure 1. Diagnostic rate by panel

Panel Name
Autoinflammatory Syndrome Panel
Bone Marrow Failure Syndrome Panel
Chronic Granulomatous Disease Panel
Complement System Disorder Panel
Comprehensive Immune and Cytopenia Panel
Congenital Neutropenia Panel
Dyskeratosis Congenita Panel
Hemophagocytic Lymphohistiocytosis Panel
Primary Immunodeficiency and Primary Ciliary Dyskinesia Panel
Primary Immunodeficiency Panel
Severe Combined Immunodeficiency Panel

Figure 2. Diagnostic rate by age

S. No.	Gene	Full forms	Function
1.	*WAS*		Defective gene
2.	*c-Myc*	Master Regulator of Cell Cycle Entry	Pan proliferation marker
3.	*TBX21*	T-Box Transcription Factor 21	T_h0 to T_h1 polarization
4.	*GATA3*	"GATA" sequence binding protein 3	T_h0 to T_h2 polarization
5.	*RORγT*	Retineic-acid-receptor-related orphan nuclear receptor gamma	T_h0 to T_h17 polarization
6.	*FOXP3*	Forkhead box P3	T_h0 to T_{reg} polarization
7.	*IRF4*	Interferon regulatory factor 4	pre-B cell differentiation, induction of B cell tolerance pathways, marginal zone B cell development, germinal center reaction and plasma cell differentiation
8.	*FPR2*	N-formyl peptide receptor 2	Monocyte and Neutrophil chemotaxis
9.	*EGR2*	Early growth response 2	Intermediate monocytes and non-classical monocyte polarization
10.	*CD38*	ADP-ribosyl cyclase	Monocyte to Dendritic cell differentiation
11.	*NDRG2*	N-myc Downstream-Regulated Gene 2	mDC polarization
12.	*TCF4*	Transcription factor 4	pDC, naïve and memory B polarization
13.	*GAPDH*	Glyceraldehyde 3-phosphate dehydrogenase	House-keeping gene

Table 1. Immunology-related panels

Keywords: next-generation sequencing, noncoding variants, copy number variants, inborn errors of immunity

Disclosures: Kim Gall has relevant financial relationships with proprietary interests with Blueprint Genetics (Employment). Zoe Powis has relevant financial relationships with proprietary interests with Blueprint Genetics (Employment). Julie Hathaway has relevant financial relationships with proprietary interests with Blueprint Genetics (Employment). Alicia Scocchia has relevant financial relationships with proprietary interests with Blueprint Genetics, a Quest Diagnostics Company (Employment). Elina Hirvonen has relevant financial relationships with proprietary interests with Blueprint Genetics (Employment). Paivi Kokkenen has relevant financial relationships with proprietary interests with Blueprint Genetics (Employment). Inka Saarinen has relevant financial relationships with proprietary interests with Blueprint Genetics (Employment). Pertteli Salmenpera has relevant financial relationships with proprietary interests with Blueprint Genetics (Employment). Massimiliano Gentile has relevant financial relationships with proprietary interests with Blueprint Genetics (Employment). Jennifer Schleit has relevant financial relationships with proprietary interests with Blueprint Genetics (Employment). Lotta Koskinen has relevant financial relationships with proprietary interests with Blueprint Genetics (Employment). Jussi Paananen has relevant financial relationships with proprietary interests with Blueprint Genetics (Employment). Samuel Myllykangas has relevant financial relationships with proprietary interests with Blueprint Genetics (Employment). Juha Koskenvuo has relevant financial relationships with proprietary interests with Blueprint Genetics (Employment). All other authors indicated they had no financial relationships to disclose.

(137) Underlying Inborn Errors of Immunity in patients with Evans syndrome and multilineage cytopenias. A single centre analyis

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Recent reports have shown that Evans Syndrome (ES) and Multilineage Autoimmune Cytopenias (MAC) are often signs of underlying Inborn Errors of Immunity (IEI) that may benefit from specific treatments.
The aim of this study is to investigate the clinical/immnunological characteristics and the underlying genetic background of a single centre cohort of patients with ES/MAC
Charts of patients with ES/MAC followed in our centre were retrospectively reviewed. Genetic studies were performed with NGS analysis of 315 genes related to haematological/immunologic disorders
40 patients(23 males,17 females) with median age at onset of 6 years (range 0-16) were studied. Eight-teen (45%) and 22/40 (55%) had a ES and MAC, respectively.
Seven-teen/40 (43%) children fitted the Autoimmune Lymphoroliferative Syndrome (ALPS) diagnostic criteria. The remaining 15 (37%) and 8 (20%) were classified as having an ALPS-like disorder and idiopathic cytopenia, respectively.Lymphoproliferation and immunodysregulation signs were present in 29/40 (72%) and in 24/40 (60%) of cases, respectively. Immunodysregulation signs and the ALPS-like phenotype were significantly more frequent(p=0,0009 and p=0,03, respectively) in patients with MAC. On the contrary, patients with ES had a positive family history in a significant higher number of cases (p=0,03).
Genetic analysis was performed in all 40 patients and variants were found in 17(42%) of them, being pathogenic and of unknown significance 13 and 4 cases, respectively. In 5/17(29%) and in 7/17(42%) patients the mutated gene was involved in the pathogenesis of ALPS (4 FAS and 1 CASP10), and ALPS-like disorders (4 TNFSF13B, 1 LRBA, 1 CTLA4, 1 STAT3), respectively. The remaining 5/17 (29%) cases were found to have mutations in genes related to other IEI (2 CARD11, 1 IKBKG, 1 ADA2, 1 LIG4).
28/40 (70%) patients required second-line treatments, including MMF, sirolimus or both in 27 (%), 18 (%), and 14 (%) cases respectively. Median follow up was 6,9 years (0,3-16,6) and mortality was 5%.
This study represents the largest monocentric cohort of genetically screened patients with ES/MAC which show a genetic background in about half cases. Therefore, an immunological screening and an extended molecular evaluation should be offered to all patients, since a genetic diagnosis may benefit from targeted treatments.

Keywords: Evans Syndrome, Autoimmune Cytopenia, Autoimmune Lymphoproliferative Syndrome, Inborn Error of Immunity

Disclosures: All authors indicated they had no financial relationships to disclose.

(138) Pooled Analysis of Headache and Migraine Incidence in Gammaplex 5% and 10% in Patients with Primary Immunodeficiency

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Introduction: Intravenous immune globulin (IVIG) infusions are administered across a broad range of infusion rates depending on the brand, labeling, and tolerability. Three individual pivotal studies have supported the efficacy, safety, and tolerability of a branded IVIG product in adults and children with primary immunodeficiency (PI). The purpose of this pooled analysis is to review the rates of headache and migraine across all completed clinical studies.
Methods: Infusion and tolerability data from three Gammaplex studies in PI were collected and pooled. In these studies, a unique infusion rate ramp-up protocol was utilized that increased every 15 minutes to a maximum rate of 8 mg/kg/min. Infusion summaries were generated to identify the proportion of infusions reaching the maximum infusion rate. Summaries of tolerability were generated to identify the proportion of infusions with associated AEs, specifically headaches and migraines, defined as occurring within 72 hours of the end of the infusion. The majority of subjects did not receive pre-medications.
Results: In the pooled analysis, 94.6% of infusions reached the maximum infusion rate. Of the total infusions, 7.15% were associated with headaches and 0.47% with migraines. The overall rates of headaches and migraines as a function of total number of infusions were 7.21% and 0.32%, respectively in all subjects (adults and pediatrics) receiving the 5% formulation and 6.85% (headaches) and 1.21% (migraines) in all subjects receiving the 10% formulation. In children receiving either formulation, 5.14% of infusions were associated with headaches and 2.14% migraines. In adults, 8.08% of infusions were associated with headaches and 0.59% migraines with either formulation.
Discussion: Adverse events such as headache and migraine have been reported with IVIG and in some cases may be related to infusion rate, a key determinant of overall infusion time for IVIG. Analyses of the occurrence of headache and migraine showed consistently low rates when compared by age ranges, percent achieving maximum infusion rate, and diagnosis.
Conclusion: Both the 5% and 10% formulations of this IVIG product were associated with a low rate of headache and migraine across various points of comparison in patients with PI, when utilizing a 15-minute ramp-up infusion protocol.

Keywords: immune globulin, primary immunodeficiency, IVIG, infusion rate, tolerability, headache

Disclosures: Kim Clark has relevant financial relationships with proprietary interests with Bio Products Laboratory (Employment). Mark Evangelista has relevant financial relationships with proprietary interests with Bio Products Laboratory (Consultant). Eric Wolford has relevant financial relationships with proprietary interests with Bio Products Laboratory (Employment). Bob Geng has relevant financial relationships with proprietary interests with BPL (Consultant), Grifols (Advisory Board, Consultant, Speaker/Honoraria includes speakers bureau, symposia, and expert witness), Kedrion (Consultant), Koru (Advisory Board, Consultant), Pfizer (Consultant, Speaker/Honoraria includes speakers bureau, symposia, and expert witness), Takeda (Advisory Board, Consultant, Speaker/Honoraria includes speakers bureau, symposia, and expert witness).

(139) Regulatory gene expression analysis of T cell, B cell and Monocyte lineage in patients with Wiskott-Aldrich syndrome

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Introduction: Wiskott-Aldrich syndrome (WAS) is an X-linked combined immunodeficiency that occurs due to a variant in WAS gene. It is characterized by reduced or dysfunctional Wiskott-Aldrich syndrome protein (WASp). WASp plays a crucial role in the terminal differentiation of all non-erythroid hematopoietic cell lineages. We studied the real-time expression of regulatory genes involved in the maturation and differentiation of T, B, and monocyte subsets.
Design and Method:
1. 6 patients with WAS gene variants were included in the study. Flowcytometric analysis of WASp protein was carried using mouse anti-human WASp-PE (B-9) on lymphocytes.
2. Complementary DNA (cDNA) converted from extracted whole blood RNA was used to perform real-time PCR analysis. Regulatory genes for T cells, B cells, and monocytes were selected as listed in Table 1. Comparison of fold change [2^(-ΔΔCT) method] between patients and controls were performed using the Mann-Whitney U test.
Results: Of the 6 patients with WAS enrolled in the study, 4 patients had premature termination variants and 2 had splice-site variants in WAS gene (Fig 1). One patient had a genetic single nucleotide deletion in exon 10 and another somatic variant resulting in reversion of mutation. Real-time PCR analysis revealed reduced WAS gene expression in 4 patients (P1, P3, P4, P6). These patients also had low WASp protein expression. Two patients, however, had elevated WAS gene expression (P2 and P5). One of these patients (P5) had low WASp protein while (P2) had normal expression. Both of these patients had variants in Exon/Intron 10. Significant down-regulation of c-Myc (pan proliferation marker) ($p=0.005$) and FPR-2 (required for monocyte and neutrophil chemotaxis)($p=0.022$) was noted. EGR2 was also reduced in 5 patients ($p=0.073$) though failed to achieve statistical significance. GATA-3 was elevated in 3/6 patients, and TBX21, RORγT, and FOXP3 were reduced in 4/6, 4/6, and 5/6 respectively. Rest other gene expressions in patients were comparable to controls.
Conclusion: Expression of pan-proliferation marker (c-Myc) and monocyte lineage marker (FPR2) were the most affected genes in the non-erythroid blood cell compartment of patients with WAS.

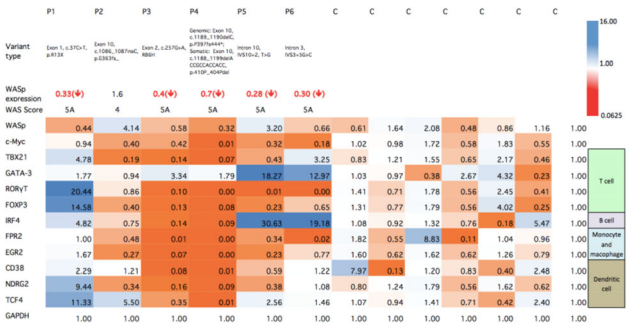

Table 1: List of genes analyzed through real-time expression in patients with WAS.

Table 1: Demographic features and outcomes for patients with humoral immune defect infected with Covid-19

		PID Patients with COVID-19	
	Received SARS-CoV-2 mAb Therapy (count)	Yes (7)	No (9)
Demographics	Age at Diagnosis (median/range)	28 (14-73)	25 (10-67)
	Diagnoses (count)	CVID (2) Hypogammaglobulinemia (2) NEMO (1) XL-SCID (1) SAD (1)	CVID (7) XL-SCID (2)
	Ethnicity (count, %)	White (4, 57.1%) Asian (1, 14.3%) Hispanic or Latino (1, 14.3%) Undisclosed (1, 14.3%)	White (3, 33.3%) Hispanic or Latino (5, 55.6%) American Indian or Alaskan Native (1, 1.1%)
Prescription	Days from symptom onset to therapy (median/range)	4 (1-10)	—
	Days from positive Covid-19 test to therapy (median/range)	2 (1-6)	—
	Which prescriber initiated mAb therapy (count, %)	Immunologist (3, 42.9%) Primary Care Provider (2, 28.6%) Emergency Medicine Provider (1, 14.3%) Pulmonologist (1, 14.3%)	—
	How many patients initiated mAb therapy request (count, %)	Patient Requested therapy (2, 2.86%) - 1 contacted immunologist - 1 presented to ED	—
	Clinical setting of mAb infusion (count, %)	Outpatient Setting (4, 57.1%) Emergency Department (3, 42.9%)	—
Outcomes	Hospital Admissions	2 of 7 patients hospitalized, for 2 and 13 days, respectively.	3 of 9 patients hospitalized, for 2, 7, and 22 days, respectively.
	ICU Admissions	0 of 7 patients required ICU stay.	1 of 9 patients required ICU stay for 8 days
	Oxygen therapy	1 of 7 patients required oxygen therapy, max of 10L flow.	2 of 7 patients required oxygen therapy, max of 5L and 2L flow respectively.

Figure 1: Heat map representing fold changes of various genes in patients with WAS.

Keywords: WASp, Real-time expression analysis, Polarization defects, Real-time PCR analysis, Master regulator gene

Disclosures: All authors indicated they had no financial relationships to disclose.

(140) Netherton Syndrome and Coconut Anaphylaxis

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Netherton syndrome is a rare, autosomal recessive disorder of skin cornification presenting with a triad of symptoms including ichthyosiform erythroderma, a bamboo pattern hair shaft abnormality termed trichorrhexis invaginata, and an atopic diathesis. Similarly, allergies to coconuts (Cocus nucifera) are very rare and few cases of anaphylaxis are reported in the literature.

We report the case of a three-year-old Cambodian American female with the rare combination of Netherton syndrome with a homozygous mutation 5 nucleotides downstream of exon 25 in the SPINK5 gene and coconut anaphylaxis without clinical tree nut allergy symptoms. Shortly after birth she developed a scaly and plaque-like erythroderma, nonspecific vomiting and failure to thrive. Laboratory findings at 31 months of age were significant for an IgE level of 1517 K/mm3 and eosinophilia of 1.3 K/mm3. Esophageal biopsies confirmed the diagnosis of eosinophilic esophagitis. Microscopic examination of hair samples showed trichorrhexis invaginate. At three years of age, the patient presented to allergy clinic for lip swelling and vomiting immediately after ingestion of coconuts. Patient tolerated peanut and tree nuts. The IgE levels showed high elevation to coconut (91 kU/L) and peanut (23.8 kU/L), minimal to no elevation to walnut, pecan, almond and cashew (up to 1.72 kUL).

Coconut allergens have previously been identified as coconut n2, coconut n4, 7S globulin, and 11S globulin. Although cross reactivity between coconuts and tree nuts have been described in the literature, children who had a positive skin test to peanuts or tree nuts did not demonstrate increased sensitivity to coconuts. Netherton syndrome involves a mutation in the SPINK5 gene, which leads to defective expression of LEKTI, a serine protease inhibitor. Defects in LEKTI lead to inability to inhibit kallekreins, which result in excessive desquamation and skin barrier defects. The atopic diathesis associated with Netherton syndrome is severe and multiple, including allergic rhinitis, food allergies, asthma, and eosinophilic esophagitis.

In summary, we report the first known case of coconut anaphylaxis in Netherton syndrome. This case attests to the severity and multiple presentations of food allergies in Netherton syndrome, likely due to excessive absorption of allergens though defective skin barriers.

Keywords: Netherton syndrome, food allergy, coconut anaphylaxis, eczema

Disclosures: All authors indicated they had no financial relationships to disclose.

(141) Multiple severe autoimmune disorders as the presenting manifestations of PID in a 10-year-old boy.

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Introduction: Common variable immunodeficiency (CVID) is one of the most common antibody deficiency diseases seen in clinical practice. Presentation is indeed variable, though most patients have hypogammaglobulinemia and recurrent infections. Other findings include autoimmune disorders and risk of malignancy. Peak age of diagnosis is around the second and third decades of life, although up to a quarter of patients will start having disease manifestations during childhood and adolescence. We present the case of a 10-year-old boy who presented with severe immune thrombocytopenia (ITP) and was subsequently diagnosed with CVID, autoimmune hepatitis, and granulomatous lung disease.

Case report: This is a 10-year-old-male who presented with severe ITP, platelets < 1K, unresponsive to standard treatment. History is positive for autism, obesity, asthma, food and drug allergies, but negative for infections. He received IVIG and his initial work up revealed low immunoglobulins (IgA of 39, IgG of < 320, normal IgM) with protective vaccine titers, and elevated liver enzymes. His B-cell phenotyping panel had inadequate numbers of memory B cells but showed skewing in the proportion of CD21+ to CD21- B cells. On follow up, his vaccine titers consistently dropped, as a result of weaning of the passive immunity provided by IVIG treatment. Diagnosis of CVID was made and IGRT was started. Liver enzymes continued rising, and biopsy revealed autoimmune hepatitis. CT scan of the chest showed innumerable pulmonary nodules, some with ground-glass halo, consistent with CVID. Pulmonary function testing showed mild restriction. Although lung tissue could not safely be obtained, a subcarinal lymph node biopsy showed mixed

lymphocytic population with rare non-specific granulomas. PID panel revealed six VUS, with one heterozygous variant on the CD19 gene related with AR-CVID. Patient is currently also receiving Romiplostim for ITP, and was started on Rituximab and Mycophenolate-Mofetil for treatment of granulomatous lung disease, autoimmune hepatitis, and ITP.
Discussion: The diagnosis of CVID is challenging, especially in children presenting with only autoimmunity. The severity of autoimmunity, specifically lung disease, in this patient is unusual. Our case highlights the heterogeneity of presentation in CVID, and the importance of recognizing autoimmune and inflammatory manifestations even when missing typical infectious features.

Keywords: CVID, ITP, Autoimmune hepatitis, Granulomatous lung disease

Disclosures: All authors indicated they had no financial relationships to disclose.

(142) Partial restoring NK cell function by enhancing of non-canonical IL-2 signaling pathway in human STAT5b-deficient NK cells

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Background: Mutations in the Signal Transducer and Activator of Transcription (STAT)5b, are associated with low numbers of NK cells and poor lytic function. IL-2 enhances cytotoxicity by promoting lytic granule convergence. Canonical IL-2 signaling requires STAT5b as a downstream effector, however, also can proceed via a non-canonical pathway that induces the Src, PI3K and MAPK proteins activation.
Here we describe a novel STAT5b homozygous mutation (c.121C>T; p.Q41X) as a cause of a NK cell functional defect with partial restoration after IL-2 stimulation. Using STAT5-deficient NK cells as human model, we herein try to elucidate the signaling components in the AKT/MAPK pathway that participate in NK cell function after IL-2 stimulation.
Methods: STAT5b expression was evaluated by Western blot. We used multiparametric flow cytometry, functional NK cell assays (standard Cr51 release assay), and microscopy to elucidate the effect of p.Q41X mutation in NK cells. The non-canonical IL-2 signaling pathway was evaluated in primary NK cells by FC.
Results: The novel STAT5b mutation (p.Q41X) determined a complete absence of protein expression. Patient had dysregulated NK cell maturation, characterized by a significant decrease in total NK cell numbers and mature CD56dim NK cell subset with low expression of terminal maturation markers and higher levels of markers associated with immature NK cells. STAT5b-deficient NK cells had decreased convergence of lytic granules to the microtubule-organizing center (MTOC) leading to impaired NK cell cytotoxic capacity. However, these defects were restored partially after IL-2 stimulation. Given the absence of STAT5b, we evaluated the non-canonical IL-2 signaling in NK cells. Prior to IL-2 stimulation, our results showed low numbers of STAT5b-deficient pAKT+ NK cells; however, under IL-2 stimulation the AKT phosphorylation recovered to levels observed in healthy donor.
Conclusions: Our work demonstrates the novel STAT5b p.Q41X mutation leads to impair the STAT5b protein expression.
The absence of STAT5b leads to aberrant maturation as well as impaired early activation events in NK cell lytic synapse formation.
Our results suggest restored granule convergence and partial improvement in killing happens through the non-canonical IL-2 pathway. Our data gives further insight into the non-canonical IL-2 signaling pathway in STAT5b deficiency.

Keywords: NK cell biology, Phenotypic and Molecular Spectrum of PID, Innate Immunity

Disclosures: Lisa Forbes-Satter has relevant financial relationships with proprietary interests with csl behring (Consultant), enzyvant (Advisory Board), Grifols (Consultant), and Takeda (Consultant). All other authors indicated they had no financial relationships to disclose.

(143) JAK3 gain-of-function variants cause CVID-like disease with Interstitial Lung Disease

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Introduction: A 64-year old male presented with chronic T-cell lymphocytosis, recurrent infections, interstitial lung disease (ILD), and CVID. Lung biopsy demonstrated marked interstitial fibrosis and CD4+ T cell inflammation with scattered random and peribronchiolar aggregates in the absence of B cells or granulomas. Two, rare JAK3 variants (S835C, A573V) were found by WES and functional studies on CD4+ T cells demonstrated persistent STAT5 phosphorylation upon stimulation with IL-15, but no phosphorylation of either STAT1 or STAT3 proteins. Herein we use molecular modeling, in vitro studies, and T cell repertoire analysis to understand the role of the JAK3 variants in the development of this unusual primary immunodeficiency (PID).
Methods: We developed molecular models of the S835C and R925S variants as well as a known GOF variant A573V. We assessed how these variants alter the phosphorylation of STAT5 protein and transcriptional responses in an IL-2 responsive HEK reporter cell line in the presence and absence of JAK3 inhibitor tofacitinib. Additionally, we assessed the patient's T cells for clonality using CDR3 sequencing of the T-cell receptor.
Results: STAT5 phosphorylation in the HEK reporter cell lines of demonstrated significantly ($P < 0.01$) increased p-STAT5 MFI in both the dual-variant S835C/R925S and known GOF variant A573V under both stimulated and unstimulated conditions. The STAT5 transcriptional response correlated with the p-STAT5 results. Molecular modeling demonstrated that both variants increased root mean squared fluctuation (RMSF) of distinct regions of the protein, resulting in transitional dynamics of the kinase domain toward an activated state. T cell clonality studies demonstrated oligoclonal skewing with a Productive Simpson Clonality of 0.2468.
Discussion: We demonstrate for the first time that GOF variants in JAK3 result in CVID with autoimmunity, oligoclonal skewing of T cells, and a unique form of interstitial lung disease. Our in vitro studies and molecular modeling demonstrate the GOF nature of the S835C and R925S JAK3 variants and confirm our prior data showing prolonged STAT5 phosphorylation in the patients PBMCs. The unique features of this PID are chronic T-cell lymphocytosis with oligoclonal skewing, a novel ILD, and defective function of STAT1 and STAT3 due to overactivity of the JAK3/STAT5 pathway.

Keywords: JAK3 GOF, CVID, T-cell lymphocytosis, Interstitial Lung Disease

Disclosures: John Routes has relevant financial relationships with proprietary interests with CSL Behring (Contracted Research) and Evolve Biologics (Contracted Research). All other authors indicated they had no financial relationships to disclose.

(144) Selective IgM deficiency: what do we know so far?

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Rationale: Selective IgM deficiency (SIgMD) was included in the new classification of Inborn Errors of Immunity in 2019 which shows how rare this deficiency is and how little we know about it. We developed a collaborative study in order to evaluate clinical and laboratory characteristics of patients with SIgMD.
Methods: 75 patients were included according to the following definitions: 1) IgM levels < 0.20 g / L in children and < 0.30 g / L in adults; 2) serum IgM levels below 2SD or according to the value in percentile 3 corrected by age; with both criteria respecting normal serum values of IgA, IgG and IgG subclasses; normal response to vaccines and absence of T cell defects and external causes.
Results: Seventy-five patients (29M:46F), 68 adults and 7 children, mean age 53 years and 97.3% with both diagnosis criteria were included. Respiratory symptoms were superior in prevalence followed by dermatological symptoms. In adults, rhinitis and asthma were more prevalent. Children presented with pulmonary infection, asthma, skin infections and diarrhea. Other findings: chromosomal disease in 14,3% and 7.35% of pediatric and adult patients, respectively. In adults, neoplasia and autoimmunity were diagnosed in 10,3% and 4,4%, respectively, while in children autoimmunity was diagnosed in 14,3%.
Conclusion: There was no difference on sex, mean age of symptom onset and order of the most affected systems between both diagnosis' criteria in children and adults. Nevertheless, the follow up of SIgMD patients is advised considering the possibility to develop autoimmunity and neoplasia.

Keywords: Selective IgM Deficiency, Hypogammaglobulinemia, IgM, Autoimmunity, Chromosomopathy

Disclosures: All other authors indicated they had no financial relationships to disclose.

(145) Pneumonia in primary antibody deficiency patients receiving immunoglobulin therapy, risk factors, and role of prophylactic antibiotics: Data from the US Immunodeficiency Network (USIDNET)

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Background: Despite immunoglobulin replacement (IgRT) therapy, some patients with Primary Antibody Deficiency (PAD) continue to develop respiratory infections. Recurrent and severe respiratory infections, particularly pneumonia, can lead to significant morbidity and mortality. Therefore, we sought to determine the risk factors for developing pneumonia in PAD patients already receiving IgRT and if the use of prophylactic antibiotics impacted occurrence.
Methods: We evaluated clinical and laboratory features of PAD patients enrolled in the United States Immune Deficiency Network (USIDNET) registry before April 2017. Patients were included if they were assigned a PAD diagnosis (common variable immunodeficiency (CVID), agammaglobulinemia, hypogammaglobinemia, and specific antibody deficiency (SAD) and had available data regarding infections before and after initiation of IgRT. Descriptive and multivariable logistic regression analyses were used to identify factors associated with pneumonia post-IgRT.
Results: A total of 1286 patients met the inclusion criteria. Following IgRT, 226 patients (17.6%) were reported to have at least one pneumonia episode. Using multivariate logistic regression analysis, we found a statistically significant increased risk of pneumonia in patients with asthma (OR: 1.79, 95% CI [1.20-2.67], p=0.004), bronchiectasis (OR: 2.81, 95% CI [1.64-4.80], p< 0.001), and interstitial lung disease (ILD) (OR: 2.90, 95% CI [1.26-6.70], p=0.013). Patients who did not receive prophylactic antibiotics had a much higher risk of pneumonia (OR: 27.65, 95% CI [8.63-88.59]; p< 0.001), compared to those who received prophylactic antibiotics. For every 50 unit increase in IgA, the odds of reporting pneumonia post-IgRT decreased significantly (OR: 0.82, 95% CI [0.69-0.97], p=0.018). Patients with X-Linked Agammaglobulinemia had a lower risk of pneumonia than other PAD diagnoses (OR: 0.84; 95% CI [0.75-0.93]; p=0.001). The infectious organism was reported in 39 of 226 patients who reported pneumonia after IgRT. Haemophilus influenzae was the most frequently reported (n=11, 28.21%), followed by Streptococcus Pneumoniae (n=9, 23.08%).
Conclusion: Our findings suggest a role for prophylactic antibiotics patients with PAD, especially in those with pre-existing lung disease. Our study is limited by the cross-sectional nature of the USIDNET database and limited longitudinal data. Prospective studies evaluating the benefits of prophylactic antibiotics are warranted.

Keywords: Primary antibody deficiency, immunoglobulin replacement therapy, prophylactic antibiotics, upper respiratory tract infections

Disclosures: Joud Hajjar has relevant financial relationships with proprietary interests with The Texas Medical center Digestive Diseases Center (Research Grant includes principal investigator, collaborator or consultant and pending grants as well as grants already received), Jeffrey Modell Foundation (Research Grant includes principal investigator, collaborator or consultant and pending grants as well as grants already received), Immune Deficiency Foundation (Research Grant includes principal investigator, collaborator or consultant and pending grants as well as grants already received) Baxalta (Research Grant includes principal investigator, collaborator or consultant and pending grants as well as grants already received), Chao Physician-Scientist Foundation (Research Grant includes principal investigator, collaborator or consultant and pending grants as well as grants already received), Takeda (Consultant/Advisory Board Member), Pharming (Consultant/Advisory Board Member), Horizon: Consultant/Advisory Board Member, and Alfaisal University (ad hoc

consultancy/speaker). All other authors indicated they had no financial relationships to disclose.

(146) Use and Outcomes of SARS-COV-2 Monoclonal Antibody Therapy in Patients with Primary Immunodeficiency

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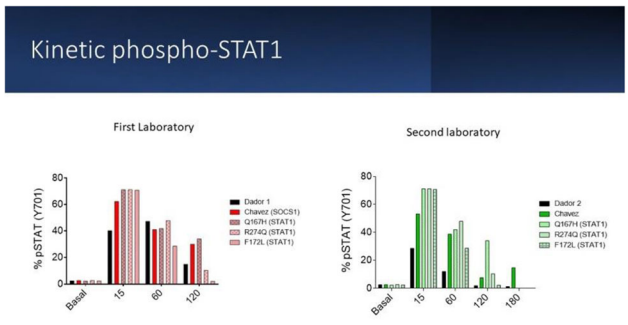
SARS-CoV-2 monoclonal antibodies (mAbs) have efficacy in reducing viral load, medical visits and hospital admission days compared to placebo in patients with COVID-19. Patients with primary immunodeficiency (PID) may particularly benefit from this therapy.
We performed a retrospective chart review of sixteen PID patients with humoral defects ages 10-73 years (median 27.5) infected with COVID-19. Diagnoses included CVID (N=9), hypogammaglobulinemia (N=2), specific antibody deficiency (N=1), X-linked SCID (N=3), and NEMO (N=1). All except one were on immunoglobulin replacement and four had received SARS-CoV-2 vaccination prior to illness.
Seven of the sixteen patients received mAb therapy with casirivimab and imdevimab (N=4) or bamlanivimab alone (N=3) a median of 4 days after symptom onset. mAb therapy was recommended by providers in immunology (N=3), primary care (N=2), and pulmonary (N=1). Two patients initiated the request for this therapy. Demographic data for treated patients was as follows: 57.1% White, 14.3% Hispanic, 14.3% Asian and 14.3% unknown. Median household income was $89,715 in the treated group and $57,652 in the untreated group. Therapy was well tolerated.
Of the patients who received mAb, two required hospital admission, one required oxygen therapy, and none required ICU care. A 70-year-old male with CVID and underlying pulmonary fibrosis from prior ARDS received bamlanivimab in the ED but worsened and required subsequent hospitalizations for COVID pneumonia where he received remdesivir, convalescent plasma, and oxygen therapy. A 14-year-old male with NEMO syndrome received mAb in the ED, but was then admitted for treatment of comorbidities. In comparison, of the nine patients who did not receive mAb therapy three required hospitalization for COVID pneumonia, one of which was complicated by bacterial pneumonia, two required oxygen therapy, and one required an extended ICU stay. There were no deaths reported in either group.
This is the first report describing prescribing practices and outcomes for PID patients who received mAb therapy. Case series limitations include the small number of patients examined and the variety of disease states and outcomes reported. As the Covid-19 pandemic continues, studies are needed to examine the outcomes for these patients and identify which patients will benefit most from this therapy.



Keywords: SARS-CoV-2, Covid-19, monoclonal antibody therapy, REGN-COV2, antibody deficiency

Disclosures: All authors indicated they had no financial relationships to disclose.

(147) Utility of HLA-DR in screening panel for inborn errors of immunity

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Introduction: Comprehensive evaluation of immune parameters at the time of screening for inborn errors of immunity (IEIs) provides valuable information about the underlying immune defect. In 2019, our centre ICMR-National Institute of Immunohaematology adopted a comprehensive screening panel which is modified from the Euro-flow recommended PIDOT tube, the difference being the addition of HLA-DR in the screening tube. In the present study, we conducted a retrospective analysis of well-characterized cases of IEI diagnosed in 2019-2020 to evaluate the utility of HLA-DR at the time of screening.
Methodology: HLA-DR expression on CD3+T, its CD4+ and CD8+ subsets, NK and double negative T cells (DNT) were compared between patients and healthy controls. All statistical calculations were done using GraphPad prism (Chicago, IL, USA) version 8 for Microsoft Windows.
Result: The HLA-DR expression on CD3 T, CD4 and CD8 T cell subsets (%) in identified IEIs, as compared to healthy controls are represented in Figure 1.
HLA-DR expression on CD3 T cells or its subsets was significantly elevated in leaky Severe combined immunodeficiency (SCID) and Omenn's phenotype($p< 0.001$), and combined immunodeficiencies($p< 0.05$) including DOCK8 deficiency along with presence of low naïve T cells. We were also able to diagnose an atypical case of MHC II deficiency with high CD4 counts due to absence of HLA-DR expression on CD3 T cells and monocytes.
HLA-DR expression on CD3/NK cells was elevated in all f HLH (familial haemophagocytic lymphohistiocytosis) patients (p 0.05) (range:16% - 64%). The expression was higher on CD8 compared to CD4 T cells (p value 0.0078), with the ratio of HLA-DR on CD8/HLA-DR on CD4 ranging from 1.2-6.1(median 2.2). HLA-DR expression on double negative T cells (DNT) was significantly elevated in autoimmune lymphoproliferative syndrome (ALPS).
Elevated HLA-DR expression was observed in those patients of common variable immunodeficiency (CVID) who had developed complications in the form of autoimmune manifestations, or bronchiectasis.
Conclusion: Evaluation of HLA-DR expression during screening can be provide corroborative clues to diagnosis of IEI along with other immunological abnormalities and help diagnose atypical cases. In addition, it can also be a pointer for early identification of complications in CVID patients.

Keywords: HLA-DR, inborn errors of immunity, CD3 T cells

Disclosures: All authors indicated they had no financial relationships to disclose.

(148) New insights into IKBKB- GOF-disease

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Introduction: Homozygous mutations in IKBKB with complete loss-of-function of IKK2 cause SCID (Pannicke et al. 2013) whereas heterozygous IKBKB mutations cause less severe combined T- and B- cell deficiencies (Cardinez et al. 2018).
Clinical characteristics: Patient A is a 16 year-old female who presented at age six with recurrent skin infections and was at first diagnosed with an IgG2 subclass deficiency. Immunophenotyping, however, revealed combined immunodeficiency (CID). Recurrent upper respiratory tract infections and signs of chronic sinusitis prevailed during adolescence. Also, she developed chronic non-malignant lymphoproliferation. She is currently treated for her CID with weekly SCIG and cotrimoxazole as PCP prophylaxis.
Patient B is a 48 year-old male who was diagnosed with CVID at age 16. He had recurrent episodes of pansinusitis and chronic otitis media. Moreover, he suffered from multiple pneumonias resulting in pulmonary lobar resection and bronchiectases since his teens. He was substituted with IVIG through adolescence and was switched to SCIG in adulthood. Infectionwise he has been stable since. In his 40es, he was diagnosed with uveitis, iridocyclitis and chorioretinitis possibly following toxoplasmosis infection leading to partial loss of vision.
Immunological and genetic characteristics: Immunophenotyping in patient A revealed an absolute reduction in T- and B-cell numbers. Functional testing showed severe impairment in both compartments. Patient B had absence of class-switched b cells, but no evidence of T-cellular abnormalities. Western Blot analysis revealed prolonged p65-phosphorylation in the nuclear and cytosolic compartment of both patients and elevated IkBa-phosphorylation upon stimulation with TNFα in EBV-transformed B-cells indicating enhanced NFkB-signaling.
Patient A carries the well-described variant c.607G>A (p.Val203Ile, heterozygous) in IKBKB, consistent with her CID phenotype. Patient B carries the variant c.368T>C (p.Leu123Pro, heterozygous). Both variants are located within the kinase domain of IKK2 and probably interrupt the helix structure in this region.
Conclusion: In conclusion, we present two patients with IKK2 dysfunction associated with GOF in NFkB-signaling, including a novel disease-causing mutation in IKBKB. Moreover, we show that IKBKB GOF may also present as CVID without obvious T cell abnormalities.

Keywords: IKBKBGOF, CID, CVID, NFkB-signaling

Disclosures: All authors indicated they had no financial relationships to disclose.

(149) Immune profiling in Multisystem inflammatory syndrome in children (MIS-C): experience from a single centre from India

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Introduction: MIS-C is considered a late manifestation of COVID-19 characterized by multi-organ dysfunction. We studied immunological characteristics in MIS-C patients diagnosed at BJ Wadia Hospital for Children, Mumbai, India from October 2020 to September 2021.
Methodology: Immune-profiling in 22 MIS-C patients, and 10 healthy controls was performed comprising of major lymphocyte and monocyte subpopulations and the expression of key activator and inhibitory receptors. We also compared the immunological abnormalities between MIS-C and severe COVID-19 disease among adults.
Results: The range of clinical manifestations and spearman correlation of patient characteristics are depicted in Figure 1.
Immunological abnormalities comprised of significantly reduced absolute T (median 597, range 318-1782/μl) and NK (median 61, range12-86/ μl) lymphocytes compared to controls. Majority of the NK cells were early NK cells. Only the percentage of B lymphocytes was reduced at enrolment, whereas at Day 14, both percentage and absolute counts were reduced.
Classical, intermediate, and non-classical monocytes were elevated compared to controls ($p< 0.0001$). The difference between classical and non-classical monocytes in PIMS-TS patients was also significant ($p< 0.0001$).
Given their role in viral infection, we focused on the activation and exhaustion of T cells and its subtypes. HLA-DR expression on T cells, CD4 T cells and CD8 T cells was elevated compared to controls, though not statistically significant. The expression of HLA-DR, PD1 and Tim3 on CD8 was more as compared to CD4 T cells ($p< 0.0001$) which is expected in viral infections and reduced over a period of two weeks to levels below controls. Regulatory T cells were significantly elevated at Day 14. As compared to adults with severe COVID-19, the patients with PIMS-TS had higher absolute and percent of T cells, ($p< 0.001$) and their subsets, activation (HLA-DR with $p< 0.0005$), and exhaustion markers ($p< 0.00001$)), absolute and percent NK cells, percent monocyte subsets ($p< 0.00001$), and B cells including percentage memory and class switched B subsets ($p < 0.0001$).
Conclusion: MIS-C results from the continuing immune insult instigated by the COVID-19 infection and immune-dysregulation resulting in hyper-activation and exhaustion of immune cells of both the innate and adaptive immune system.

Keywords: MIS-C, immuneprofile, activation, exhaustion

Disclosures: All authors indicated they had no financial relationships to disclose.

(150) Immunophenotyping by flow cytometry facilitates diagnosis of T-cell prolymphocytic leukemia: A case report

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T-cell prolymphocytic leukemia (T-PLL) is a rare, aggressive, mature T-cell lymphoproliferative disorder with a median age at presentation of 65 years, accounts for 2% of mature lymphocytic leukemias. Patients typically present with widely disseminated disease at diagnosis, and primary clinical features include a striking leukocytosis with atypical lymphocytosis, hepatosplenomegaly, lymphadenopathy, skin lesions, and serous effusions. A precise diagnosis is important in determining optimum patient management and treatment. Using multiparameter flow cytometry with a large combination of antibodies, the immunophenotypic features of T-PLL may help distinguish this entity from other T-cell malignancies. A 52-year-old male presented with a history of weakness, palor, weight loss, enlarged cervical and axillary lymph nodes, gross splenomegaly, maculo-papular skin rash of two months duration. There was marked leucocytosis, anemia and thrombocytopenia (WBC-793,863/cm, Hb-7.5gm/dl, Platelet-40,000/cmm) with high serum LDH (1219 U/L).
The peripheral blood film showed gross shift to the left with most of the cells are monomorphic mononuclear cells with high nuclear/cytoplasmic

ratio and basophilic scanty agranular cytoplasm resembling lymphoid blast (about 81% prolymphocytes). The bone marrow aspirate smear was hypercellular with an excess of prolymphocytes (74%). Leukemia genetic profile by real Time PCR showed BCR-ABL gene- Negative; t (12;21) (P13; q22) –Negative; t (4;11) (q21; q23) –Negative; t(9;11)(q21-22;q23) –Negative; t(11;19)(q23;P13.3) –Negative. TCL1 gene rearrangement was demonstrated by FISH. Immunophenotyping of acute leukemia full panel was not consistent with acute leukemia. Flow cytometric analysis of blood with lymphoma panel revealed a distinct population of atypical cells of which 99.7% were CD3 positive that represents T-lymphocytes. These cells showed positivity for CD2, CD5, CD7, CD4, CD8, cyCD3 but negativity for CD1a, TdT, CD30, BCL2, CD95, CD25 and marker of immaturity CD34. Markers of B cells (CD19, CD20, CD10, CD22, CD23, FMC7, kappa, lambda) and NK cell (CD56) were negative. CD52 showed strong expression, a target of alemtuzumab frequently used to treat this neoplasm. Based on clinical data, morphologic features, immunoprofile and cytogenetics/FISH, the case was diagnosed as T-cell prolymphocytic leukemia (T-PLL). The patient started on alemtuzumab but subsequently lost to follow up. Flowcytometry immunophenotyping is a useful tool in distinguishing T-PLL from other mature T-cell neoplasms.

Keywords: T cell, Prolymphocytes, Immunophenotyping, CD52, lymphoproliferative disorders

Disclosures: All authors indicated they had no financial relationships to disclose.

(151) The impact of Reconstitution of Specific Antibodies by Intravenous Immunoglobulin in Lower Rates of Reinfection in Solid Organ Recipients with Infection: A Multicenter Randomized Clinical Trial

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Background and Aims: In a multicenter randomized clinical trial, we evaluated the safety, efficacy and immunological reconstitution of an intravenous immunoglobulin (IVIG) protocol to decrease the rate of reinfection in solid organ recipients with severe infections and secondary antibody deficiency.
Methods: Distribution: Heart 20, Lung 15, Kidney 5, Liver transplantation 4 were randomized. Patients with post transplant severe infections and secondary antibody deficiency (defined as IgG < 600 mg/dL) were included. IVIG protocol: Two doses of 15 grams (interval between doses 7-15 days) followed by another 3 doses of 20 grams (interval between doses 15-30 days) of a 5% IVIG product. 39 patients that completed the protocol were analysed [IVIG in combination with conventional antimicrobial therapy (n=21) versus conventional antimicrobial therapy alone (n=18)]. Specific antibodies were tested at inclusion in the clinical trial and 30-45 days after last IVIG dose (last-visit) in a subgroup of patients to assess the kinetics of humoral immunity reconstitution.
Results: The primary outcome measure (rate of reinfection) was significantly lower in patients randomized to receive IVIG as compared with patients receiving only conventional antimicrobial therapy (28.6 vs 66.7%, chi-square test, p=0.017). Significantly higher levels of specific IgG anti-cytomegalovirus, IgG anti-clostridium difficile toxins A and B and IgG1 anti-tetanus toxoid antibodies was demonstrated at last-visit in patients who received IVIG as compared with patient that were treated with antimicrobial therapy alone. Reconstitution of specific antibodies profile was more clearly associated with clinical response than IgG reconstitution. A correlation between total IgG and specific antibodies was only observed in IVIG group. A significant decrease of serum BAFF levels was demostrated in IVIG treated patients. IVIG infusions were well tolerated. The prevalence of severe adverse events was similar in both groups none of which was considered to be related with IVIG by investigators.
Conclusions: In a multicenter randomized clinical trial we have demonstrated that IVIG is associated with a lower rate of reinfection in solid organ transplantation with severe infection and secondary IgG hypogammaglobulinemia. The role of specific antibody reconstitution seems to be a relevant component of efficacy. Future clinical trials are warranted in this indication.

Keywords: Solid Organ Transplantation, Infection, Secondary Antibody Deficiency, Intravenous Immunoglobulin, Randomized Clinical Trial

Disclosures: Elizabeth Sarmiento has relevant financial relationships with proprietary interests with Grifols Inc USA (Contracted Research). Ikram Ezzahouri has relevant financial relationships with proprietary interests with Grifols Inc USA (Contracted Research). Javier Carbone has relevant financial relationships with proprietary interests with Grifols Inc USA (Research Grant includes principal investigator, collaborator or consultant and pending grants as well as grants already received, Speaker/Honoraria includes speakers bureau, symposia, and expert witness). All other authors indicated they had no financial relationships to disclose.

(152) WHIM syndrome diagnosed by myeloid next generation sequencing in an 18-year-old male with leukopenia

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WHIM syndrome (warts, hypogammaglobulinemia, infections and myelokathaxis) is a combined immunodeficiency that is caused by autosomal dominant mutations in CXCR4, leading to gain of function activity. This leads to failure of mature neutrophils to exit the bone marrow. CXCR4 is also important in the cell trafficking of T-cells and B-cells. Hence, lymphopenia is a common feature of this condition. There is variability in clinical presentation of WHIM syndrome, and the majority of patients do not exhibit all the above four features.
An 18-year-old male presented to our clinic for the evaluation of leukopenia (neutropenia and lymphopenia). He had no history of warts. Infection history was significant for one scrotal abscess requiring drainage, but was otherwise unremarkable. The absolute neutrophil count was 180/mm3 and the absolute lymphocyte count was 390/mm3. His lymphocyte enumeration showed T cell lymphopenia and significant B cell lymphopenia (CD3 56.4%, 237 T-cells/mm3, CD19 1.8%, 8 B-cells/mm3). Cellular immunocompetence profile showed a normal lymphocyte response to PHA. His immunoglobulin levels were normal and he had robust antibody titers to tetanus, diphtheria and several strep pneumoniae serotypes. Neutropenia and lymphopenia have continued to wax and wane with most recent absolute neutrophil count of 50/mm3. Bone marrow biopsy showed a normocellular marrow with normal trilineage hematopoiesis. Myeloid next generation sequencing identified a CXCR4(NM_003467)c.1014del(p.Ser339LeufsTer27) frameshift deletion in exon 2, which likely explains his phenotype. To our knowledge, this variant has not been described in the literature. He has a family

history of leukopenia in his father and maternal grandmother, but neither have been evaluated for this.
The patient's lack of warts, hypogammaglobulinemia, and recurrent infections despite his profound neutropenia and lymphopenia is of particular interest. This exemplifies the diversity of clinical presentation seen in some primary immunodeficiency disorders. Given the profound B-cell lymphopenia, which is likely due to altered B lymphocyte trafficking, we checked a primary immunodeficiency NGS panel to evaluate for other molecular causes that may explain his leukopenia, and the results are pending.
We are considering starting him on prophylactic antibiotics given his profoundly low neutrophil count. Additional considerations include the use of G-CSF, plerixafor and selective CXCR4 antagonists.

Keywords: WHIM syndrome, CXCR4, leukopenia, next generation sequencing

Disclosures: Talal Mousallem has relevant financial relationships with proprietary interests with Chiesi (Advisory Board, Research Grant includes principal investigator, collaborator or consultant and pending grants as well as grants already received). All other authors indicated they had no financial relationships to disclose.

(153) Primary Ciliary Dyskinesia Genetic Findings in a Cohort with Bronchiectasis

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Introduction: Primary ciliary dyskinesia (PCD) is a genetically heterogeneous condition characterized by abnormal motile cilia structure and function. Individuals present with recurrent respiratory infections (often associated with bronchiectasis), infertility, and sometimes, situs abnormalities. To date, 51 genes have been reported in association with PCD, but our understanding of their frequency and variant classification is minimal. Here we describe the genetic findings in a cohort of individuals with syndromic or idiopathic bronchiectasis with emphasis on PCD, along with incidental findings that highlight the importance of considering multiple diagnoses.
Methods: Individuals with bronchiectasis underwent research-based exome or genome sequencing with clinical-grade interpretation. All variants reported to patients were validated by Sanger sequencing.
Results: Of the 237 individuals referred for bronchiectasis, 23 (9.7%) individuals received a report containing at least one PCD-related variant in a homozygous, compound heterozygous, or heterozygous state. We detected variants in 14 distinct PCD-related genes, and variants in DNAH5 were detected most frequently (n = 9, 23.7%). Regarding variant classification, most variants were pathogenic (n = 17, 44.7%) or of uncertain significance (VUS) (n = 17, 44.7%). Additionally, 15 (6.3%) individuals were identified as monoallelic carriers of a pathogenic or likely pathogenic variant in CFTR; there is limited but replicated evidence suggesting that carriers may develop bronchiectasis over time. There were 12 instances of incidental findings in the cohort, including in ACMG secondary findings genes. Two instances of incidental findings occurred in the individuals with PCD, including a patient with hearing loss that was homozygous for a pathogenic variant in GJB2 that was determined to be the underlying etiology.
Conclusion: Here we summarize the molecular findings in a cohort of individuals with bronchiectasis. Given the genetically heterogeneous nature of PCD, it is important to characterize the frequency of variants in PCD-related genes to better understand the underlying cause of disease. Additionally, these results underscore the importance of considering multiple genetic etiologies as this has implications for recurrence risk and medical management. Given what is known about the genetic architecture of bronchiectasis, the multiple etiologies (including PCD), it is likely that there is further genetic contribution yet to be elucidated.

Keywords: Bronchiectasis, Primary Ciliary Dyskinesia, Genetic, Exome, Genome, Cilia, Clinical

Disclosures: All authors indicated they had no financial relationships to disclose.

(154) Immune Profile of Inadequate Antibody Response to mRNA SARS-CoV-2 Vaccine in Adolescent Kidney Transplant Recipients

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Introduction: mRNA SARS-CoV-2 vaccines are highly efficacious in the general population but have shown diminished response in immunosuppressed adult solid organ transplant recipients. Adolescent kidney allograft recipients at Rady Children's hospital have also showed diminished efficacy when compared to the healthy adult and adolescent population. We investigated immunological parameters that could be associated with a blunted antibody response.
Methods: Adolescent kidney transplant recipients who received mRNA SARS-CoV-2 vaccine had SARS-CoV-2 spike protein antibody levels measured 4-8 weeks after their second vaccine dose. Immunological labs including lymphocyte subsets, immunoglobulin levels, and vaccine titers and immunosuppressive medication dosing were evaluated prior to vaccination. Patients were compared in groups of vaccine responders vs non-responders via a Mann-Whitney U test. The impact of increasing mycophenolate mofetil dosage on immune parameters was analyzed via a linear regression model.
Results: Fourteen of 27 vaccinated subjects had a positive spike antibody level. There was no significant difference in immunoglobulin levels, T-cell populations, or vaccine titers. There was a trend toward negative spike antibodies with higher doses of mycophenolate mofetil, MMF, at 91 mg/m2/day median difference (p=0.06). All four patients receiving azathioprine instead of MMF developed spike antibodies. Non-responders had lower hemoglobin levels (β=-1.30, p=0.009) and lower platelet count (β=-56.00, p=0.057). MCH levels were normal in both groups. Non-responders showed a trend toward increased naïve B-cell percentage (β= 12.50, p=0.11) and decreased total memory B-cell percentage (β=-12.54, p=0.080). Increasing MMF dosage was associated with an increase in naïve B-cell percentage (β=0.016, p=0.0032) decrease in total memory B-cell percentage (β=-0.016, p=0.0034) and IgG level (β=-0.35, p=0.012).
Conclusion: Disruption in B-cell population could be due to immunosuppression with MMF. Non-responders showed trends toward high MMF dosage, increased naïve B-cell percentage, and decreased total memory B-cell percentage. Increasing MMF dosage was associated with all trends as well as decreased IgG levels. Decreased hemoglobin levels and normal MCH signal that anemia is not due to iron deficiency but could be due to bone marrow suppression caused by MMF. Altered B-cell populations and MMF therapy are a potential biomarker and culprit for reduced efficacy of SARS-CoV-2 vaccine in adolescent kidney allograft recipients.

Keywords: vaccine, transplant, mycophenolate

Disclosures: All authors indicated they had no financial relationships to disclose.

(155) Suppresor of cytokine signaling 1 (SOCS1) deficiency in a common variable immunodeficiency patient

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Introduction: Suppressor of cytokine signaling (SOCS) proteins function as important negative regulators of cytokine signaling, which impacts on multiple immune pathways. These proteins exert their action by interacting with Janus kinases (JAKs), tyrosine kinase-2 (TYK2) and certain surface cytokine receptors. SOCS1 binds and inhibits the phosphorylation of JAK1/2 and TYK2, thus, acting as a negative regulator of type I and II Interferon mediated signals. Aim: to describe clinical features and laboratory findings of a patient with CVID due to novel SOCS1 variants. Results: An 8-year-old male, sixth son of non-consanguineous parents, with no relevant prenatal history. Personal history: vitiligo, cat-scratch disease with no complications. Family background: asthma. He started with abdominal pain due to splenomegaly. First laboratory tests showed leukopenia and thrombocytopenia. Lung images showed bilateral small nodules associated with subcarinal and retroperitoneal lymph nodes. Malignancies and infectious diseases were ruled out. Bronchoalveolar lavage had an abnormal cytological pattern with increased lymphocytes infiltration. Lung biopsy: tuberculoid-like necrotizing granuloma in the superior lobe and granulomatous-lymphocytic interstitial lung disease (GLILD) in the middle lobe with negative EBERs and CMV, positive CD3 and CD20. Immunological findings revealed panhypogammaglobulinemia. Partial response to vaccines with normal response to tetanus toxoid. Moderate CD4+ and severe B cells lymphopenia. Low naive T-cells with concomitant increase levels of central memory CD4+ and terminal effector CD8+ cells. High expression of activation markers. Increased circulating follicular T cells (Tfh) with a skew towards a Tfh1 profile. Elevated double-negative T cells and reduced Th17+CD4+ T cells. Normal counts of FOXp3+, CTLA4 and ICOS expression. Impaired B-cell subsets showed low switched-memory cells with high frequencies of CD21low B cells. Normal lymphoprolipheration assay (CD4+ and CD8+). He initiated intravenous immunoglobulin replacement, 4 antituberculous drugs, high dose prednisolone and mycophenolate with good response. Whole exome sequence revealed two heterozygous c.365G>A and c.368C>A variants in the same allele of SOCS1 gene. Enhanced phospho-STAT1 kinetic assay confirmed the pathogenic role of these variants. Conclusion: we describe the first SOCS1 deficient Argentinean patient with CVID phenotype and dysregulation. This case highlights the importance of molecular diagnosis in developing countries for possible future targeted therapies.

	Abs. count	Ref. range
CD3 +	21,039	2533-6778/mm^3
CD4 +	8989	1392-5210/mm^3
CD8 +	12,073	652-2449/mm^3
CD19 +	4018	745-3499
NK Cells	1316	194-994/mm^3
CD8+ Effector Memory	0.06%	0.37-10.32%
CD8+ Naïve	96.97%	47.10-91.30%
CD4+ Effector Memory	0.08%	0.34-5.53%
CD4+ Naïve	97.90%	61.9-89.05%
IgG	462	165-781 mg/dL

Keywords: SOCS1, Immune dysregulation, GLILD, CVID, STAT1

Disclosures: All authors indicated they had no financial relationships to disclose.

(156) Severe respiratory syncytial virus infection and Haemophilus bacteremia as a presentation for aplastic anemia

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Case Report. A 22-month-old boy with a minor upper respiratory infection was admitted to intensive care for acute respiratory failure and septic shock. Pancytopenia (most severely, neutropenia at 0/mm3 and thrombocytopenia at 22,000/mm3) and elevated inflammatory markers were noted. Sepsis with respiratory syncytial virus and nontypeable Haemophilus influenzae bacteremia were diagnosed. Recovery was slow, and included 12 days of extracorporeal membrane oxygenation and 25 days of need for mechanical ventilation. While bacteremia quickly resolved, nasopharyngeal viral RNA-positivity persisted for 3 weeks. There remains no improvement on pancytopenia for now >11 weeks, despite trials of filgrastim. C-reactive protein remains high, and periodic elevations on ferritin and transaminases were seen. He is now a hematopoietic cell transplant candidate.
The child's past history was significant for conception by in vitro fertilization, mild eczema, and on-and-off minor respiratory infections after starting day care. Developmental milestones were intact. Routine vaccinations were received. No pre-illness complete blood count has been

done in the patient, though there was evidence of sub-par pneumococcal vaccine responses and class 2/3 food IgE responses at age 10 months.
After initial suspicions for hemophagocytic lymphohistiocytosis, a diagnosis of aplastic anemia was made. Bone marrow was grossly hypoplastic, with residual lymphocytes with few myeloid and erythroid progenitors. A 116-gene panel for bone marrow failure syndromes was negative; a hemophagocytic lymphohistiocytosis gene panel is pending. A 407-gene primary immunodeficiency panel showed variants of unknown significance in CLCN7, NLRP1, PSTPIP1 and SH3BP2. Diepoxybutane clastogen testing for Fanconi anemia was inconclusive. Telomere studies showed low-normal or very low telomere lengths for all leukocyte subpopulations, but were not sufficiently supportive for a dyskeratosis congenita diagnosis. For this case, it remains unclear if the patient has a genetic immune predisposition that allowed for a severe viral/bacterial co-infection, or if his infection/s or initial drug exposures triggered a prolonged aplastic anemia.

Keywords: Aplastic anemia, Respiratory syncytial virus, Haemophilus influenzae, Children, Infection

Disclosures: All other authors indicated they had no financial relationships to disclose.

(157) Improved long-term immune reconstitution surveillance after hematopoietic stem cell transplant for primary immunodeficiency with the Program for Integrated Immunodeficiency and Cellular Therapy

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Introduction: Assessing the long-term quality and durability of immune reconstitution in a comprehensive and systematic fashion after hematopoietic stem cell transplant (HSCT) for primary immunodeficiency (PID) is crucial to identifying clinically actionable changes before complications arise. Immune reconstitution after HSCT for PID can vary significantly based on the underlying diagnosis and the type of graft and conditioning regimen used. Formed in late 2011, the Program for Integrated Immunodeficiency and Cellular Therapy (PIICT) at the Children's Hospital of Philadelphia (CHOP) integrates the expertise of Immunology and Cellular Therapy to provide long-term care for patients with severe primary immunodeficiencies who have undergone HSCT.
Aims: This study aims to evaluate the effectiveness of CHOP's multidisciplinary PIICT clinic in facilitating comprehensive, longitudinal evaluations of immune reconstitution at two and five years after HSCT for primary immunodeficiencies.
Methods: Laboratory data from patients who underwent HSCT at CHOP from 2000 to late 2019 for primary immunodeficiency diagnoses, including severe combined immunodeficiency (SCID), chronic granulomatous disease (CGD), Wiskott-Aldrich syndrome, hemophagocytic lymphohistiocytosis (HLH), IPEX syndrome, and hyper-IgM syndrome, were retrospectively reviewed. At two and five years post-HSCT, it was noted whether evaluation including T and B cell phenotyping, engraftment studies, total immunoglobulins, lymphocyte mitogen stimulation, T cell receptor excision circles, and T cell receptor spectratyping were completed, with a cutoff of six months before and after these timepoints. Data from before and after the advent of the PIICT clinic in late 2011 were compared.
Results: Each component of the comprehensive immune reconstitution evaluation was assessed at a significantly higher rate at the important two and five year timepoints post-HSCT for PID after the introduction of CHOP's PIICT clinic.
Conclusions: Achieving robust immune reconstitution after HSCT for PID is essential for preventing late morbidity and mortality due to opportunistic and other serious infectious complications. An integrated, multidisciplinary approach will likely help facilitate comprehensive, systematic surveillance of long-term immune reconstitution after HSCT for PID, with the goal of improving lifelong patient outcomes.

Keywords: Primary immunodeficiency, Bone marrow transplant, Immune reconstitution, Late effects

Disclosures: Jennifer Heimall has relevant financial relationships with proprietary interests with ADMA (Advisory Board), CIRM (Consultant, Other Financial or Material Support, Data Safety Monitoring Board), CSL Behring (Advisory Board, Consultant, Research Grant includes principal investigator, collaborator or consultant and pending grants as well as grants already received), Horizon (Advisory Board), Regeneron (Contracted Research), and UpToDate (Other Financial or Material Support, Section Author). All other authors indicated they had no financial relationships to disclose.

(158) Systematic exploration of mosaic variant patterns in blood samples of a primary immunodeficiency cohort referred for research exome sequencing.

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Exome sequencing detects somatic mosaic variants that are present at lower variant allele fractions (VAF) than those typically observed for heterozygous germline variants. Low VAF can result from clonal hematopoiesis (CH) that has been associated with increased risk of hematological malignancies. The extent to which defects in inborn errors of immunity (IEI) influences CH is not well known. We analyzed the pattern of somatic variants from blood samples of patients who participated in research exome sequencing at the NIAID, a subset of whom had a genetic diagnosis in an immune disorder-related gene.
We detected 167,703 rare somatic mosaic variants (VAF less than 0.3) from exome sequences generated from blood-derived DNA of 2,841 individuals using LoFreq2, an algorithm that detects variants with low VAF. To determine the effect of germline defects in IEI on CH, we characterized the pattern of mosaic variants in 62 patients harboring germline pathogenic (P) or likely pathogenic (LP) variants in GATA2. Consistent with published reports, in patients with a P/LP GATA2 variant, we detected mosaic variants in several genes including ASXL1, STAG2, and DNMT3A. We also observed variants in KANSL1 and CTCF among others in these patients. We compared these findings with two groups of patients: 1) patients diagnosed with a germline P/LP variant in NLRP3 (NLRP3 group, n=34) and 2) patients without a genetic diagnosis (ND, n=1,330).
In contrast to our findings in GATA2 patients, we did not detect any somatic variants in ASXL1 or DNMT3A in the NLRP3 group. Additionally, the percentage of patients with somatic variants in STAG2 and KANSL1 were significantly lower in the NLRP3 and the ND group. In genes previously reported to be recurrently mutated in myelodysplastic syndromes, 39.3% of the variants were putative loss of function in GATA2 patients compared to 7.8% in the NLRP3 group and 26.5% in the ND group.
Our data identified pattern of somatic variants specific to patients with GATA2 deficiency. Further investigation of the nature and pattern of mosaic variants may provide insights into how IEI may affect CH and contribute to newer methods for prognostication or potential new diagnoses.

Keywords: Mosaic variants, Clonal hematopoiesis, Inborn errors of immunity

Disclosures: All other authors indicated they had no financial relationships to disclose.

(159) Persistently positive COVID-19 Antibodies after 19 months in an asthmatic patient

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Introduction: Despite more than 1.5 years of the ongoing COVID-19 pandemic, there remain many unknowns. In particular, the longevity of protection from reinfection versus vaccination has been a concern. While studies have demonstrated that prior infection decreases risk of reinfection, a more recent analysis reported increased risk of infection with prior infection alone compared to fully vaccinated patients. And while prior data showed that even just one dose of a mRNA COVID-19 vaccine in those with previous infection could produce antibody titers similar to the 2-dose series in those without prior infection, there is limited data on the durability of vaccine response in those with previous infection and full vaccination. We present a case of a patient with COVID-19 infection at the beginning of the pandemic and evidence of sustained antibody response.
Case: 44-year-old male with mild-to-moderate persistent asthma was diagnosed with COVID-19 infection in March 2020 by nasopharyngeal SARS-CoV-2 PCR after travel to Madrid, Spain. He was hospitalized for COVID pneumonia and ARDS, requiring intubation. He did not receive any biologic therapies, but only received brief course of steroids. He recovered and was discharged after 2.5 weeks of hospitalization. SARS-CoV-2 total IgG antibody testing in April 2020 was positive, prior to availability of specific nucleocapsid and spike protein antibody testing.
He received COVID-19 vaccination with Pfizer 2 dose series in January 2021. Now 8-9 months later, he continues to have positive SARS-COV-2 nucleocapsid and spike antibodies (>250 U/mL, ref: < 0.80 U/mL). He has not had known reinfection and subsequent repeat PCR testing has been negative on several occasions.
Discussion: Persistence of high titer, neutralizing antibodies is the desired effect of vaccination or previous infection to prevent reinfection. Studies have demonstrated that initial infection with SARS-CoV-2 most often leads to seroconversion, but the degree of antibody titer may vary with symptomatology (asymptomatic patients have been reported to have lower titers). Therefore vaccination, even in those with previous infection, is recommended. The presented patient demonstrates that prior infection, in combination with vaccination, can induce long lasting high titer antibodies.

Keywords: COVID-19, Antibody, Vaccine

Disclosures: All other authors indicated they had no financial relationships to disclose.

(160) Novel NF-kappa B Inhibitor Alpha Gain of Function Variant in an Infant with Lymphocytosis, and Recurrent Serratia Bacteremia

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NF-kappa B inhibitor alpha (NFKBIA) encodes a protein, IkBa, that inhibits the NF-kappa-B signaling pathway which plays an important role in the activation of the immune response. The gain-of-function (GOF) variant of NFKBIA is associated with autosomal dominant ectodermal dysplasia with immunodeficiency and is characterized by defective B and T cell function and the lack of memory B and T cells despite marked peripheral blood lymphocytosis. The clinical phenotype is variable with many patients needing bone marrow transplants.
Case Description: A 7-week old male infant born prematurely at 33 weeks via emergency C-section for non-reassuring fetal heart tones in the setting of IUGR and oligohydramnios was noted to have thrombocytopenia and a diffuse erythematous rash at birth as well as multiple congenital abnormalities (micrognathia, ear cupping, 13 ribs bilaterally, and cardiac calcifications). He also had encephalomalacia on head imaging thought to be antenatal in origin. The patient had a normal TREC count. There was concern for atypical SCID given his history of recurrent MSSA and Serratia bacteremia and profoundly low lymphocyte proliferation to mitogens in the setting of elevation in all lines of lymphocyte subsets on flow cytometry and hypogammaglobulinemia. The patient was started on antimicrobial prophylaxis with Azithromycin, Fluconazole and Bactrim, and IgG replacement therapy. Expedited whole exome sequencing was obtained and revealed a mutation in NFKBIA c.91G>A;p.Asp31Asn, a novel de novo heterozygous variant. Confirmatory testing performed at Dr. Casanova's lab on fibroblasts cultured from patient's skin biopsy showed abnormal IkBa degradation upon TNF and IL-1 stimulation. Also, the patient's fibroblasts had decreased IL-6 production upon TNF and IL-1 stimulation as compared to healthy controls consistent with a gain of function mutation. While his clinical course has been complicated by recurrent episodes of Serratia bacteremia and intractable status epilepticus with MRI findings of diffuse cerebral volume loss and hypomyelination, patient is currently being stabilized prior to planned stem cell transplant.
Conclusion: NFKBIA gain of function variant should be suspected in children with recurrent infections, marked lymphocytosis and defective T cell function. We have confirmed that NFKBIA p.Asp31Asn is a gain of function mutation based on fibroblast analysis.

Figure 1

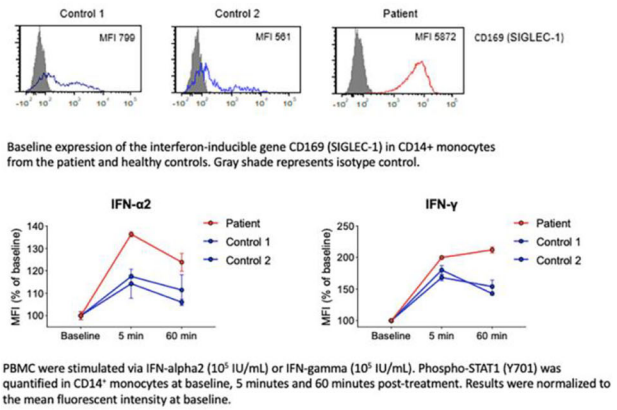

Figure 2

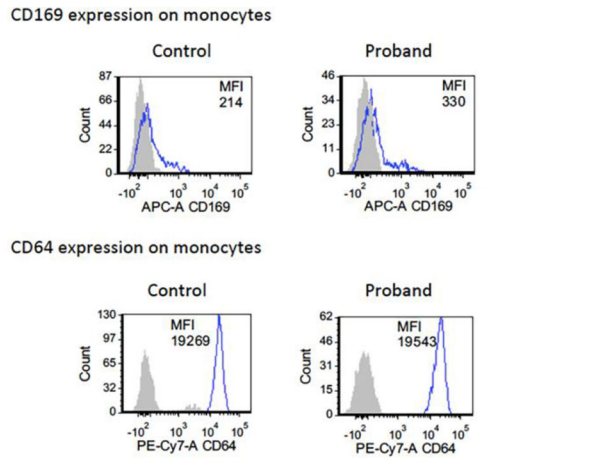

Table 1.

Keywords: NF-kappa-B, novel variant, immune dysregulation

Disclosures: All authors indicated they had no financial relationships to disclose.

(161) Newborn infant with Exostosin-like 3 (EXTL3) genetic mutation causing Severe Combined Immunodeficiency (SCID), clinodactyly, and neurological delays.

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Rationale: Exostosin-like 3 (EXTL3) genetic mutation is an autosomal recessive disorder with altered bioregulatory synthesis of heparin sulfate (HS), a key component of skeletal, neurological, and immune development. Biallelic EXTL3 genes mutations can lead to severe combined immunodeficiency (SCID), skeletal dysplasia, and neurodevelopmental delay. State newborn screening detecting abnormal T-cell excision circles (TRECs) in affected individuals allows for early identification and treatment. We describe an infant who was identified on newborn screening with subsequent confirmatory genetic testing.

Methods: EXTL3 genetic evaluation was performed by Invitae Diagnostic and rapid whole exome sequencing (WES) by PGxome.
Results: A female infant was reported to have abnormal T-cell excision circle (TRECs) on state newborn screen born to non-consanguineous parents. She was admitted for further evaluation. Initial studies demonstrated an absolute lymphocyte count of 3542 on DOL 4 with subsequent peripheral flow cytometry demonstrating a T-/B+/NK+ phenotype. IgA and IgM levels were undetectable, but IgG was within normal limits at 997 (614-1536). Mitogen stimulation was decreased to ConA, PWM, and PHA. Next Generation Sequencing (NGS) Primary Immune Deficiency panel identified biallelic mutations in the EXTL3 gene (c.1006C>T (p.Pro336Ser). WES also showed biallelic mutations in EXTL3, but did not identify other potential causes of SCID. Both parents were found to be heterozygous carriers. 22q.11 deletion was not detected on fluorescence in situ hybridization (FISH). Interestingly, there were several other mutations of uncertain significance and a pathogenic TMC8 heterozygous mutation (c.1084G>T (p.Glu362*). Artificial thymic organoid assay noted a thymic defect. The patient was transferred for transplantation and underwent an HLA 10/10 unrelated donor cord blood transplant with reduced intensity conditioning that included fludarabine, melphalan, and thiotepa. The patient engrafted with 100% donor chimerism. She has not subsequently required immunoglobulin supplementation. She exhibited global developmental delay, skeletal dysplasia (clinodactyly and hip dysplasia), patent foramen ovale, and failure to thrive requiring supplemental nutrition.
Conclusion: To our knowledge, this is the first reported case of EXTL3 deficiency identified via newborn screening. Both parents were found to have the defect. This novel case underscores the importance of newborn screening, value of genetic testing, and early treatment strategies for SCID.

Keywords: Exostosin-like 3 (EXTL3), Primary Immune Deficiency (PID), Heparin sulfate (HS), Exostosin-like 3 (EXTL3) defect

Disclosures: All authors indicated they had no financial relationships to disclose

(162) Successful bone marrow transplantation in an immunodeficient patient with a progressive loss of hematopoietic cells: 7- years post-transplant

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Primary immunodeficiency disorders (PIDs) are heterogenous diseases with impairment in the development and/or the function of immune cells. Recently, we identified a de novo variant in CXXC5 gene (c.814C>T) by whole exome sequencing in a patient initially diagnosed with childhood antibody deficiency, who progressed to bone marrow failure. With substitution of an evolutionarily conserved arginine residue with a cysteine residue (p.R272C) within the CpG DNA binding CXXC domain, the protein encoded by the variant CXXC5 gene had partial loss of function in DNA binding and cell cycle control of hematopoietic stem/progenitor cells.
Progressive bone marrow failure is uncommon in patients with humoral immunodeficiency, but the patient had a gradual decrease in the number of all hematopoietic cell types, highlighted by the absence of peripheral B cells after twenty years of the initial diagnosis. Moreover, recurrent sinopulmonary infections in the patient lead to debilitated lungs requiring transplantation, but bone marrow transplantation was performed first

from his HLA matched unaffected brother to restore the immune system. Reconstitution of the immune cells was efficient with hundred percent donor cells observed after two years post-transplant and remarkable improvement in the number of hematopoietic cells 7-years post-transplant. The B cell population which was undetectable in the patient before the transplant is now in the normal range (127 cells/μl, Ref. 91-610 cells/μl]. Absolute CD3 cell count, which was 57 cells/μl before transplant has now increased to 537 cells/μl [570-2400], and other hematopoietic populations have also reconstituted efficiently. Of interest, the patient showed normal lymphocyte function in response to mitogens and recall antigens. Post-transplant, the patient has had only one episode requiring hospitalization, likely a viral infection, and in the last one year, he had no serious infections and no diarrheal episodes. His lung functions have improved, and lungs transplant is currently not recommended. The remarkable improvement in his health following successful reconstitution of the immune system with the bone marrow transplant suggests the disease being of hematopoietic origin. This 7-years post-transplant summary provides an update of a successful outcome in a patient with highly unusual antibody deficiency culminating into bone marrow failure.

Keywords: Bone marrow transplant, antibody deficiency, Whole exome sequencing, lungs transplant, hematopoietic, HLA, B cells, T cells, CpG DNA, CXXC5

Disclosures: All authors indicated they had no financial relationships to disclose.

(163) Pediatric SOCS1 Haploinsufficiency Presenting with Refractory Thrombocytopenia and Inflammatory Symptoms with Functional Reconstitution Following JAK Inhibition

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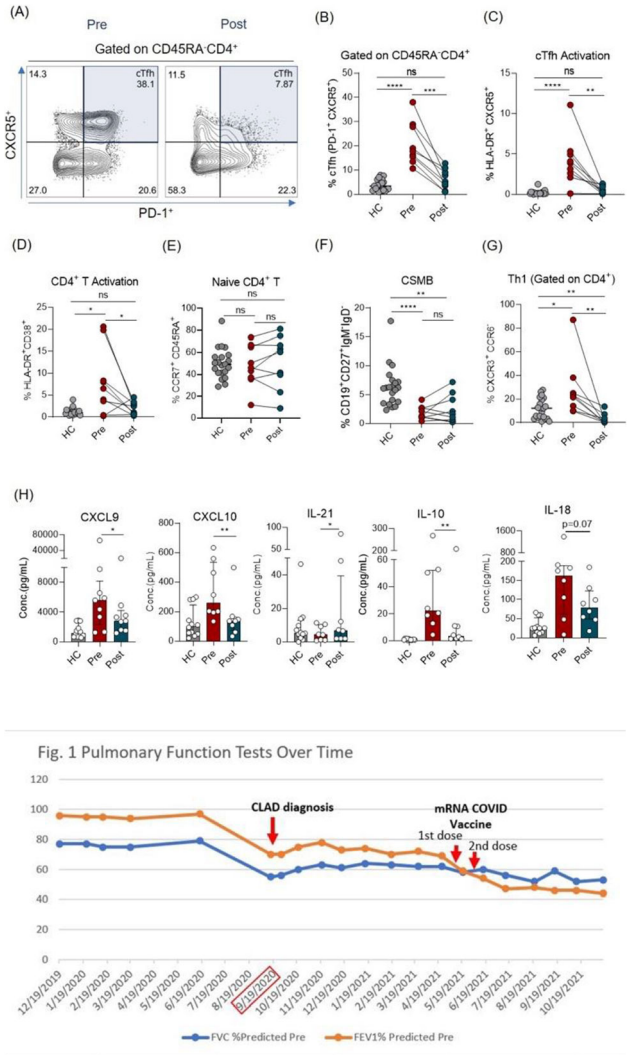
BACKGROUND: Evaluation for congenital immune dysregulation conditions in patients presenting with atypical features of immune thrombocytopenia purpura (ITP) is key, as this can impact treatment decisions, therapy response, and prognosis. Loss of the suppressor of cytokine signaling 1 (SOCS1) function is described to manifest with an autoinflammatory syndrome, with or without immunodeficiency, due to lack of negative feedback of JAK-STAT cytokine regulation.
CASE PRESENTATION: We present a 6-year-old female with thrombocytopenia of 4,000/uL identified during evaluation for severe arthralgias unresponsive to corticosteroid treatment over a 6-month period. Laboratory results were consistent with ITP, including positive platelet autoantibodies. Bone marrow evaluation revealed hypocellularity for age (~50%). Immunoglobulins were within reference range. Peripheral blood and bone marrow karyotyping were completed given concern for developmental delays and necessity to rule-out malignancy with germline deletion at 16p13.2p13.11 noted, which includes the SOCS1 gene. Comprehensive next generation sequencing for additional inborn error of immunity variants was unremarkable. Functional studies of surface expression of interferon-inducible genes (CD169 (SIGLEC-1)) and STAT1 phosphorylation via analysis of CD14+ monocytes revealed excess interferon signaling, consistent with a SOCS1 defect (Figure 1). B-cell-activating factor was found to be extremely elevated at 6432 pg/mL. Her clinical course was complicated by bleeding and refractory platelet response to first line therapy of intravenous immunoglobulin and prednisolone. Escalation to high dose methylprednisolone, rituximab (375 mg/m2/weekly x4 doses), and romiplostim resulted in control of thrombocytopenia and bleeding manifestations. She maintains a normal platelet count to date. Rheumatologic symptoms initially subsided with initiation of corticosteroids, however returned after taper. She has now transitioned to JAK inhibition therapy via Tofacitinib with resolution of arthralgias and correction of functional testing abnormalities (Figure 2).
CONCLUSION: This case highlights the impact of investigating for immune dysregulation conditions with broader genetic testing including targeted next generation sequencing panels or microarray analysis in patients with atypical autoimmune cytopenia presentations or failure of response to standard therapy. Additionally, the case adds the novel finding of bone marrow hypocellularity to the clinical phenotype of SOCS1 haploinsufficiency, as this has not yet been reported, with additional excellent clinical and functional response to JAK inhibition.



Keywords: Thrombocytopenia, SOCS1, JAK Inhibitor

Disclosures: Kelly Walkovich has relevant financial relationships with proprietary interests with AstraZeneca (Advisory Board), Horizon Pharma (Advisory Board), Pharming Health Inc (Advisory Board), Sobi Pharmaceuticals (Other Financial or Material Support, Steering committee member), X4 Pharma (Other Financial or Material Support, Local principal investigator for industry sponsored study). All other authors indicated they had no financial relationships to disclose.

(164) Umbilical Cord Blood Transplant is a Promising Option in Patients with Primary Immune Disorders

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Background: There is no consensus about the best stem cell donor for children with primary immune deficiency disorders (PIDD) in the absence of a matched related donor (MRD).
Methods: From 2008-2021, we performed an Umbilical Cord Blood Transplant (UCBT) in 55 children with PIDD, with a median age 5 mo. (range, 1-36 mo). SCID: (41), IPEX (2), CGD (4), Hyper IgM (1), STAT5b deficiency (1), IKBKB (1), LAD (2), and WAS (4). 36 patients had persistent infections prior to transplant. 36% percent of patients were 6/6 matched, and 64% were 5/6 HLA matched. Patients were enrolled on a prospective clinical trial using a fully ablative regimen consisting of busulfan, cyclophosphamide, and fludarabine without serotherapy.
Results: The median time to neutrophil and platelet recovery were 17 days (range,5-39 days) and 37 days (range,20-92 days), respectively. All but one evaluable patient achieved neutrophil engraftment. The median donor engraftment was 93.5% (range 65-100%) and 96.6% (range 62-100%) at 100 days and 1 year respectively. The overall survival (OS) at 2 years was 91% (95% CI:79-96%) with a median follow up of 4.3 years, range: 0.3-11. Five patients died, from severe GvHD (n=2), and MOF (n=3). Infection related mortality was not seen. The cumulative incidence of aGvHD grade II-IV by day 100 was 13% (n=7). Limited skin chronic GvHD has been observed in 2 patients. All patients with viral infections at the time of transplant cleared the infection at a median time of 54 days (range, 44-91 days). The median absolute CD3 counts by day 42 and 60 were 467 and 780, respectively. All evaluable patients have had correction of their immune defect.
Conclusion: We conclude that in the absence of a MRD, UCBT following myeloablative conditioning without serotherapy is an excellent curative option in young children with primary immune disorders even in the setting of significant infections.

Keywords: Primary Immune Disorders and Stem Cell Transplant, Umbilical Cord Blood Transplant for Primary Immune Disorders, Absence of serotherapy in the setting of umbilical cord blood transplant

Disclosures: Lisa Forbes-Satter has relevant financial relationships with proprietary interests with csl behring (Consultant), enzyvant (Advisory Board), Grifols (Consultant), and Takeda (Consultant). Helen Heslop has relevant financial relationships with proprietary interests with Allovir (Ownership Interest includes stock, stock options, patent or other intellectual property), Fresh Wind Biotechnologies (Advisory Board), Gilead Bioscience (Advisory Board), GSK (Advisory Board), kiadis (Advisory Board), Kuur Therapeutics (Research Grant includes principal investigator, collaborator or consultant and pending grants as well as grants already received), Novartis (Advisory Board), Tessa Therapeutics (Advisory Board). All other authors indicated they had no financial relationships to disclose.

(165) T cells abnormalities do exist in X-linked agammaglobulinemia: our preliminary experience from Chandigarh, India

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Introduction: X-linked agammaglobulinemia (XLA) is a primary humoral immune-deficiency with markedly reduced or absent B lymphocytes in the peripheral as a result of developmental arrest at the Pre-B cell stage in the bone marrow. B Lymphocytes have been reported to play role in development and functions of T cells, patients with XLA may have associated T cell abnormalities. However, there is paucity of literature on this aspect. There is no literature on T cell abnormalities in XLA carriers.
Methods: Patients with XLA (diagnosis based on pathogenic variant in BTK gene) and heterozygous female carriers with BTK gene variants were included from the Pediatric Immunodeficiency Clinic, Postgraduate Institute of Medical Education and Research, Chandigarh, India. A flow panel comprising of CD45, CD19, CD3, CD4, CD8, HLA-DR, CXCR5, CD45RA, CD45RO was prepared. Interleukin 17 and T regulatory cells expression was assessed using CD4, Foxp3 and IL-17 antibodies in carriers, patients and healthy controls.
Results: In this study, we enrolled 14 patients with XLA, 4 carrier females, 8 controls. Percentage of CD4+ helper T cells were found to be significantly reduced in patients with XLA as compared to healthy controls (39.1964±18.6074 vs 57.12875±5.8157, p value 0.037). An increased proportion of activated T lymphocytes (CD3+HLADR+) was seen in patients with XLA as compared to healthy controls (35.5728 ±16.5755 vs 15.3675±5.9887, p value 0.009). CXCR5+CD45RA- T follicular helper cells were significantly decreased in patients with XLA as compared to the carrier females (1.9369±1.5023 vs 8.8925±1.8840, p value 0.002) and healthy controls (1.9369±1.5023 vs 11.5425±4.6267, p value 0.000). There was no statistically significant difference in other T cell markers amongst the 3 groups.
Interleukin 17 expression was seen in 2 carriers (1.9433±2.45571) and 6 patients (2.7300±0.32527) and and regulatory T cells was seen in 7 patients (4.8500±2.57387) and 2 carriers (3.7971±2.34354). However, there was no significant difference seen among patients and controls.
Conclusions: Patients with XLA may have T cell abnormalities especially low CD4+ helper T cells, low T follicular helper T cells, increased activated T cells and abnormal T cell proliferation.

Keywords: X-linked agammaglobulinemia, T cell abnormalities, flow cytometry

Disclosures: All authors indicated they had no financial relationships to disclose.

(166) Specific Antibody Deficiency as an Uncommon Risk for Neisseria Meningitis

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Introduction: Specific antibody deficiency (SAD) is defined as an inadequate antibody response to polysaccharide antigens in patients with normal serum immunoglobulins and usually manifests as recurrent rhinosinusitis and bronchopulmonary infections. By contrast, risk for neisserial infection is typically associated with complement deficiency, particularly C5-9 and properdin deficiency. In the literature, there have been no clear associations between SAD and meningococcal disease. We examine a case where an otherwise healthy patient developed Neisseria meningitis infection as a first manifestation of SAD.
Case Description: A 27 year-old male with no prior history of recurrent infections developed Neisseria meningitis requiring prolonged hospitalization. Lab work initially showed low IgG which normalized, otherwise the remainder of his immunoglobulin levels were within normal range, in addition to normal lymphocyte enumeration, mitogen panel, C3, C4, CH50, and AH50 assays. The patient's baseline pneumococcal titers were undetectable (0/23 protective) and remained low after vaccination with both polysaccharide (PPSV23) and conjugate (PCV13) vaccines, resulting in 3/23 and 1/23 protective serotypes, respectively. Targeted genetic testing for primary immunodeficiency disorders was negative for causative mutations. He was diagnosed with SAD and started on daily antibiotic prophylaxis. He has not developed any subsequent infections. Haemophilus influenzae titers were also found to be low with booster vaccine pending at this time.
Discussion: Severe bacterial infections such as meningitis are uncommon in patients with SAD, although in some cases have been reported in those with severe hypogammaglobulinemia, low B cell count, or low switched memory B cells. Our patient demonstrated a significantly impaired response to polysaccharide antigen, suggesting a poor response to encapsulated bacteria thereby potentially increasing his susceptibility to neisserial infections. This may be a rare case of SAD presenting with Neisseria meningitis as the first infective episode prior to diagnosis. Given the patient's poor response to vaccination and prior history of a single low IgG, it is also possible that meningitis was a sentinel infection of nascent CVID which will eventually be uncovered. At this time, patient's post-vaccination haemophilus influenzae titers are pending. Depending on his clinical course, in addition to bacterial prophylaxis, this patient may benefit from IVIG in the future.

Keywords: Specific Antibody Deficiency, Neisseria meningitis, encapsulated bacteria

Disclosures: Victoria Dimitriades has relevant financial relationships with proprietary interests with CSL-Behring (Advisory Board) and Horizon Therapeutics (Advisory Board). All other authors indicated they had no financial relationships to disclose.

(167) Unbiased clustering approach facilitates the VUS Classification in a Patient with CTLA-4 Haploinsufficiency

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Heterozygous mutations in CTLA-4, an inhibitory receptor found on immune cells, are known to cause immunodeficiency and immune dysregulation. Here, we present a 12-year-old African American female with a history of recurrent lip angioedema and fever, positive ANA, and ankle swelling who was evaluated for scarring alopecia and enlarging scalp denuding lesion with recurrent E coli superinfection and left knee pain. Patella biopsy revealed sterile inflammation, and full body MRI revealed metaphyseal enhancement of the bilateral femur and tibia consistent with chronic recurrent multifocal osteomyelitis. Initial immunophenotyping revealed normal regulatory T cell numbers, a decrease in CD8 T cells, a slight increase in transitional B cells but normal immunoglobulin levels. A 407 gene primary immunodeficiency genetic sequencing panel (Invitae, Inc.) identified two variants of uncertain significance (VUS) in CTLA-4 (c.257C>G, p.Ala86Gly), and AIRE (c.793G>A, p.Ala265Thr). Parental genetic testing revealed the father carried the AIRE variant and the mother carried the CTLA-4 variant. Immunosuppression with anti-TNF therapy was initiated with subsequent improvement in the scalp lesion but residual alopecia.
The Ala265Thr AIRE variant was transfected into HEK293 cells to evaluate expression of AIRE-inducible genes by qPCR. Induction of gene expression was the same between the variant and wild type, suggesting that the variant is not pathogenic. CTLA-4 Ala265Thr was categorized as a variant of uncertain significance, but in silico was predicted to be pathogenic. Ala86 was previously reported to cause CTLA-4 haploinsufficiency when muted to valine, and defective CD86 transendocytosis was demonstrated in patient T cells. Interestingly, K-means clustering performed on 100 consecutive comprehensive B cell panel reports identified a cluster of 3 subjects including this patient with similar B cell phenotypes. This cluster was characterized by normal total B-cell numbers but increased IgD-only CD27+ B cells. Chart review indicated that one patient had a confirmed CTLA-4 haploinsufficiency and the other suffered from a chronic neutrophilic dermatosis. As a result, we decided to initiate abatacept therapy. This case highlights the use of an unsupervised clustering technique to assist in VUS interpretation, particularly with regards to incompletely penetrant monogenetic immune diseases such as CTLA-4 haploinsufficiency that present with variable clinical manifestations.

Keywords: CTLA-4, primary immunodeficiency, AIRE, clustering

Disclosures: All other authors indicated they had no financial relationships to disclose.

(168) SARS-CoV-2 Vaccine and Booster Immunization Response in Patients with Humoral Immunodeficiency

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Background: Given that patients with immunodeficiency were excluded from vaccine trials, the response to SARS-CoV-2 immunization in these patients is largely unknown, both for primary vaccination series and for booster dose vaccination. We sought to evaluate the antibody response to SARS-CoV-2 vaccine as well as underlying immunophenotypic markers for response in patients with humoral immunodeficiency.
Methods: We assessed levels of anti-SARS-CoV-2 antibodies (both anti-spike and anti-nucleocapsid) in patients with humoral immunodeficiency compared to matched healthy controls at set time points (baseline, 4-6 weeks following initial series vaccination, and 4-6 weeks following booster dose immunization [if received]). We also assessed neutralization assays and antibodies to the SARS-CoV-2 receptor binding domain (RBD).
Results: 62 patients with humoral immunodeficiency were matched to healthy controls. Patients with humoral immunodeficiency had lower mean anti-spike antibody levels compared to controls (1699 U/mL vs. 3307 U/mL, p=0.02). We observed a linear correlation between anti-spike antibody level and neutralization function and total anti-RBD antibody levels in patients with humoral immunodeficiency. Patients with low CD19+ total B cells, low CD4+ helper T cells, and low class-switched memory (CD27+IgD/M-) B cells were most likely to have low anti-spike antibody levels. An anti-spike antibody response < 100 U/mL was

associated with prior rituximab use (OR 5.5; CI 1.5-20.4; p=0.01). Additional dose immunization with an mRNA vaccine increased anti-spike antibody levels (mean anti-spike antibody 1171 U/mL pre- to 8058 U/mL post-additional dose, p< 0.01).
Conclusions: Patients with humoral immunodeficiency had lower anti-spike antibody levels following SARS-CoV-2 vaccination, and this was particularly notable in those patients with low B cells, low helper T cells, and/or low class-switched memory B cells. Antibody responses improved following additional dose vaccination.

Keywords: SARS-CoV-2, vaccine response, humoral immunodeficiency

Disclosures: Jocelyn Farmer has relevant financial relationships with proprietary interests with Bristol Myers Squibb (Research Grant includes principal investigator, collaborator or consultant and pending grants as well as grants already received) and Pfizer (Research Grant includes principal investigator, collaborator or consultant and pending grants as well as grants already received). All other authors indicated they had no financial relationships to disclose.

(169) Immunosuppressive therapy-related CD30+, EBV+ lymphoproliferative disease in a patient with autoimmune hemolytic anemia treated with brentuximab vedotin and rituximab

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Background: Lymphoproliferative disorders (LPD) are a known complication of immunosuppressive therapy for solid organ transplant, however, its occurrence following prolonged use of mycophenolate mofetil (MMF) for autoimmune hemolytic anemia (AIHA) is rare. Most commonly, LPD are positive for both CD20 and EBV. Traditional treatment includes reduction in immunosuppression and anti-CD20 therapy. Unfortunately, anti-CD20 therapy is often insufficient, requiring escalation to cytotoxic chemotherapy. Brentuximab vedotin, a CD30-directed antibody-cytotoxic drug conjugate, is approved for patients with Hodgkin lymphoma and anaplastic large cell lymphoma and has also been reported in patients with inborn errors of immunity (IEI) and LPD to reduce therapy-related toxicity. Here, we present a case of CD30+, EBV+ LPD in a patient with AIHA following long term MMF use, treated with brentuximab vedotin and rituximab.
Case Summary: The patient is a 23-year-old female with warm autoimmune hemolytic anemia treated primarily with corticosteroids and MMF since age 15 years. She developed fevers and severe abdominal pain. Imaging revealed diffuse hypermetabolic lymphadenopathy in cervical, supraclavicular, mediastinal, and retroperitoneal regions. Left supraclavicular lymph node biopsy diagnosed an infectious mononucleosis-like, CD30+, EBV+ lymphoproliferative disease with immunoblasts positive for CD30 and Epstein-Barr encoding region (EBER) by in situ hybridization, but largely negative for CD20. EBV DNA had been detectable in the plasma at low levels for 8 months, with moderate increase in viral titer over the preceding month. MMF was discontinued and therapy was initiated with rituximab and brentuximab vedotin. EBV DNA levels became undetectable after two doses of rituximab and brentuximab vedotin with concurrent improvement in her lymphoproliferation and hemolytic anemia. Whole exome sequencing was negative for underlying IEI.
Conclusion: This case serves as a reminder of the potential side effects of immunomodulating therapies, including those utilized for AIHA. It also highlights the use of targeted immunotherapies for lymphoproliferative diseases, as a mechanism to avoid cytotoxic chemotherapy in secondary immunodeficiency related lymphoproliferative disease.

Keywords: Autoimmune hemolytic anemia, Lymphoproliferative disease, Secondary immunodeficiency, Immunotherapy

Disclosures: Kelly Walkovich has relevant financial relationships with proprietary interests with AstraZeneca (Advisory Board), Horizon Pharma (Advisory Board), Pharming Health Inc (Advisory Board), Sobi Pharmaceuticals (Other Financial or Material Support, Steering committee member) and X4 Pharma (Other Financial or Material Support, Local principal investigator for industry sponsored study). All other authors indicated they had no financial relationships to disclose.

(170) Subgroup Analyses of Survival Among Patients With Congenital Athymia After Treatment With Allogeneic Processed Thymus Tissue-agdc

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Allogeneic processed thymus tissue-agdc (APTT) is an approved treatment for immune reconstitution in pediatric patients with congenital athymia. Patients were enrolled in 10 clinical trials that evaluated the efficacy (survival) and safety (including incidence of adverse events [AEs]) of APTT.1 Of the 105 patients who received APTT in clinical studies, 95 were included in the efficacy analysis population1; 72.6% (n=69) were alive at the time of most recent follow up. This subgroup analysis aimed to better understand the impact of baseline characteristics on survival and AE profiles after APTT administration; categories included complete DiGeorge syndrome (cDGS) phenotype, use of immunosuppressive therapies, sex, race, hepatic and renal function at screening, and disease etiology. Statistically significant differences in survival were found within 1 subgroup. Survival rates were significantly higher for patients without renal impairment compared with those who had elevated (>0.4 mg/dL) baseline serum creatinine levels (77.4% [n/n=65/84] vs 40.0% [n/n=4/10], respectively; P=0.005). Survival was generally consistent across the remaining subgroups analyzed; no statistically significant differences were observed within subgroups by cDGS phenotype, immunosuppression use, sex, race, hepatic function, or disease etiology. Survival rates after APTT treatment were similar for patients with typical vs those with atypical cDGS phenotype (76.0% [n/n=38/50] vs 69.0% [n/n=29/42], respectively; P=0.453). Similarly, survival rates were comparable between patients receiving vs those not receiving immunosuppression (71.0% [n/n=44/62] vs 75.8% [n/n=25/33], respectively; P=0.665). Incidence of AEs were also analyzed by subgroup to better understand the impact of baseline characteristics on AE profiles. Incidence of some AEs were higher in patients with atypical vs typical cDGS phenotype and in patients on immunosuppression vs those not on immunosuppression. AE profiles across the remaining subgroups were generally consistent with the overall population with no clinically relevant differences. Based on these subgroup analyses, renal impairment is a risk factor for death following APTT administration. Survival was generally comparable across all other subgroups demonstrating the efficacy of APTT for patients with congenital athymia across various baseline characteristics.
Reference:
1. Markert ML, et al. J Allergy Clin Immunol. Published online August 4, 2021. doi:10.1016/j.jaci.2021.06.028.

Keywords: thymus, congenital athymia, athymia, complete DiGeorge syndrome, CHARGE syndrome, 22q11.2 deletion, immune reconstitution

Disclosures: M. Louise Markert has relevant financial relationships with proprietary interests with Enzyvant (Other Financial or Material Support, Royalties) and Enzyvant (Other Financial or Material Support, Portion of salary was paid by funding from Enzyvant). Stephanie Gupton has relevant financial relationships with proprietary interests with Enzyvant (Employment). Elizabeth McCarthy has relevant financial relationships with proprietary interests with Enzyvant (Other Financial or Material Support, Portion of salary was paid by funding from Enzyvant). Christine Steinhart has relevant financial relationships with proprietary interests with Enzyvant (Employment). Kevin Healy has relevant financial relationships with proprietary interests with Enzyvant (Employment).

(171) MYSM1 regulates kinetics of DNA damage responses in developing B lymphocytes

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Germline variants in MYSM1 have been identified in patients with primary immune deficiency characterized by B cell lymphopenia, hypogammaglobulinemia, and increased sensitivity to genotoxic agents. MYSM1 is a deubiquitinase that removes ubiquitin from histone H2A to promote gene transcription. MYSM1 has also been shown to localize to DNA breaks and to interact with ubiquitinated H2A at irradiation-induced DNA damage foci. However, the function of MYSM1 in DNA damage and the contribution of this activity to observed immune deficiency have not been defined. We find that lymphocytes from a patient with a deleterious variant of MYSM1 have increased gH2AX, a marker of DNA damage, in the absence of exposure to DNA damaging agents. Early T and B cells generate DNA double-stranded breaks (DSBs) through RAG endonuclease activity to assemble their antigen receptor genes. Activation of appropriate responses to RAG DSBs and their timely resolution are essential for normal lymphocyte development. To define the activity of MYSM1 in DNA damage responses in developing lymphocytes, we used abelson transformed (abl) pre-B cells, which induce RAG DSBs when treated with the abl kinase inhibitor imatinib. We first assessed DSB generation and repair using abl pre-B cells transduced with a GFP reporter plasmid. MYSM1-deficient pre-B cells express GFP equivalent to wild-type pre-B cells indicating normal RAG activity and DSB repair. However, MYSM1-deficient cells have persistent DNA damage foci with increased recruitment of DNA damage response factors at late time points after signaling is resolved in control cells. The continued DNA damage signaling with loss of MYSM1 triggers prolonged activation of p53. We also find loss of MYSM1 leads to persistent accumulation of DNA damage factors in response to irradiation-induced DSBs in both pre-B cells and non-B cells. Further, MYSM1 overexpression yields rapid resolution of DNA damage foci compared to control cells. Collectively, our results establish a novel role for MYSM1 in extinguishing DNA damage responses after DSB repair, which is critical for mitigating p53-mediated cell death programs and promoting B cell maturation. These findings provide new insights into the pathophysiology of immune deficiency in patients with MYSM1 variants that reveal important considerations for clinical management.

Keywords: MYSM1, deubiquitinase, DNA damage, B cell, lymphocyte

Disclosures: Jeffrey Bednarski has relevant financial relationships with proprietary interests with Horizon Pharmaceuticals (Advisory Board) and Sobi (Advisory Board). All other authors indicated they had no financial relationships to disclose.

(172) Sirolimus treatment improves both cytopenia and underlying immune dysregulation in Evans syndrome

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Introduction: Pediatric Evans syndrome (pES) is a rare autoimmune disorder characterized by co-occurrence of autoimmune hemolytic anemia and immune thrombocytopenia. Despite an improved understanding of genetic defects in immune regulatory pathways as the cause of pES, the underlying immune anomalies in pES are poorly understood. Recently we showed that pES is characterized by circulating T-follicular helper cells (cTfh) expansion, increased T cell activation, decreased naïve CD4+ T and class-switched memory B (CSMB) cells (Kumar et al., Blood 2021). Sirolimus is known to improve the cytopenia associated with pES, but it is unclear how it affects the underlying immune dysregulation. To address this, we longitudinally evaluated the immune profiles of pES patients on sirolimus treatment.
Methods: Over a 2017-2021, 11 patients with pES were evaluated longitudinally up to two years on sirolimus therapy and compared with 21 healthy controls. High-dimensional immunophenotyping of T and B cell compartment and cytokine/chemokine profiling were performed to monitor the changes in immune abnormalities. In addition, clinical assessment of cytopenia and immunoglobulin levels were performed.
Results: Here, we show that sirolimus therapy significantly reduces the cTfh expansion in patients with pES. Within cTfh compartment, we found a decrease in activation, exhaustion and senescence markers following sirolimus treatment suggesting an overall improvement in functional status of this subset. We also observed a significant decrease in CD4+ and CD8+ T cell activation post sirolimus treatment. A resolution of Th1 skewing was observed both in CD4+ T cells and cTfh subset after treatment. A decrease in CXCL9 and CXCL10 chemokine levels support the decrease in IFN-γ mediated inflammation. Decreased IL-18 levels after sirolimus treatment suggest improvement in innate inflammation. Although there was an improvement in T cell activation and cTfh frequency, we observed variable results for CSMB and CD4+ naïve T cell populations on sirolimus treatment (Figure 1).
Conclusion: Sirolimus treatment results in both improvement in cytopenia and more importantly attenuation of markers of T cell immune dysregulation that define pES. This improvement in immune dysregulation on sirolimus therapy is not restricted to only ALPS but also noted across several different genetic drivers of pES.

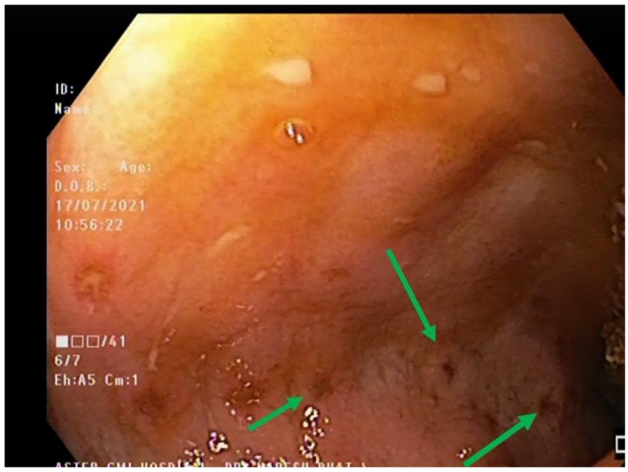

Figure 1. Immune profiling reveals improvement in immune dysregulation in patients with pES after sirolimus treatment. (A) Representative flow plots showing frequency cTfh cells in a pES patient before (Pre) and after (Post) sirolimus treatment. (B-C) Frequency of cTfh and cTfh activation in paired pES patients during pre and post sirolimus treatment. (D-G) Plots showing frequencies of CD4+ T activation, naïve CD4+ T, CSMB and CD4+ Th1 subsets before and after sirolimus treatment. (H) Bar plots showing plasma concentrations of CXCL9, CXCL10, IL-21, IL-10 and IL-18 during pre and post sirolimus treatment.

Keywords: Evans syndrome, Sirolimus, Immune Dysregulation

Disclosures: All other authors indicated they had no financial relationships to disclose.

(173) Utility of Multiplex Ligation dependent Probe Amplification for detecting copy number variations in Primary immunodeficiency Disease

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Primary immunodeficiencies also referred as inborn errors of immunity manifest as an increased susceptibility to infectious diseases, autoimmunity, auto inflammatory diseases, allergy, and/or malignancy. These conditions are caused by monogenic, germline gene variants that result in loss of expression, loss-of-function or gain-of-function of the encoded protein. Multiplex Ligation Dependent Probe Amplification (MLPA) is a molecular technique based on semi-quantitative PCR for detection of copy number variants like duplications and deletions in the genome. We report our 3-year experience in setting up facilities for MLPA for diagnosis of PIDs in Chandigarh, North India. Out of 53 patients who were suspected to affect with Primary Immunodeficiency diseases were checked with MLPA, we observed a copy number variations in 24 of these 53 patients.11 patients affected with T-B-NK+ SCID had a homozygous deletion in 1-4 of DCLRE1C gene and parents were heterozygous carriers for this deletion. 2 patients with Hereditary Angeioedema have a heterozygous deletion in Exon 8 of SERPING1 gene and 1 with a heterozygous deletion in Exon 6 of F12 gene. 5 patients were observed affected with DiGeorge syndrome sharing a common hotspot heterozygous deletion in TBX gene (Exon 2, 7). One female patient with CGD was found to be a carrier for CYBB gene (Exon 7-8 deletion). Her mother and sister were also found to have a similar heterozygous deletion in the CYBB gene; one patient was affected with Autosomal Recessive hyper IgE syndrome found to have homozygous deletion in DOCK8 gene (Exon 12-48)

Keywords: MLPA(Multiplex Ligation Dependent Publication), SCID (Severe combined Immunodeficiency disease), PID primary immunodeficiency disease

Disclosures: Vignesh Pandiarajan has relevant financial relationships with proprietary interests with Indian Council of Medical Research (Research Grant includes principal investigator, collaborator or consultant and pending grants as well as grants already received), Jeffrey Modell Foundation (Research Grant includes principal investigator, collaborator or consultant and pending grants as well as grants already received). All other authors indicated they had no financial relationships to disclose.

(174) Infectious Clinical Phenotype of STAT3 Dominant-Negative Disease

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Introduction: STAT3 dominant-negative disease (STAT3 DN) is characterized by elevated IgE, eczema, recurrent skin and pulmonary infections, and connective tissue, skeletal, and vascular abnormalities. The full spectrum of infectious complications seen in STAT3 DN is not fully understood.
Objective: To describe the diversity of clinical infectious complications in a large cohort of patients with STAT3 DN.
Methods: We retrospectively reviewed the medical records of 151 STAT3 DN patients followed at NIAID since 2005 focusing on the infectious complications.
Results: Patients ranged in age from 3 to 70 years (median 26 years), were 56% female, and had a mean HIES clinical score of 65.8 (median 69). STAT3 mutations were in the DNA binding (55%), SH2 (42%), or transactivation (3%) domains. Common clinical features of the cohort include newborn rash (83%), mucocutaneous Candidiasis (81%), recurrent skin abscesses (83%), retained primary teeth (77%), and characteristic facial appearance (77%). Bronchiectasis was seen in 66% of patients and pneumatoceles in 46% of patients, and for those with bronchiectasis and/or pneumatoceles, chronic infection occurred in 51% of cases, including Pseudomonas aeruginosa (30%), Aspergillus species (36%), Nontuberculous Mycobacteria (15%) and other infection (30%). Other serious infections in the cohort include sepsis/bacteremia (24 cases, 16%), osteomyelitis (12 cases, 8%), necrotizing fasciitis (4 cases, 3%), and visceral abscesses (9 cases, 6%). Endemic mycoses disseminated infections included Histoplasma (5 cases), Coccidiodes (4 cases including 2 CNS infections), and Cryptococcus (4 cases including 3 CNS infections). There were 16 fatalities, 13 of which were from infections (including 12 pulmonary infections). Chronic therapies to prevent and treat infections included IVIG/SQIG (44%), antifungals (81%), and antibiotics (99%).
Conclusion: As expected, patients frequently experienced mucocutaneous Candidiasis, cutaneous abscesses, and pneumonias. More invasive infections such as visceral abscesses, osteomyelitis, sepsis, and necrotizing fasciitis were seen at a frequency higher than was expected based on previous reports of STAT3 DN patients. The majority of patients were maintained on chronic therapy aimed to prevent infection. Further study of the diverse infectious clinical features and therapies for STAT3 DN is necessary to improve patient outcomes and prevent life-threatening infections.

Keywords: STAT3 dominant-negative disease (STAT3 DN), Autosomal dominant Hyper IgE syndrome (AD-HIES), Job's Syndrome

Disclosures: Jennifer Heimall has relevant financial relationships with proprietary interests with ADMA (Advisory Board), CIRM (Consultant, Other Financial or Material Support, Data Safety Monitoring Board), CSL Behring (Advisory Board, Consultant, Research Grant includes principal investigator, collaborator or consultant and pending grants as well as grants already received)
Horizon (Advisory Board), Regeneron (Contracted Research), UpToDate (Other Financial or Material Support, Section Author). All other authors indicated they had no financial relationships to disclose.

(175) Pulmonary deterioration in a lung transplant patient after mRNA COVID-19 vaccination

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Introduction: Adverse reactions to COVID-19 vaccines have been documented in the general population, however little is known in patients with solid organ transplants. Given that COVID-19 is a respiratory virus, it is thought that morbidity and mortality associated with its infection are worse in post-lung transplant patients in comparison to the general population. Herein, we describe a lung transplant patient who developed respiratory deterioration following an mRNA COVID-19 vaccine.
Case/Discussion: A 53-year-old male with bilateral lung transplant for cystic fibrosis at age 40 and stable chronic allograft lung dysfunction (CLAD) on tocilizumab and photopheresis presented with worsening dyspnea after he commenced the series of COVID-19 vaccinations. He had a 15% decrease in FEV1 (FVC: 3.00L, 57.7%, FEV1: 2.38L, 58.9%; FEV1/FVC: 79%) from baseline two weeks after his first dose of the BNT162b2 mRNA COVID-19 vaccine and an additional 8 % drop in FEV1 (FVC: 3.11L, 59.7%, FEV1: 2.20L, 54.5%; FEV1/FVC: 71%) two weeks after the second dose. He was suspected of having CLAD exacerbation and was admitted for high-dose steroids and IVIG. Laboratory workup revealed leukocytosis with neutrophilia (ANC: 20.4k/μL), normal IgG, IgA and IgM, elevated IgE (232mg/dL), elevated IL-10 (32.7pg/mL), elevated IL-6 (7.1pg/dL) and elevated soluble CD25 (1045.6pg/mL). Computed tomography angiogram showed bilateral subsegmental pulmonary emboli. COVID-19 anti-nucleocapsid antibody was undetectable and anti-spike was positive with a low titer (70.10U/mL). Echocardiogram was unremarkable. The patient was started on apixaban with improvement in dyspnea without recovery of lung function which displayed a slow continuous worsening of his restrictive airway syndrome with a parallel decrease in both FVC and FEV1 (Five months later: FVC: 2.75L, 53%, FEV1: 1.76L, 44%; FEV1/FVC: 64%).
The risk of pulmonary embolism has been shown to be substantially increased after COVID-19 infection but not mRNA COVID-19 vaccine. Although our patient had pulmonary embolism, this may not have been the sole reason for his deteriorating lung function given the elevation in inflammatory cytokines. Patients with immune dysregulation, including transplant patients, may be a higher risk of complications associated with immune-mediated hyperinflammation caused by the mRNA COVID-19 vaccine. Close follow up should be considered for these patients after immunization.

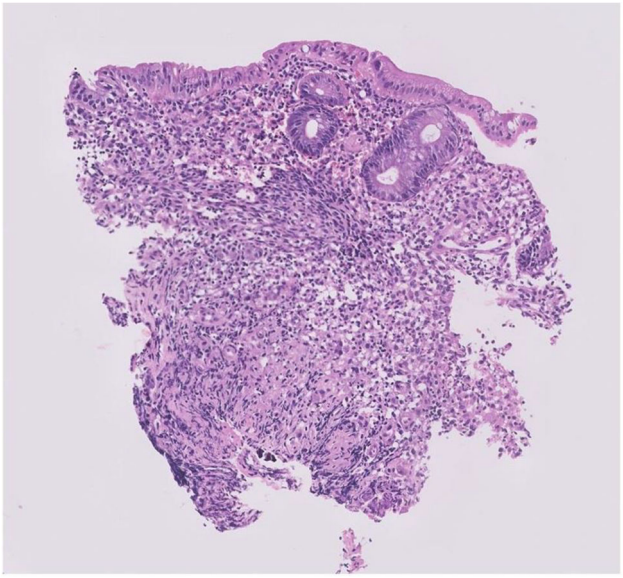

Figure 1. Pulmonary function tests in our patient evidencing worsening function after vaccination with mRNA COVID-19 vaccine

Keywords: immune dysregulation, mRNA COVID-19 vaccine, lung transplant

Disclosures: All other authors indicated they had no financial relationships to disclose.

(176) Very early onset inflammatory bowel disease in a child with oculocutaneous albinism

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Background: Hermansky-Pudlak syndrome (HPS) is a rare genetic multisystem disorder characterized by the presence of oculocutaneous albinism, a bleeding diathesis, and immunodeficiency. However, some individuals also develop pulmonary fibrosis and granulomatous colitis.
Case: A 14-month-old boy, firstborn of a non-consanguineous marriage presented with a history of recurrent episodes of diarrhea from a young age. He was well until 7 months of age when he developed loose stools 10-15 episodes/day which were semi-solid in consistency, green-colored containing mucus, and associated with excessive crying while passing motions. He was treated with antibiotics on multiple occasions following which his symptoms would resolve temporarily.
On examination, he was noted to have erythema in the perianal region with a fistula at 6 'o'clock position. On evaluation his complete blood counts showed anemia (10.4g/dl), neutrophilic leukocytosis (17,600/cumm, N-51%) and thrombocytosis (8,12,000/cumm) with elevated erythrocyte sedimentation rate (ESR) & C-reactive protein (CRP). Stool examination was normal & culture was sterile. Fecal calprotectin levels were very high (11042 microg/g). Colonoscopy reported the presence of multiple ulcers along the sigmoid colon and biopsy showed features of

inflammatory bowel disease (Figure 1,2). Hence a diagnosis of very early onset IBD (VEO-IBD) was made, and he was treated with steroids & azathioprine following which his diarrhea improved and perianal lesions healed. He was also noted to have light-colored hair, skin, and eyes. Fundus examination showed presence of depigmented iris and a pale fundus. In view of presence of VEO-IBD in an infant with oculocutaneous albinism, an underlying primary immune deficiency was suspected, and a genetic evaluation was carried out. A pathogenic heterozygous mutation c.111-2A>G was identified in exon 3 of DNTBP1 gene and a diagnosis of HPS type 7 was established. However, he did not have any bleeding manifestations. Electron microscopy showed the presence of dense bodies and platelet function studies were normal. He is presently on steroids and azathioprine and is on close follow-up.

Conclusion: We present a young boy with HPS type 7 with VEO-IBD. This is the first report of inflammatory colitis in HPS 7. Absence of bleeding manifestations is an unusual occurrence in this type of HPS.

Table 1. What has been most helpful in learning to live with your illness? And why?

Theme	Example
Perspective	"The most helpful thing has been to realize that I need to take things day by day. I don't know what will happen in the future, but I can address and handle what each day may bring." "That no matter how bad things are, there are those whose struggles are worse, so I need to focus on the positive and be thankful."
Acceptance	"Learning to accept that there is nothing I can do to change the reality of my situation."
Illness knowledge	"Knowledge changes everything. The more I know about the illness, the better off I seem to be."
Personal experience	"Experience. Experience has been the most important part to learning to live with an immune illness. I have had my illnesses for 34 years and I have learned so much on how to cope and handle a flareup, manage my stress and so much more. I will only learn more as I age with this." "Generally learning to care for myself and listen to my body"
Social support- Family/ Friends	"I have a good support system of family that wants me to thrive, encourages me to rest, take care of myself." "Support from friends and spouse."
Support groups/ disease community	"Finding a Facebook group with other people who have the same disease also helps! It helps me to not feel so alone and like such a freak. It's easy to feel lonely and isolated with this disease, especially right after being diagnosed."
Competent and empathic care	"Having good doctors who take the time to explain why certain tests are being done, what we are looking for, etc. I have been very lucky to have had doctors who have treated me like part of a team and have validated my thoughts and observations."
Lifestyle changes	"Giving up even trying to do things that require physical strength or stamina. Or limiting those things to the point I'm not devastated when I can't do what I want to."
Treatment/ future treatment	"Knowing and seeing the rapid pace of technological advances that are occurring and knowing that a cure or at least better treatments are on the way." "Having access to Ilaris has been a game changer for me. This medication works so well for me so that I can lead a near normal life."
Psychological interventions	"Talking about it with therapist. Meditation. Writing about it." "It has been truly beneficial for me to speak with a therapist on a regular basis. Talking about it out loud helps. Without talking to my therapist, I most likely would not talk much about it because others do not truly understand. I'd talk to one or two trusted people, if that. This is also because I am far more than my illnesses. Speaking to my therapist weekly helps me to speak about the unspeakable in my life."
Diagnosis	"My illness along with others was not recognized/diagnosed until about 10 years ago ... and I have been living with this for a lifetime. I am now 70. For most of my life I have been negated, shamed, belittled...told that I had a psychological illness, that I did not like school...etc., etc. I lost myself, didn't know how to read my body, who I was. It is only recently, that I now have been validated...that I am "seen" and "heard" ... it is like learning to walk all over again."
Knowing it wasn't their fault	"Knowing that there is nothing I did to cause the disease is helpful because I have no guilt about it."
Research to help others	"How much the research from my experience with it will help others younger than me deal with this disease."
Social privilege	"Being able to retire with enough funds so that I don't have to be stressed about trying to work with pain and fatigue. Having a good medical insurance plan so that I can see specialists and get treatment."
Absence of symptoms	"The only thing that has been most helpful in learning to live with this, is that I rarely get sick. If I was someone who was ill all the time, I wouldn't feel so optimistic about my future."
Self-advocacy	"Listen to your doctors but don't be afraid to push back if you feel a plan of action doesn't work for you. Sometime healthcare professionals need to be reminded that you're a person with other needs and desires beyond the particular problem they are presented with."
Faith	"I have a great faith in God that has ensured peace and stability."

Figure 1: Colonoscopy showing multiple ulcers in the sigmoid colon

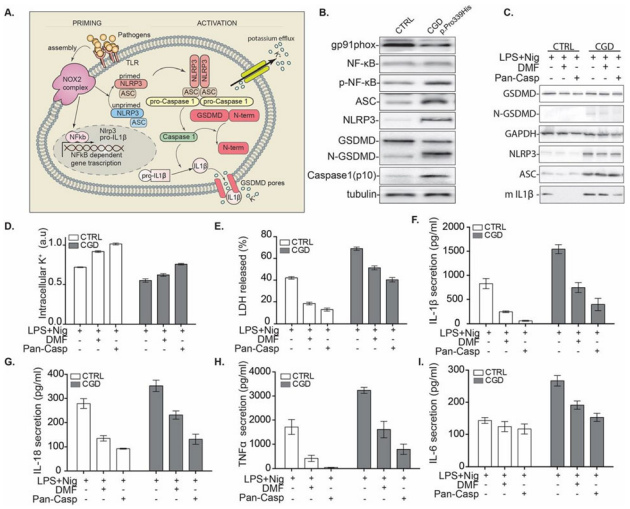

Figure 2: Colonic biopsy- Focal area of crypt loss. Inflammatory granulation tissue showing mixed inflammation with loose histiocytic clusters.

Keywords: Oculocutaneous albinism, Hermansky Pudlak syndrome, Very early onset inflammatory bowel disease

Disclosures: All other authors indicated they had no financial relationships to disclose.

(177) Two distinct "brain-homing" monocyte subsets identified in pediatric acute-onset neuropsychiatric syndrome (PANS) are immunosuppressive and neuroprotective

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[1]Stanford University

Pediatric Acute-onset Neuropsychiatric Syndrome (PANS) is characterized by an abrupt onset of obsessive-compulsive disorder and a constellation of other psychiatric and somatic symptoms. Around 80% of PANS patients undergo repeated episodes of flare and remission. We have found elevated levels of circulating monocytes in PANS patients compared to healthy controls. Human monocytes in the blood can be divided into 3 subsets, the largest (~85%) being CD14+CD16- "classical" monocytes. Monocytes of all 3 subsets can differentiate into tissue-homing macrophages and dendritic cells during inflammation. We compared the immunophenotypes of peripheral monocytes in PANS patients (n = 18) and controls (n = 10) to determine their pro- vs anti-inflammatory immunophenotypes. Using flow cytometry, we found that a pro-inflammatory monocyte-derived dendritic cell subset was significantly increased in PANS flare compared to healthy controls. We also observed an increased level of M1-macrophage-type cells in the circulation of PANS patients during flare. Both these cell types were reduced significantly in improved patients. In addition, we used a novel antibody panel focused on markers on human monocytes that we predicted would identify brain-homing cells, including markers associated with the extravasation of monocytes across the blood brain barrier (BBB). This brain-homing subset was significantly reduced during PANS flare, with a subsequent increase when clinical features of PANS improved. We found

these cells in the cerebrospinal fluid of flaring PANS patients, confirming their brain-homing and BBB-crossing potential. To understand the function of these monocytes, we performed single-cell RNA-sequencing. Cluster distribution of myeloid cells revealed two distinct subsets (CCR2lo and CCR2hi) that expressed our pre-defined brain-homing markers and Monocle analysis (a pseudotime trajectory analysis) argued that these cells derive from CD14+ monocytes. Gene-set enrichment analysis showed that the CCR2hi brain-homing subset expresses genes associated with immune suppression, consistent with an anti-inflammatory role. The CCR2lo brain-homing subset expressed genes suggesting possible reparative function with specificity for the brain. Together, our data support a model in which distinct myeloid cell subsets contribute to PANS brain inflammation and its suppression.

Keywords: PANS, Monocyte, Neuroinflammation, Brain-homing, Dendritic cell, Macrophage

Disclosures: All other authors indicated they had no financial relationships to disclose.

(178) Making the Invisible Visible: Understanding What's Helpful in Learning to Live with a Suspected Inborn Error of Immunity

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Inborn Errors of Immunity (IEI) constitute a wide range of symptoms, some of which are "invisible." Prior research has established the potential for negative quality-of-life consequences among individuals with suspected IEI, particularly among those who are isolated, have depression or anxiety, or have long diagnostic journeys. Relatively underrepresented in this literature, however, are qualitative methods that explore patient perceptions of their challenges and opportunities. Healthcare providers can benefit from understanding their patient's perspective of their illness to effectively address their medical and psychosocial needs. This study aims to interrogate psychosocial impacts of having an IEI to better understand how patients adapt to their condition. We define adaptation as a dynamic and multi-dimensional process of coming to terms with implications of a health threat. A survey including open-ended questions was sent to patients who were enrolled on a Centralized Sequencing Protocol and were suspected of having an IEI. Here, we present responses to the question: What has been most helpful in learning to live with your illness? And why?

Out of 1038 invited participants, 252 (24% response rate) responses were coded and analyzed thematically (59% female, mean= 48 years). See Table 1. Many patients reported that they benefit from competent providers with a nuanced understanding of their disease and who provide effective treatments, which encourages further biomedical research into new disease associations and therapies. However, patients also reported seeking support from family, friends, and the disease community in coping with their challenges. Many also reported the benefit of lifestyle changes, reconceptualizing their illness, and having a sense of control in the clinic and their personal lives. Healthcare providers can promote these adaptation strategies by encouraging patients to play an active role in their treatment and connecting them to support systems and psychological interventions. An important minority of individuals indicated there was nothing helpful in learning to live with their illness. These individuals could benefit from practices to better identify their challenges and interventions to promote successful adaptation to illness. Future research will analyze the remaining portions of the survey to assemble a more complete understanding of adaptation in this cohort.

Table 1. What has been most helpful in learning to live with your illness? And why?	
Theme	**Example**
Perspective	"The most helpful thing has been to realize that I need to take things day by day. I don't know what will happen in the future, but I can address and handle what each day may bring." "That no matter how bad things are, there are those whose struggles are worse, so I need to focus on the positive and be thankful."
Acceptance	"Learning to accept that there is nothing I can do to change the reality of my situation."
Illness knowledge	"Knowledge changes everything. The more I know about the illness, the better off I seem to be."
Personal experience	"Experience. Experience has been the most important part to learning to live with an immune illness. I have had my illnesses for 34 years and I have learned so much on how to cope and handle a flareup, manage my stress and so much more. I will only learn more as I age with this." "Generally learning to care for myself and listen to my body"
Social support- Family/ Friends	"I have a good support system of family that wants me to thrive, encourages me to rest, take care of myself." "Support from friends and spouse."
Support groups/ disease community	"Finding a Facebook group with other people who have the same disease also helps! It helps me to not feel so alone and like such a freak. It's easy to feel lonely and isolated with this disease, especially right after being diagnosed."
Competent and empathic care	"Having good doctors who take the time to explain why certain tests are being done, what we are looking for, etc. I have been very lucky to have had doctors who have treated me like part of a team and have validated my thoughts and observations."
Lifestyle changes	"Giving up even trying to do things that require physical strength or stamina. Or limiting those things to the point I'm not devastated when I can't do what I want to."
Treatment/ future treatment	"Knowing and seeing the rapid pace of technological advances that are occurring and knowing that a cure or at least better treatments are on the way." "Having access to Ilaris has been a game changer for me. This medication works so well for me so that I can lead a near normal life."
Psychological interventions	"Talking about it with therapist. Meditation. Writing about it." "It has been truly beneficial for me to speak with a therapist on a regular basis. Talking about it out loud helps. Without talking to my therapist, I most likely would not talk much about it because others do not truly understand. I'd talk to one or two trusted people, if that. This is also because I am far more than my illnesses. Speaking to my therapist weekly helps me to speak about the unspeakable in my life."
Diagnosis	"My illness along with others was not recognized/diagnosed until about 10 years ago ... and I have been living with this for a lifetime. I am now 70. For most of my life I have been negated, shamed, belittled...told that I had a psychological illness, that I did not like school...etc., etc. I lost myself, didn't know how to read my body, who I was. It is only recently, that I now have been validated...that I am "seen" and "heard" ... it is like learning to walk all over again."
Knowing it wasn't their fault	"Knowing that there is nothing I did to cause the disease is helpful because I have no guilt about it."
Research to help others	"How much the research from my experience with it will help others younger than me deal with this disease."
Social privilege	"Being able to retire with enough funds so that I don't have to be stressed about trying to work with pain and fatigue. Having a good medical insurance plan so that I can see specialists and get treatment."
Absence of symptoms	"The only thing that has been most helpful in learning to live with this, is that I rarely get sick. If I was someone who was ill all the time, I wouldn't feel so optimistic about my future."
Self-advocacy	"Listen to your doctors but don't be afraid to push back if you feel a plan of action doesn't work for you. Sometime healthcare professionals need to be reminded that you're a person with other needs and desires beyond the particular problem they are presented with."
Faith	"I have a great faith in God that has ensured peace and stability."

Table 1. What has been most helpful in learning to live with your illness? And why?

Keywords: Adaptation, Inborn errors of immunity, Psychosocial, Patient perspective, Patient care

Disclosures: All other authors indicated they had no financial relationships to disclose.

(179) The effects of adenosine deaminase deficiency on human neutrophils.

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[2]University of Toronto

Introduction: Inherited defects in adenosine deaminase (ADA) 1 cause profound T and B cell immunodeficiency. We have previously reported

frequent neutropenia in patients with ADA deficiency, however, the mechanism for this phenomenon was not clear. The impaired function of the ubiquitously expressed ADA enzyme might also affect the myeloid lineage, therefore the role of ADA in these cells was investigated.
Methods: Peripheral blood cells from a patient with ADA deficiency who was treated with polyethylene glycol conjugated ADA (PEG-ADA) for 29 years were analyzed. To distinguish between extrinsic and intrinsic effects of ADA deficiency, induced pluripotent stem cells (iPSC) from an ADA-deficient patient and healthy controls were differentiated ex-vivo into multipotent hematopoietic progenitors (MHP), which were subsequently differentiated in methylcellulose into oxidase producing neutrophils. Cultures were also treated with PEG-ADA.
Results: The ADA-deficient patient had normal absolute neutrophils counts, however most of the neutrophils were dysplastic with presence of many hypo-lobulated neutrophils, bi-lobar neutrophils resembling those seen in pseudo-Pelger-Huet anomaly, and neutrophils with Dohle bodies inclusions. The number of CD34+CD45+ MHP generated from the ADA-deficient iPSC was significantly reduced. Moreover, all ADA-deficient granulocyte-containing colony forming units (CFU) and particularly granulocyte-CFU were reduced. The percentage of mature neutrophils (CD11b+CD45+CD16+CD66b+) generated from ADA-deficient iPSC was significantly reduced and these cells often had an increased number of nuclear lobules. Interestingly, the viability and apoptosis of neutrophils derived from ADA-deficient iPSC were not different than that of healthy controls. Treating ADA-deficient iPSC with PEG-ADA reversed the abnormalities observed in MHP and in mature neutrophils. Chemical inhibition of ribonucleoside reductase, an enzyme important for the de novo synthesis of deoxyribonucleotides, in ADA-proficient iPSC caused a significant decrease in the number of MPH, granulocyte-CFU, and mature neutrophils, similar to the abnormalities seen in ADA-deficient cells, suggesting that abnormal DNA assembly and repair contributes to the myeloid defects.
Conclusions: ADA deficiency directly interferes with the development of human myeloid cells and neutrophils. Further studies into the clinical implications, management options, and mechanisms of the neutrophil abnormalities in ADA-deficient patients are needed.

Keywords: adenosine deaminase deficiency, Neutrophils, dysplasia

Disclosures: All authors indicated they had no financial relationships to disclose.

(180) Lower baseline IgG level and autoimmune complications predict poor antibody response to COVID-19 mRNA vaccines in primary antibody deficiency

Junghee Shin*[1], Jennefer Par-Young[1], Serhan Unlu[1], Andrew McNamara[1], Hong-Jai Park[1], Min Sun Shin[1], Yuliya Afinogenova[1], Elena Zidan[2], Jason Kwah[1], Armand Russo[1], Florence Hsu[1], Jason Catanzaro[1], Michael Racke[3], Richard Bucala[1], Craig Wilen[1], Insoo Kang[1]
[1]Yale University 1,2,3,4,5,7,9,10,11
[2]medical resident/Yale New Haven Health - Bridgeport Hospital
[3]Medical director/Quest Diagnostics

Background: Patients with primary antibody deficiency (PAD) have increased susceptibility to sinopulmonary infections and poor responses to vaccines. In this time of COVID-19 pandemic, PAD patients are a high risk population for poor outcome of COVID-19. However, the immune response to COVID-19 vaccines in PAD patients is largely unknown.
Objective: We studied anti–SARS-CoV-2 spike receptor-binding domain (SRBD) antibody response and SRBD specific CD4+ T-cell activation after COVID-19 mRNA vaccination in PAD patients. We also investigated the predictive markers for response to COVID-19 vaccines in PAD patients by studying the relation of COVID-19 mRNA vaccine response with their underlying clinical and immune parameters.
Methods: We collected peripheral blood mononuclear cells and plasma of healthy controls (n=19) and patients with primary antibody deficiency (n=25) before and 3-4 weeks following the first and second doses of COVID-19 mRNA vaccines. The humoral response was evaluated by testing anti–SARS-CoV-2-SRBD titers (IgG, IgA, IgM and IgG subclasses) and neutralization activity against the SARS-CoV-2 USA-WA 1/2020 strain in vitro. SRBD-specific CD4 T-cell activation was measured by OX40 and 4-1BB expressing CD4 effector memory cells.
Results: From the PAD patient cohort, one patient had X-linked agammaglobulinemia (XLA) and 12 patients met the criteria for common variable immune deficiency (CVID). Non-CVID PAD patients had the diagnoses of IgG deficiency (n=5), selective IgG subclass 2 deficiency (n=5) and specific antibody deficiency (n=2). Only the XLA patient and 50% (6/12) of CVID patients did not generate anti-SRBD IgG. Anti-SRBD IgA, IgG subclasses 1 and 3 showed a similar pattern as anti-SRBD IgG. The titers of anti-SRBD IgG, IgA and IgG subclasses 1 and 3 significantly correlated with the inhibition of the SARS-CoV-2 USA-WA 1/2020 strain. Patients with poor anti-SRBD antibody response had significantly lower baseline IgG levels (277 vs. 651 mg/dL, p=0.025) and a higher frequency of autoimmune manifestations (p=0.003) compared to patients with adequate antibody response to COVID-19 vaccines. All patients generated a SRBD-specific CD4 T-cell activation response after the first and second doses of mRNA vaccines.
Conclusion: PAD patients with lower baseline IgG levels and autoimmune complications appear to generate a poor antibody response to COVID-19 mRNA vaccines.

Keywords: primary antibody deficiency, COVID-19 mRNA vaccines, humoral response, cellular response, autoimmunity

Disclosures: Michael Racke has relevant financial relationships with proprietary interests with Quest Diagnostic (Employment). All other authors indicated they had no financial relationships to disclose.

(181) Recurrent serositis with hypogammaglobulinemia in a Costa Rican male adult

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[2]MedStar Union Memorial Hospital

We present a 56 year old-male, previously healthy. His past medical history included recurrent dermatitis, characterized by intermittent pruritic, erythematous plaques and papules. Also, he has had recurrent episodes of chest pain characterized by pleuritis with lung effusion and pericarditis. Each episode of serositis occurs every 2-3 months. The flares were accompanied with recurrent fever. The CRP values have varied from 0.3mg/L when he is asymptomatic to 250mg/L during his worst flare.
During his initial evaluations, infectious diseases were ruled out, as well as systemic autoimmune disease.
Echocardiogram documented mild pericardial thickening when he has had some flares only.
Malignancy was ruled with a negative CT, normal abdominal US, normal EGD and colonoscopy. Pleuritic fluid cytology showed normal lymphocytic cells without atypia.
The only relevant laboratory finding was hypogammaglobulinemia with IgG in 381 mg/dL, with IgG1 being the low subclass in 138.9 mg/dL.
Production of specific antibodies by T-dependent and T-independent antigens were documented positive.
He has been treated with daily steroids. However, every time the dose has been tapered down, he relapses. Other medications that have been added

to try to taper down prednisone dose, but without success were colchicine, hydroxychloroquine, methotrexate, azathioprine, and high doses of IGIV. A possible inborn error of immunity was suspected, specifically PIRD or autoinflammatory disorder. An NGS panel of 407 genes specific for PID was requested. A higher risk allele was identified, exon 4 c.2104C> T (p. Arg702Trp). No other relevant pathogenic variants or VUS were detected.
Subcutaneous tocilizumab was started with an excellent clinical response. In Costa Rica there is no availability of monoclonal anti IL-1 antibodies.
The spectrum of NOD2-associated autoinflammatory disease has been classically associated with Blau Syndrome in childhood. Recently the development of autoinflammatory manifestations has been described in adults with the presence of NOD2-mutations, such as Yao Syndrome.
More studies are required about this high-risk allele and its genotype-phenotype association, particularly in Syndromes of Undifferentiated Recurrent Fever (SURF). However, the importance of this case report is that NOD2-associated autoinflammatory disease could be of adult onset.

Keywords: CRP C-reactive protein, CT computed tomography, US Ultrasound, EGD Esophagogastroduodenoscopy, PIRD Primary immune regulatory disorders, NGS Next-generation sequencing, VUS Variant of uncertain significance, SURF Syndromes of Undifferentiated Recurrent Fever

Disclosures: All authors indicated they had no financial relationships to disclose.

(182) Selective Immunoglobulin M Deficiency (SIgMD): assessment in an outpatient Clinic in Brasilia, Brazil.

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[2]Clinica Ferraroni

Rationale: SIgMD is a rare inborn error of immunity, defined as serum IgM levels below two standard deviations (SD) of mean with normal serum IgG and IgA. There are few papers in this issue with difficulty do determine its prevalence.
We evaluated patients in an outpatient private clinic of Allergy and Immunology from 2004 to 2021. We identified 4 patients were according to the following definitions:
a) IgM below 20 in children and below 30 in adults and b) Serum IgM levels below 2 standard deviations equivalent to the 3rd percentile corrected by age; with both criteria respecting normal serum values of IgA, IgG and IgG subclasses; normal response to vaccines and absence of T cell defects and external causes. Results: Four adult patients (3M:1F) mean 50,5 years fulfilled the diagnosis criteria. Respiratory symptoms were superior in prevalence followed by dermatological symptoms. Rhinitis was more prevalent, affecting 3 of the 4 patients. Asthma was observed in only one patient (Samter's Triad). Furthermore, among the dermatological symptoms, atopic dermatitis, Gilbert's pityriasis rosea and folliculitis were observed. Other findings: 25% (1 of 4) of patients had colon neoplasm. Conclusion: according to the scarce literature, neoplasia and allergy are common in this population. We must consider follow up of SIGM patients in concern of autoimmunity and neoplasia.

Keywords: Immunoglobulin M, IgM, Hypogammaglobulinemia, Inborn Error of Immunity

Disclosures: All authors indicated they had no financial relationships to disclose.

(183) Treatment Barriers in Chronic Granulomatous Disease

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Improved survival with Chronic granulomatous disease (CGD) is largely due to routine use of prophylactic medications. Use of standard of care (SOC) medications such as trimethoprim-sulfamethoxazole, itraconazole, and interferon (IFN) gamma has previously reported to be variable. In addition, improved outcomes for hematopoietic cell transplant (HCT) suggest early evaluation for HCT should be considered. Limitations exist in understanding real life practices surrounding medication use and HCT evaluation in patients with CGD. We designed a survey in collaboration with the Immune Deficiency Foundation (IDF) and the CGD Association of America (CGDAA) to identify factors to understand barriers to treatment. The IRB approved survey was launched through IDF and completed by 76 participants: 41 adults (mean age [SD]: 40.4 [16.8] years) and 35 parent/ caregivers of children (mean age [SD]: 12.2 [8.6] years) with CGD. 79% of participants identified as White Non-Hispanic, 68% identified as male, and 72% of participants had X-linked CGD. 16% of participants were not taking prophylactic antibiotics or antifungals on a regular basis. 34% (n=26/76) of participants never received IFN gamma treatment and half of these participants never had this treatment discussed by their CGD specialist. Of the 47 participants who have received IFN gamma, 55% (n=26) of participants were currently not on IFN gamma treatment, with 42% (n=11) of these participants citing side effects as the primary reason for discontinuation. 48% of patients reported difficulty with transition from pediatric to adult care settings. 83% participants had not received HCT and of these 57% were not being considered for this treatment. 33% of participants believed there were barriers to receiving any form of treatment due primarily to the following reasons: 1) difficulty in finding a physician knowledgeable in CGD (32%); 2) financial cost of treatment was prohibitive (28%). This survey highlights the need to educate physicians and families regarding latest treatment options for CGD.

Keywords: Chronic Granulomatous Disease, Immunodeficiency, Transplant, Interferon gamma, Prophylaxis

Disclosures: Felicia Morton has relevant financial relationships with proprietary interests with Horizon Therapeutics (Other Financial or Material Support, Horizon Therapeutics is now a sponsor of the CGDAA. However, they were not a sponsor at the time of survey development and distribution.). Jennifer Puck has relevant financial relationships with proprietary interests with Invitae (Employment, Ownership Interest includes stock, stock options, patent or other intellectual property) and UpToDate (Other Financial or Material Support, Royalties). All other authors indicated they had no financial relationships to disclose.

(184) Novel reversion of truncated SH2D1A variant

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Here we present a case of a 32-year-old man with a presumptive diagnosis of Common Variable Immunodeficiency (CVID), later found to have X-linked lymphoproliferative disease (XLP). Focused exome sequencing analysis of the genes associated with primary immunodeficiency on the DNA extracted from the peripheral blood sample revealed a de novo hemizygous frameshift variant (c.245dupA, p.Asn83Lysfs*22) in the SH2D1A gene. This variant is predicted to cause loss of normal protein

function through either protein truncation or nonsense mediated decay and has been classified as pathogenic.
Somatic reversions were previously reported in XLP patients with missense mutations, predominantly in CD8+ T-cells. These T-cells demonstrate Epstein Bar Virus (EBV) specific cytotoxicity, possibly protecting XLP patients from severe EBV infection. Only one patient was reported to have a small population (2%) of Natural Killer (NK) cells expressing SLAM-Associated Protein (SAP). Our patient had 17% of circulating NK cells, 7% of CD8 T-cells expressing SAP by flow cytometry, and normal NK cell cytotoxicity. There was some evidence of low-level normal allele mixed with the mutant allele in the DNA sample extracted from NK cellsby Sanger sequencing suggestive of mosaicism that may be the result of somatic reversion of the SH2D1A variant. Additional functional studies are being pursued to further evaluate the impact of this variant.
Interestingly, our patient has outlived the median survival of XLP patients by many years and did not have any major infections or complications. He remains on monthly replacement IVIg therapy. EBV quantitative PCR over the last 2 years has been low ranging from ~2,438-5,371 copies/ml, presumably kept at bay by his reverted lymphocytes. It is unclear if the percentage of his SAP+ T-cells and NK cells can be used as a marker to predict his clinical course. Additional studies are needed to elucidate the relationship between mosaicism and clinical outcome.
Our case also adds to the body of knowledge highlighting the importance of obtaining genetic testing in patients with inborn errors of immunity. As a result of focused exome sequencing, we are now monitoring our patient for important sequelae of XLP such as hemophagocytic lymphohistiocytosis and B-cell lymphomas.

Keywords: Somatic reversion, SH2D1A truncation, X-linked lymphoproliferative disease

Disclosures: All authors indicated they had no financial relationships to disclose.

(185) Novel Mosaic STAT3 Gain-of-Function Variant in a Healthy Mother

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Genetic mosaicism has been increasingly recognized as an important mechanism underlying inborn errors of immunity. Germline, heterozygous, gain-of-function (GOF) variants in STAT3 result in early-onset, multi-organ autoimmunity, lymphoproliferation, and immune deficiency. Here, we report a patient with recurrent infections, hypogammaglobulinemia, T cell lymphopenia, and multiorgan polyautoimmunity who was found to have a novel heterozygous STAT3 variant (c.1165A>T, p.T389S). Interestingly, this patient's asymptomatic mother underwent genetic testing revealing that she is mosaic for the p.T389S variant. To investigate the functional consequence of the variant, we introduced the p.T389S variant into a STAT3 plasmid by site-directed mutagenesis. We co-transfected this plasmid with a STAT3-responsive firefly luciferase reporter construct into the STAT3 deficient A4 cell line. At baseline, and with IL-6 cytokine stimulation, the variant conferred significantly increased transcriptional activity compared to WT. Baseline STAT3 phosphorylation was not increased in primary cells from the STAT3 GOF patient. We then isolated peripheral blood mononuclear cells from the patient's mother and performed cell sorting and DNA isolation to determine the variant allele frequency (VAF) in the individual cell types by droplet digital PCR. Mosaicism for the p.T389S STAT3 variant was detected in the patient's mother's whole blood (at 9.58% VAF), saliva (7.7%), CD3+ T cells (16.71%), CD19+ B cells (3.5%), CD56+ NK cells (7.08%), and CD14+ monocytes (6.48%). Further analysis of the CD3+ T cell subsets demonstrated a VAF of 10.1% in CD4+T cells but interestingly, the VAF was highest in CD8+ T cells (34.07%), indicating a selective survival advantage of these cytotoxic T cells. Here, we present an example of gonosomal mosaicism, in which the mother's somatic and gonadal cells harbored a STAT3 variant that conferred GOF, leading to transmission and overt disease in the mother's son. Although a critical VAF for phenotypic expression of disease was not achieved in this mother, the accumulation of CD8+ T cells with STAT3 GOF suggests that this individual may be at risk for disease in the future. Studies are ongoing to further characterize the transcriptional effects on the CD8+ T cells. Thinking forward, genetic mosaicism is likely under-recognized and should be considered when screening patients for IEI.

Keywords: STAT3, mosaic, immune dysregulation

Disclosures: All authors indicated they had no financial relationships to disclose.

(186) Idiopathic T Cell Lymphopenia of Infancy in New York State - Immunologic and Perinatal Characteristics

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Objective: Newborn TREC screening identifies infants with T cell lymphopenia (TCL) that warrant further evaluation for clinically significant T cell immunodeficiency. Among those with abnormal screens are subpopulations of infants with TCL without an identifiable cause. We aim to characterize demographic, laboratory, and clinical characteristics that differentiate infants with transient vs. persistent idiopathic TCL. By definition, transient TCL resolves by approximately 12 months of age.
Methods: A single-center retrospective analysis was performed from September 2010 through October 2020. Data was extracted from chart review of 49 eligible term infants with abnormal TREC screening at corrected gestational age 37 weeks or greater, and descriptive statistics were calculated for initial TREC levels and T cell lymphocyte counts at initial referral. Mann-Whitney tests compared lymphocyte counts and birth weight by percentile for gestational age. Chi-square analysis assessed associations between delivery mode (vaginal or cesarean section), neonatal intensive care unit (NICU) stay and small for gestational age (SGA) status and TCL type.
Results: 22 patients demonstrated persistent TCL while 28 patients had transient TCL. The persistent cohort was 54% male and 22% white, while the transient cohort was 64% male and 21% white. Median initial TRECs did not differ between the two groups (66.5 vs. 73 TRECs/μL of blood, P=0.638). The median initial lymphocyte counts were significantly lower in the persistent compared to the transient cohort for CD3+ (1192 vs. 2135 cells/μL, $p < .01$), CD4+ (890 vs. 1460 cells/μL, $p < .01$) and CD8+ (319 vs. 538 cells/μL, $p < .01$). Delivery mode, newborn NICU stay, or SGA were not significantly associated with TCL type. There was no significant difference in median birth weight by Fenton Growth percentile between the two groups.
Conclusions: Apart from the persistent TCL cohort consisting of more females and exhibiting lower initial T cell counts, the two cohorts did not differ by the demographic, laboratory or perinatal clinical characteristics studied. Work is underway to analyze other perinatal variables such as

maternal health factors. Future studies with larger samples are needed to clarify the role of these perinatal factors in term infants.

Keywords: idiopathic lymphopenia, T cell receptor excision circle assay, perinatal risk factors, newborn screening

Disclosures: All authors indicated they had no financial relationships to disclose.

(187) Immunological Biomarkers and Lung Histology in Elevated IL18 - Pulmonary Alveolar Proteinosis and Recurrent Macrophage Activation Syndrome (IL-18PAP-MAS) Compared to Other Inflammatory Lung Diseases

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Background: Pulmonary alveolar proteinosis (PAP) with macrophage activation syndrome (MAS) and elevated IL-18 (IL-18PAP-MAS) is a clinical syndrome that has recently been reported in rare patients (pts) with systemic juvenile idiopathic arthritis (SJIA)-like disease. The pathomechanisms of IL-18PAP-MAS lung disease remain elusive and we aimed to characterize its immunological biomarkers by comparison to other inflammatory diseases.
Methods: Eight pts with IL-18PAP-MAS were enrolled in an IRB approved protocol (NCT02974595). Serum, whole blood RNA, bronchoalveolar lavage (BAL) samples and lung biopsies from IL-18PAP-MAS pts were compared to samples from pts with several inflammatory diseases, including STING associated vasculopathy with onset in infancy (SAVI) and sarcoidosis, and healthy controls (HC). Serum and BAL cytokines were measured by Luminex assay; CXCL9 and CXCL10 transcript levels were quantified by Nanostring. Lung biopsies were scored for inflammatory cell infiltrate, type 2 pneumocyte hyperplasia, cholesterol crystals and fibrosis. Chest CTs were reviewed and scored.
Results: All 8 patients had high elevation of serum IL-18 levels and high CXCL9 gene expression and CXCL9/CXCL10 ratio (IFN-gamma response markers) were higher in IL-18PAP-MAS compared to SAVI, NOMID and HC. BAL fluid from IL-18PAP-MAS pts (n=2) had higher expression of IL-18 and free IL-18, which were solely detected in IL-18PAP-MAS pts (n=2) in contrast to SAVI (n=2) and sarcoidosis (n=10). Lung histologic features (n=3) showed innate immune cells including high expression of neutrophils, histiocytes and alveolar macrophages with fewer lymphocytes and B cell infiltrates compared to SAVI (n=7), and low numbers of parenchymal and peribronchial lymphoid aggregates. Cholesterol clefts and mucous plugging were cardinal features in IL-18PAP-MAS. Distinctive radiological features included consolidation, intralobular septal thickening, and pulmonary nodules, with higher inflammatory vs damage scores in contrast to SAVI.
Conclusion: Histological pulmonary features of IL18 PAP-MAS differ from lung manifestations of SAVI and sarcoidosis, which includes recruitment of innate immune cells, predominantly neutrophils and alveolar macrophages. BAL fluid shows high expression of total and free IL-18 of IL-18 PAP-MAS but not in SAVI and sarcoidosis pts suggesting a role of free IL-18 in the distinct pathogenesis of PAP in IL-18PAP-MAS.
Funding: This work was supported by the NIH IRP of NIAID

Keywords: autoinflammatory diseases, pulmonary alveolar proteinosis, macrophage activation syndrome, IL-18, lung disease, CXCL9

Disclosures: All authors indicated they had no financial relationships to disclose.

(188) The Spectrum of Genetic Variants Detected in a Primary Immunodeficiency Panel in a Clinical Diagnostic Laboratory

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Introduction: Primary immunodeficiency disorders (PID) are a heterogeneous group of >400 disorders that impact the immune system and may be inherited in a multifactorial fashion. The clinical features of PIDs range in severity and age of onset, but may include increased susceptibility to infectious disease, autoimmunity, autoinflammatory disease, allergy, and malignancy. To date, over 380 genes have been identified as causative for monogenic immune disorders. To optimize genetic testing for PIDs, an exome-based panel including 586 genes with reported association to PIDs was developed [Inborn Errors of Immunity/Primary Immunodeficiency (PID) panel].
Methods: The PID panel uses next generation sequencing via the Illumina NovaSeq 6000 platform (Illumina, San Diego, CA, USA) to cover the coding regions of the targeted genes plus ~10 bases of non-coding DNA flanking each exon. We also analyze other regions within or near genes in which pathogenic variants have been identified. The following quality metrics are used: ~96.6% of target bases are covered at >20x and mean coverage of target bases 120x. The PID panel also utilizes the exome sequencing data to identify chromosomal imbalances that may be associated with immunodeficiencies. Data were collected on PID panels reported in 2021. Data collected included indication for testing, test outcome (positive, negative, or indeterminate), and turnaround time.
Results: In 2021, over 250 PID panels were reported with an average turnaround time of 15 days. Of those tests reported, ~10% had a definitive diagnosis, while ~80 of cases had variant(s) that may explain the patient's clinical features. The remaining cases were negative. Findings included a deletion of exon 3 of the XIAP gene, a variant in the CYBB gene, and compound heterozygous variants in the ZAP70 gene. Of note, for the latter two cases additional clinical information and family testing aided upgrading the reported variants to causative.
Conclusion: PIDs are clinically and genetically heterogenous disorders. Genetic testing may provide beneficial information for both patients and families but must cover a wide range of genes and utilize all available resources (clinical information and family testing) to aid interpretation.

Keywords: Genetic Testing, Primary Immunodeficiency, Exome-based Large Panel, Exome-wide CNV

Disclosures: All authors indicated they had no financial relationships to disclose.

Friday Lightning Poster

(189) Lymphocytes utilize somatic mutations, epigenetic silencing and the proteasome to avoid expressing truncated WASP

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Background: The gene WAS encodes WASP, an actin cytoskeleton-organizing protein critical to leukocyte and platelet function. WASP deficiency causes Wiskott-Aldrich Syndrome (WAS), a sex-linked disorder characterized by combined immunodeficiency, microthrombocytopenia and eczema. Like WASP-deficient humans, WASP-deficient mice produce normal numbers of functionally defective T cells. In contrast, mice that express a T-cell restricted transgene encoding a truncated WASP lacking the c-terminal verprolin homology (V), cofilin homology (C) and acidic region (A) domains (WASPΔVCA) experience an early break in T lymphopoiesis and reduced TCR & e_x1D6FC;β expression.
Here, we report a WAS patient with a novel germline frameshifting mutation predicted to generate a truncated protein lacking the c-terminal C and A domains (WASPΔCA). Assessment of the patient's PBMCs for WASP expression identified three distinct cytotoxic T lymphocyte populations with variable expression of CD8, TCR & e_x1D6FC;β and WASP.
Methods: To determine if somatic WAS mutations could potentially explain variability in WASP, TCR & e_x1D6FC;β and CD8 expression, we deeply sequenced WAS exons, introns, promoters and 5' untranslated regions at 10,000 read depth in the patient's genomic DNA from various B and T cell populations. The transcriptional and translational consequences of genomic variants were explored by sequencing cell population-specific WAS cDNA transcripts and by probing the lysates of WAS overexpressing HEK293 lines with an anti-WASP detection antibody.
Results: The patient's three distinct cytotoxic T lymphocyte subsets each carried either the germline exon 11 frameshift WAS mutation or a variety of somatic mutations to either revert the germline frameshifting mutation, restore the native reading frame, or skip exon 11 entirely during post-transcriptional splicing. The somatic mutations were incorporated into WAS transcripts which encoded either stable, near full-length proteins or unstable, non full-length proteins. Cultured patient lymphoblasts expressed increasingly detectable levels of WASPΔCA when treated with MG-132, a proteasome inhibitor.
Conclusion: Although we can stably express WASPΔCA in embryonic kidney cell lines, we demonstrate through deep sequencing, transcriptional profiling and protein analysis that patient lymphocytes employ a variety of genetic, epigenetic and proteasomal strategies to avoid negative biologic consequences of WASPΔCA.

Keywords: Wiskott-Aldrich Syndrome, WASP, proteasome, WAS

Disclosures: All authors indicated they had no financial relationships to disclose.

(190) Curation and Expansion of Human Phenotype Ontology for Inborn Errors of Immunity

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The Human Phenotype Ontology (HPO) aims to provide a standardized vocabulary of phenotypic abnormalities. Adapting HPO as the tool for patient phenotyping enables efficient patient data exchange and facilitate seamless communication between clinicians and researchers to detect novel disease-causing genes and address phenotype-genotype correlations. Therefore, the need for accurate HPO terms and metadata to describe clinical information is increasingly clear. Despite the ongoing efforts, there are still crucial, disease-specific gaps in HPO when describing rare immune mediated disorders.
Our initiative supported by ESID and ERN RITA brings together geneticists, medical doctors, bioinformatics, and immunologists. Organized into four functional working groups, we aim to re-evaluate and complete HPO ontology terms and re-annotate diseases. In our first phase, we have revised four branches of the HPO tree and have introduced 57 new HPO terms. In our second phase, our focus was the systematic re-annotation of immune related diseases using an expert reviewed text-mining approach. We have collected an expert-curated knowledge-base of reviews and case reports detailing phenotypes of patients for 73 diseases. This knowledge-base served as the basis of our automated annotations scheme that used text mining to extract phenotypic annotation and translate it to HPO codes that go through a two-tier expert review. We show that our approach lead to a mean 4.7-fold increase in the number of true HPO terms annotating diseases, and significantly improved patient-to-diagnosis and disease-disease similarity.
With the continued systematic re-evaluation, we expect to (i) unify the nomenclature of patient phenotyping (ii) standardize patient characterization: clinician/researcher can characterize patients in a language independent manner (iii) allow for efficient data exchange between clinicians, laboratories and centers (iv) facilitate matching phenotypically similar patients to enable gene discovery (v) allow for similarity measures across diseases/shared phenotypes.

Keywords: Human Phenotype Ontology, Inborn errors of Immunity, Autoinflammation, Autoimmunity, Immune dysregulation

Disclosures: Markus Seidel has relevant financial relationships with proprietary interests with Amgen (Research Grant includes principal investigator, collaborator or consultant and pending grants as well as grants already received, Speaker/Honoraria includes speakers bureau, symposia, and expert witness), CSL Behring (Other Financial or Material Support, travel grant)
Novartis (Research Grant includes principal investigator, collaborator or consultant and pending grants as well as grants already received), and Takeda (Research Grant includes principal investigator, collaborator or consultant and pending grants as well as grants already received). All other authors indicated they had no financial relationships to disclose.

(191) Understanding the Etiology of Very Early Onset Inflammatory Bowel Disease in a Novel LCK Variant – of Human and Mouse

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Background: Partial T cell defect primary immunodeficiency disorders (PIDD) are a heterogeneous group of genetic disorders characterized by incomplete reduction of T cell number and/or function. Unlike severe T cell immunodeficiencies, partial T immunodeficiencies are commonly associated with hyper-immune dysregulation, including autoimmunity and inflammatory complications. Lymphocyte cell-specific protein-tyrosine kinase (LCK) is a Src family tyrosine kinase that initiates T cell receptor (TCR) signaling. Given its role in TCR signal transduction, LCK is critical to T cell development and function. Here we report the clinical and immunological phenotypes of a novel LCK variant which results in partial T cell defects and immune dysregulation.
Methods: To determine the causes of the abnormalities seen with the human LCK p.Pro440Ser defect, we generated a cell line and a mouse model that harbor the mutant and performed downstream immunophenotypic and functional assessments.
Results: A novel homozygous mutation in LCK (p.Pro440Ser, LCK P440S) was identified in two siblings who were born to consanguineous parents, presenting with recurrent viral and fungal infections, and early-onset pulmonary and gastrointestinal inflammatory complications. The immunological phenotype included T lymphopenia, impaired vaccine responses, and increased CD21lo B cells. While a previously-described LCK mutation (p.Leu341Pro) also resulted in these T and B cell defects, inflammatory complications were not described. The LCK P440S mutation results in decreased protein expression and defective TCR signaling. To address questions pertaining to T cell development and immune dysregulation, a mouse model harboring the murine homolog of this mutation was created (Lck mut mouse). The Lck mut mouse demonstrated impaired thymocyte development with concomitant T cell lymphopenia, decreased regulatory T cells, and spontaneously-developed inflammatory bowel disease (IBD), recapitulating the human phenotype. While Lck knock-out (KO) mice replicate the T cell aberrations in Lck mut mice, Lck KO mice do not develop IBD, suggesting that partial loss of Lck function drives IBD.
Conclusions: Our findings explain the abnormal immune system development in the human P440S patients, help advance our understanding of IBD in the context of perturbed T cell development/function arising from defective TCR signaling, and establish a model system with which to develop therapies against IBD.

Keywords: LCK, T cell development, Primary immunodeficiency disorders, T cell signaling, Immune dysregulation, Very early onset inflammatory bowel disease, Bone marrow transplant, Viral and fungal susceptibility, Interstitial lung disease

Disclosures: All authors indicated they had no financial relationships to disclose.

(192) Evaluation of Lymphocyte Reconstitution and Anti-drug Antibodies in an Open-Label Study of PEGylated Recombinant Adenosine Deaminase (Elapegademase) in Patients with ADA-SCID

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Enzyme replacement therapy (ERT) is the first-line therapy for effective metabolic detoxification and immune recovery in patients with adenosine deaminase-deficient severe combined immunodeficiency (ADA-SCID). Elapegademase is a PEGylated recombinant bovine adenosine deaminase (ADA) ERT developed to replace the bovine-derived ADA used in the manufacture of pegademase. A multicenter, open-label, crossover trial from pegademase to elapegademase in patients with ADA-SCID (NCT01420627) was performed to assess efficacy outcomes for elapegademase. Study objectives included assessment of lymphocyte counts, safety, and development of anti-drug antibodies (ie, anti-elapegademase and anti-pegademase IgG and IgM, and anti-PEG antibodies). Once pegademase dosage was adjusted to achieve full metabolic detoxification (dAXP ≤0.02 mmol/L and ADA activity ≥15 mmol/h/L), patients began elapegademase therapy at an equivalent enzymatic dose to pegademase and pegademase was discontinued. The study population consisted of 7 patients (mean age [SD]: 21.3 [9.5] years) with ADA-SCID. Upon switching to elapegademase, 1 patient withdrew after 2 doses due to injection site pain caused by EDTA in the original formulation; EDTA was removed from the formulation for the subsequent 6 patients enrolled. The mean [SD] duration of elapegademase therapy was 135.7 [83.5] weeks. All 6 completer patients met the predefined criterion for maintenance of full metabolic detoxification during elapegademase therapy, with minor exceptions at 1–3 time points in 4 patients. Mean [SD] ADA activity at the end of study (elapegademase - 39.6 [5.4] mmol/h/L) was approximately twice the levels of pegademase at baseline (17.1 [3.5] mmol/h/L). Elapegademase therapy resulted in increased CD4+ and CD19+ lymphocyte counts compared with pegademase therapy, though the degree of increase varied between patients. Total lymphocytes and CD3+, CD8+, and CD16+/56+ subset counts were maintained or improved, with no specific lymphocyte subpopulation demonstrating consistent increases across patients. Elapegademase had a comparable safety profile to pegademase; no patient developed a severe infectious complication during the study. Three of the 7 patients had transient, non-neutralizing anti-drug antibodies without effect on ADA levels or activity. This study found that elapegademase is well tolerated, maintains metabolic detoxification, and is associated with improvements or maintenance in total and subset lymphocyte counts in patients with ADA-SCID.

Keywords: Immunodeficiency, enzyme replacement therapy, ADA-SCID, metabolic detoxification, lymphocyte reconstitution

Disclosures: Heather Lehman has relevant financial relationships with proprietary interests with University of Buffalo (Research Grant includes principal investigator, collaborator or consultant and pending grants as well as grants already received), and University of Buffalo (Contracted Research, Revcovi Registry trial from Chiesi). Tracy Fausnight has relevant financial relationships with proprietary interests with Chiesi (Contracted Research). Joseph Wiley has relevant financial relationships with proprietary interests with Leadiant Biosciences, Inc. (Employment, Employed by Leadiant Biosciences, Inc., the company that licensed the sale of Revcovi in the US). All other authors indicated they had no financial relationships to disclose.

(193) Immunologic Characterization of Patients with Various Immune Defects using Epigenetic Immune Cell Quantification

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In this study we aimed at immunologic characterization of a cohort of 267 patients with a variety of primary and secondary immune defects using a panel of 13 epigenetic immune cell quantification assays. Using the same cohort, we previously showed that epigenetic immune cell quantification of T-, B- and NK lymphocytes provides essentially identical results to traditional flow cytometry with the benefit of being able to use small volumes (< 40 µl) of archived (frozen/dried) blood samples for analysis (Ramirez, CIS 2021; oral abstract).
We extended the epigenetic analysis of the cohort to regulatory T (Treg), Th17, Tfh, PD-1+, CCR6+ cells, monocytes and granulocytes. Subgroup analysis was performed based on available genetic and/or phenotypic patient data and according to IUIS classification (Tangye et al., 2020).
IUIS subgroups with sufficient number of cases for statistical analysis were Predominantly Antibody Deficiencies (n=169) and Diseases of Immune Dysregulation (n=24). The remaining cases represented 7 additional IUIS subgroups and did not reach sufficient numbers for statistical analysis. It was shown that the two subgroups for which we could perform statistical analysis have significantly reduced T and B cell compartments as well as CCR6+ cells compared to healthy controls. In particular Th17 cells were significantly decreased in patients with severe reduction of serum immunoglobulins. Furthermore, it was shown that the ratio of Tregs to pan-T cells in patients with immune dysregulations was decreased in male patients whereas female patients showed an increased ratio compared to healthy controls. Striking differences in immune cell profiles were also observed in individual cases from the other IUIS subgroups and will be presented as selected case studies.
This study underscores the suitability of epigenetic immune cell quantification for the immunologic characterization of a variety of immune defects. We propose this method as a suitable tool for molecular diagnostic applications, at the point of care, as well as for newborn screening for early detection of inborn errors of immunity since this technology can also be applied to dried blood spots.

Keywords: Primary immune deficiencies, Epigenetic immune phenotyping, DNA Methylation, Immune inborn error

Disclosures: Janika Schulze has relevant financial relationships with proprietary interests with Epimune GmbH (Employment). Steffi Walter has relevant financial relationships with proprietary interests with Epimune GmbH (Employment). Jeannette Werner has relevant financial relationships with proprietary interests with Epimune GmbH (Employment). Christoph Sachsenmaier has relevant financial relationships with proprietary interests with Epimune GmbH (Employment). All other authors indicated they had no financial relationships to disclose.

(194) Gut immunopathology and fecal microbiota alterations in mice carrying Rag1 hypomorphic mutations

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Hypomorphic Recombination Activating Gene 1 (RAG1) mutations have been found in patients presenting with delayed-onset combined immune deficiency with granulomas and/or autoimmunity (CID-G/AI) and atypical severe combined immune deficiency (atypical SCID). Studies have shown how these mutations alter the repertoire of T and B cells, but less is known about their effect on target organs. To investigate the role of these mutations in intestinal disease, we studied the interplay of gut immunity and microbiota in a hypomorphic Rag1 mouse model carrying the homozygous mutation R972W (Rag1w/w mice), corresponding to the human mutation R975W described in patients with atypical SCID. Previous immunological characterization of this model showed partial preservation of T and B lymphocytes.

Analysis of gut tissue in Rag1w/w mice revealed severe spontaneous colitis with lymphocytic infiltrate, which becomes histologically evident after 3 weeks of age. To assess the contribution of genetics and environment on the pathogenesis of gut inflammation, we combined flow cytometry, single-cell RNA-seq and microbiome (16S sequencing) studies. Phenotypical and gene expression analysis of T cells infiltrating the colon lamina propria showed a skewing towards a Th1/Th17 phenotype in Rag1w/w mice, and analysis of the fecal microbiota composition revealed a severe restriction of microbial diversity in mutant mice.

To evaluate the role of the microbiota in inducing gut inflammation, we administered broad-spectrum antibiotics to Rag1w/w with two different approaches: starting at weaning (3 weeks) or by treating pregnant mothers (already exposing the mice during fetal life). In both cases, the lymphocytic infiltrate was quantitatively normalized but the colon lamina propria T cells maintained the skewing towards the Th1/Th17 phenotype, indicating a dramatic effect of the genotype on the colitis induction. Furthermore, hematopoietic stem cell transplantation (HSCT) resulted in an almost complete donor chimerism with donor-derived T cells in the colon lamina propria showing a wild-type phenotype, without Th1/Th17 skewing.

Overall, we showed that Rag1 mutant hypomorphic mice intrinsically present a Th1/Th17 signature. In this altered immune landscape, the exposure to microbiota drives gut lymphocytic infiltrate with the development of colitis. Antibiotics can thus limit the inflammation but only HSCT is able to correct the pathological Th1/Th17 phenotype.

Keywords: Combined Immunodeficiency, RAG mutation, Microbiota, Inflammatory bowel disease

Disclosures: All other authors indicated they had no financial relationships to disclose.

Saturday Lightning Poster

(195) Phenome-wide association (PheWAS) in a cohort enriched for primary immunodeficiencies using HLA genotypes inferred from research exome and genome sequencing

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Human leucocyte antigen (HLA) alleles have been implicated in the etiology of many autoimmune-related diseases. HLA typing is routinely performed to assess compatibility of recipients and potential donors during hematopoietic stem cell transplant. Additionally, certain HLA variants have pharmacogenetic implications and can be used to inform individualized drug dosing. In this study, we investigated the effect of HLA genotypes on a diverse set of phenotypes in patients with immune disorders using a phenome-wide association study (PheWAS) approach. We called HLA genotypes for 3,789 patients referred to the National Institute of Allergy and Infectious Diseases (NIAID) Centralized Sequencing Program (CSP), 3,237 of whom received exome sequencing and 552 of whom received genome sequencing. HLA genotypes were called using the HLA-LA package, with confidence up to 4 digits, 2 fields. We validated HLA calls from this approach within a subset of patients who also received clinical HLA genotyping. We then used the HLA genotypes to perform a PheWAS analysis corrected for sex, age, age squared, and population structure. Our findings replicated a previously-reported multiple sclerosis (MS) association with HLA-DRB*15:01 ($P = 1.055e-7$). However, we failed to replicate a known association between the HLA-DQB1*06 allele and MS. Additionally, both hydrocephalus and disorders of sphingolipid metabolism and other lipid storage disorders were significantly associated with HLA-B*35:17 ($P = 2.33e-07$). Our study demonstrates that accurate HLA genotyping can be obtained from exome and genome data and utilized for PheWAS analysis. Our PheWAS findings validated a previous association between MS and an HLA-DRB allele and identified other alleles for further validation. Additional studies would allow for further elucidation of the relationship between the HLA system and clinical and subclinical phenotypes in immune disorders.

Keywords: Human leucocyte antigen alleles, PheWAS, Multiple sclerosis

Disclosures: All authors indicated they had no financial relationships to disclose.

(196) A Tertiary Care Clinical Sequencing Program for Patients with Suspected Immune Defects: Results from the First 1000 Families

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Prospective genetic evaluation of patients with suspected inborn errors of immunity (IEI) at our referral hospital presents clinical and research challenges. To address this, we developed a program to integrate exome sequencing, systematic phenotyping, and clinical return of results in 1,505 individuals from 1,000 families referred between 2017-2019. Chromosomal microarray was also completed on 374 probands. A multi-layered reanalysis pipeline was implemented in 2021. Participants were 50.8% female, 30.1% age 18 years or younger (mean = 36.5 years) and presented with a diverse range of mostly immune-system related phenotypes. In total, 328/1,000 probands (32.8%) had findings consistent with 362 molecular diagnoses. Ninety-two of these molecular diagnoses (25.4%) involved genes not identified by the 2021 International Union of Immunological Sciences as a cause of an IEI and not typically covered by commercially available IEI gene panels. These included 17 probands with 18 diagnostic copy number variations, 33 probands with 34 American College of Medical Genetics and Genomics-recommended secondary findings, and 31 probands with multiple molecular diagnoses. Reanalysis within 24-38 months of initial analysis added 22 new molecular diagnoses, the largest fraction of which were due to new disease-gene associations (9/22, 40.9%). Receiving a molecular diagnosis was correlated with younger age, male sex, and a higher number of organ systems involved. This cohort also facilitated discovery of new gene-disease associations such as a disorder related to defects in SASH3. Critically, the review of IEI treatment options by Hammarström and colleagues, combined with these findings, suggest that 236/362 (65.2%) of the reported molecular diagnoses could translate into at least one management option including supportive therapy (n = 139), preventive therapy (n = 176), allogenic hematopoietic stem cell or other transplant (n = 107), targeted therapy (n = 73), gene therapy (n = 1, currently available through clinical trials), or other precision management (referencing diagnoses from the secondary finding list, n = 48) pursued either concurrently or sequentially. A systematic program of clinical molecular genetics and phenotypic evaluation in a large cohort generated both expected and unexpected molecular diagnoses that contributed to improvements in the understanding of basic immunity, molecular diagnostics, and clinical care.

Keywords: Genomics, exome, chromosomal microarray, copy number variation, secondary findings, immunology, inborn errors of immunity, genetics, return of results

Disclosures: All authors indicated they had no financial relationships to disclose.

(197) In vitro investigation of Toll-like receptor 8 inhibition as a potential therapeutic strategy against hyper-inflammation in TLR8-GOF patients to improve long-term outcome

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Toll-like receptor 8 (TLR8) is an endosomal receptor that recognizes single-stranded RNA and activates NF-kB to upregulate a pro-inflammatory transcriptional signal. We recently described a cohort of six unrelated male patients with somatic (n=5) and germline (n=1) GOF mutations in TLR8 leading to neutropenia, lymphoproliferation, and bone marrow failure. Since its description, two additional patients with mosaicism for the previously described TLR8 p.P432L variant (VAF~12%) and a novel TLR8 p.P432Q variant (VAF~7%) have been identified by targeted review of TLR8 gene in patients with a similar phenotype. Functional analysis revealed that TLR8 p.P432Q also confers a GOF. Treatment of these patients has been challenging with multiple patients requiring HSCT and having transplant related complications including poor engraftment and/or survival. As TLR8-GOF leads to hyper-inflammation, which can have a detrimental effect on the transplantation outcome, we hypothesize that inhibition of TLR8 signaling pathway can serve as an effective therapeutic strategy to suppress disease-associated inflammatory response in the setting of transplantation and improve its overall outcome. We tested the in-vitro antagonistic potency of two different classes of TLR8 inhibitors:1) CU-CPT9a, an oligonucleotide that binds to and stabilizes the resting state of TLR8; and 2) CPG-52364, a quinacrine derived small molecule inhibitor (SMI) of TLR7/8/9 previously used in a clinical trial for lupus, that functions by altering the endosomal pH and blocking TLR activation. Experiments performed in NF-κB reporter cells and patient myeloid cells derived from iPSCs demonstrated that while CU-CPT9a inhibits wild-type TLR8, it does not effectively inhibit the activity of disease-causing TLR8 variants. These results correlated with structural modeling data that predicted variant resistance to CU-CPT9a due to stearic clashes or predisposition of variant TLR8 conformation to the active state, which is not favorable for CU-CPT9a binding. By contrast, pre-treatment of cells with CPG-52364 resulted in a profound suppression of NF-κB activation and production of inflammatory cytokines, suggesting that use of SMIs such as CPG-52364 might be an effective strategy in suppressing TLR8-GOF induced inflammation. Identification of additional patients and further investigation of the mechanism and functional consequences of TLR8 GOF can provide guidance for evidence-based therapy for improving long-term outcome.

Keywords: Inborn errors of immunity, somatic mosaicism, toll-like receptor 8 inhibitors

Disclosures: Gregory Guilcher has relevant financial relationships with proprietary interests with bluebirdbio (Research Grant includes principal investigator, collaborator or consultant and pending grants as well as grants already received). All other authors indicated they had no financial relationships to disclose.

(198) Advanced In Silico Functional Analysis Confirms Pathogenicity of CD40L Variants in Atypical Cases of X-Linked Hyper-IgM Syndrome.

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X-Linked Hyper-IgM Syndrome (XHIGM) is an inborn error of immunity caused by pathogenic variants in CD40LG affecting class-switch recombination and T-cell costimulation. Patients with typical XHIGM present early with opportunistic and recurrent bacterial infections. Laboratory anomalies include decreased class-switched memory B cells, and hypogammaglobulinemia with normal/elevated IgM. Flow cytometry evaluates for expression of CD40L on activated CD4+ T-cells and functional binding with a soluble form of its receptor (CD40-muIg). Genetic testing serves as confirmation. We describe two patients with atypical clinical presentations, abnormal CD40LG/CD40-muIg flow cytometry, and novel CD40LG variants. Patient1 was diagnosed at 11y with DLBCL and treated with R-CHOP. Persistent hypogammaglobulinemia prompted evaluation, which revealed a variant of unknown significance (VUS) in CD40LG, p.Lys143Asn, and qualitative defects of CD40L with normal protein expression but diminished binding. Patient2 had symptom onset at 6mo with recurrent febrile episodes, oral ulcers, arthritis, and diarrhea throughout childhood as well as bronchiolitis, pneumonia, and Cryptosporidial diarrhea by 3y of age. A broad diagnostic evaluation identified a VUS, p.Met36Arg, and demonstrated decreased protein expression and binding of CD40L. In both cases, the atypical clinical presentations warranted further diagnostic analysis. We used advanced in silico protein modeling and dynamic simulations to determine the structural and functional impact of these variants to inform their classification. The Lys143Asn variant prevents stabilizing hydrogen bond formation at S65 on CD40, which significantly reduced time-dependent binding to CD40L in molecular dynamic studies. Asn143 also disrupts two other bonds that Lys143 forms with N79 on CD40, however additional molecular mechanic and dynamic data show that this substitution would not interfere with normal trimerization of CD40L. Thus, while binding would be decreased, circulating levels of the variant CD40L would remain unaffected. The Met36Arg variant interrupts the highly hydrophobic intramembrane helix, a residue conserved across species. Molecular dynamic simulations predict effects on the insertion, maintenance, or orientation of membrane-bound CD40L, impacting both protein expression and binding. The use of advanced protein analysis enabled the classification of these VUS as pathogenic. In silico protein modeling can be a useful adjunct in the functional evaluation of atypical genetic variants in known inborn errors of immunity.

Keywords: Hyper IgM, CD40 Ligand, novel variant, XHIGM, atypical case, Inborn Error of Immunity, in silico

Disclosures: All authors indicated they had no financial relationships to disclose.

(199) Characterization of inflammasome dysfunction in XIAP deficient phagocytes

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The X-linked inhibitor of apoptosis (XIAP) protein is an anti-apoptotic protein, a member of the inhibitor of the apoptosis protein family (IAP). XIAP is ubiquitously expressed and is a potent inhibitor of programmed apoptosis by directly blocking the activated forms of caspases-3, -7, and -9 via its BIR2 and 3 domains. Additional functions of XIAP rely on its ubiquitin ligase activity involved in regulating important signaling pathways (e.g., NF-KB, MAPK pathways) (Chaudhary et al., 2016; Schilling et al., 2014). Among other important functions is the role of XIAP in the signal transduction of the NOD-like receptors NOD1 and NOD2, which play a pivotal role in innate immunity.
Hemizygous loss of function mutations in XIAP leads to XIAP deficiency. It can be considered as an autoinflammatory disease since the clinical phenotype encompasses several auto-inflammatory features: Haemophagocytic Lymphohistiocytic syndrome (HLH), sometimes occurring in the absence of a documented infectious agent or inflammatory bowel disease, mimicking Crohn's disease.
Interestingly, while some earlier reports (Jost Cell reports 2014) have shown that deletion of XIAP induces NLRP3 inflammasome activation which seems dependent on the TNF signaling in mice, the precise mechanisms by which XIAP deficiency induces an autoinflammatory syndrome are not defined.
Using a THP1 monocytes/macrophages cell line, we generated by CRISPR-Cas12 gene-editing an XIAP knock-out cell line to investigate the fundamental mechanism underlying the dysregulation of the inflammatory response in the XIAP-deficient context. Using this cell line, we have shown that XIAPKO monocytes, when differentiated into macrophages using phorbol myristate acetate (PMA), exhibit an enhanced inflammatory profile with increased IL-1beta secretion associated with an excessive NLRP3 inflammasome activation and by excessive pyroptosis. Interestingly, blocking IL-1beta signaling during the macrophage differentiation lowered the secretion of inflammatory cytokines. Using XIAP isoforms devoid of ubiquitin ligase activity, we have shown that the regulation of the NLRP3 inflammasome by XIAP is independent of its ubiquitin ligase activity.
The study of our cellular XIAP deficiency model will help us refine the mechanisms by which XIAP regulates both inflammasome activation and apoptosis in macrophages. Hopefully, our approach will help us define new therapeutic targets for managing patients with this condition.

Keywords: Immunodeficiency, Apoptosis, Inflammasome, XIAP, macrophages

Disclosures: All authors indicated they had no financial relationships to disclose.

(200) NOX2-derived ROS controls the inflammatory response by regulating pyroptosome assembly and GasderminD cleavage

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Chronic Granulomatous Disease is a mendelian disorder caused by loss-of-function mutations genes encoding subunits of the NADPH oxidase complex 2. While infections constitute an apparent part of the immunological phenotype, auto-inflammatory manifestations are also a prominent feature of the disease since 80% of CGD patients will develop autoinflammatory complications by the age of 20.
Increasing reports have underlined the role of the NLRP3 inflammasome in the pathophysiology of inflammation in CGD. However, the precise mechanism provoking a disproportionate inflammatory response in CGD patients remains elusive. Interestingly, the NOX2-deficiency model – characterized by defective production of cytosolic Reactive Oxygen Species (ROS) is at odds with the classical concept that chronic inflammation is caused by prolonged and sustained ROS production. These opposite views suggest that efficient regulation of the inflammatory response requires a well-balanced ROS signaling.
Using a NOX2-deficient phagocytic THP-1 cell line and CGD patients' primary monocytes, we have shown that the defective redox signaling in CGD phagocytes is responsible for post-translational priming of the pyroptosome as evidenced by an enhanced oligomerization of its principal component ASC. Increased pyroptosome formation is facilitating the

cleavage of GasderminD (GSDMD), a known effector of pyroptosis. Interestingly, GSDMD cleavage does not result in excessive pyroptosis in unstimulated macrophages but further activates the NLRP3 inflammasome by facilitating the release of mitochondrial DNA in the cytosol and by lowering the intracellular K+ concentration through its membrane pores. Altogether, our data unveil the role of NOX2-derived ROS in the post-translational regulation of the pyroptosome and the pivotal role of GSDMD in the amplification of the inflammatory response in CGD. Our study paves the way for potential targeted therapies in CGD patients with inflammatory manifestations.

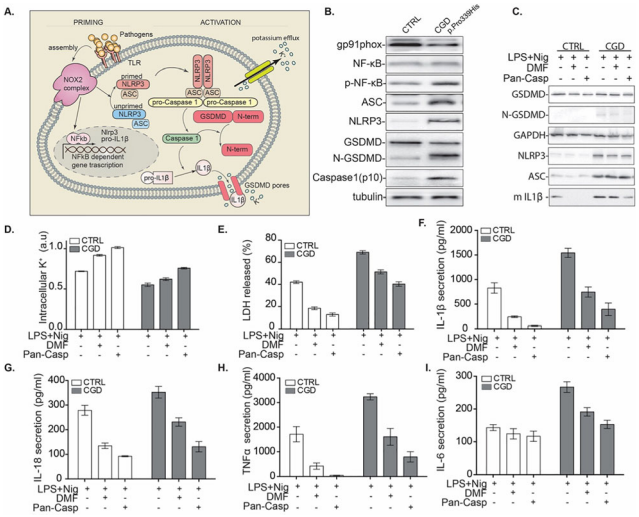

Figure 1. A. NOX2-derived ROS regulates the NLRP3 inflammasome transcriptional priming through the NF-KB pathway. They also enhanced the post-translational priming of NLRP3 and ASC, leading to excessive IL-1β cleavage, GSDMD pores inflammasome that further activates NLRP3 through increased K+ efflux. B. Increased NF-KB signaling, NLRP3 activation, ASC oligomerization, and GSDMD cleavage in monocytes from a CGD patient (p.Pro339His mutation) stimulated with LPS as compared to healthy control. C. The GSDMD cleavage is reduced by treatment with dimethyl fumarate (DMF) or a pan-caspase inhibitor in a CGD patient's monocytes treated with LPS+ nigericin. D. Lower K+ concentration in CGD monocytes stimulated by LPS+ nigericin as compared to healthy control. DMF and the pan-caspase inhibitor reduce the K+ efflux. E. A moderate increase (<2 fold) in pyroptosis in monocytes from CGD patients is counteracted by DMF and pan-caspase inhibitor treatment. Both DMF and the pan-caspase inhibitor can reduce the hypersecretion of IL-1β (F), IL-18 (G), IL-6 (H), and TNF-α (I) in monocytes from CGD patients stimulated with LPS+nigericin.

Keywords: Chronic Granulomatous Disease, Cytosolic Reactive Oxygen Species, NLRP3 inflammasome, ASC, Gasdermin D, Dimethyl Fumarate, NOX2

Disclosures: All authors indicated they had no financial relationships to disclose.