J Clin Immunol (2017) 37 (Suppl 1):S1–S74
DOI 10.1007/s10875-017-0442-2

ABSTRACTS

2017 LASID Meeting Abstracts

Published online: 30 September 2017

PO- 001

Jakinibs in the Immunodysregulation in Patients with Gain of Function (GOF) *STAT1* or *STAT3* Mutations – An International Experience

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Background: Autosomal dominant gain of function (GOF) mutations in signal transducers and activators of transcription (STAT) 1 & 3 cause a spectrum of clinical phenotypes. STAT1-GOF generally presents with chronic mucocutaneous candidiasis (CMC), susceptibility to dimorphic fungal and invasive viral infections, and combined immunodeficiency. STAT3-GOF causes early onset autoimmunity and lymphoproliferation including autoimmune hematologic cytopenias, autoimmune hepatitis, and inflammatory lung disease. Both commonly present with severe enteropathy and endocrinopathy.
Methods: Patients with confirmed GOF mutations in *STAT1* or *STAT3* who were treated with a Jakinib (ruxolitinib or tofacitinib) were identified at eight centers internationally. Retrospective chart reviews were performed to determine clinical manifestations, indications for treatment, dosage, lengths of treatment, and treatment associated complications.
Objectives: We sought to define the requirement for MCM10 in human NK cell development and homeostasis.
Results: Six patients with STAT1-GOF and 5 patients with STAT3-GOF were treated with a Jakinib. Ten patients received ruxolitinib and 1 received tofacitinib. Indications for starting a Jakinib were immunodysregulation refractory to other immunosuppressive medications, immunosuppression prior to hematopoietic stem cell transplant (HSCT), hemophagocytic lymphohistiocytosis (HLH) and/or as adjuvant to chronic progressive infection, severe enteropathy, hematologic cytopenias, arthritis, or interstitial lung disease. In STAT3-GOF patients, tocilizumab (interleukin(IL)-6R antagonist) was started preceding a Jakinib in 3 patients, concurrently in one and after the Jakinib in another. Of these 5 patients, three had dramatic reduction in disease burden with the Jakinib; one patient developed sepsis and DIC and died; one patient had improvement of his enteropathy but succumbed to worsening lung disease. Of the 6 GOF-STAT1 patients, the addition of the ruxolitinib drastically improved the autoimmune manifestiations and CMC in four patients and stabilized disease in one prior to HSCT; one patient with disseminated coccidiomycosis died from progressive disease and respiratory failure. In the patients who died following therapy, their invasive infections (not CMC) complicated immnomodulation.
Conclusions: Jakinibs are promising for the severe immune dysregulation associated with STAT1-GOF & STAT3-GOF disease. Infections appear to pose significant risk for the use of Jakinibs in STAT GOF disease. Early initiation of the Jakinib alone in STAT1-GOF or in combination with IL-6R blockade in STAT3-GOF may be beneficial in preventing life-threating immune dysregulation.

PO-002

Wiskott-Aldrich Syndrome with Normal Sized Platelets

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Introduction: Wiskott-Aldrich Syndrome (WAS) is a X-linked congenital immunodeficiency characterized by mutations in the WAS gene the WASP protein. The main clinical manifestations are thrombocytopenia with small size platelets, eczema, recurrent infections and a higher incidence of autoimmune diseases and cancer.
Case report: Male patient with classical symptoms of this syndrome (eczema, thrombocytopenia and recurrent infections), but platelets with normal size (mean platelet volume: 9,8 fl). There are few reports of this syndrome in patients with normal sized platelets, which delayed the referral to the immunologist. This patient had been diagnosed as Evans Syndrome and atopic dermatitis until four years old. He shows recurrent severe infections starting in the first year of life, four pneumonia (three with pleural effusion) and hospital admission. Confirmation of WAS diagnosis was made by genetic testing (pathogenic mutation in WAS gene, location exon 3, cDNA c.354delT, protein p118A fsX8, type frameshift). Then, we started a monthly intravenous immunoglobulin and referred to bone marrow

transplantation (BMT). Early diagnosis allows treatment with antibiotic therapy and use of intravenous immunoglobulin due to the risk of serious infections and referral for BMT, the unique curative treatment.
Discussion: Clinical suspicion should exist if the patient develops unexplained thrombocytopenia even that platelets were normal in size.

PO-003

Moesin (MSN) Mutation Leading to Primary Immunodeficiency: Case Report

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Introduction: Moesin is a protein that binds actin filaments to the plasma membrane and is encoded by the MSN gene. There are only 7 male patients from 5 different families with hemizygotic mutations in this gene. They presented early infections, persistent leukopenia and hypogammaglobulinemia. This condition is characterized by marked leukopenia and impaired proliferation and migration of T cells.
Case report: A 9-year-old male patient, non-consanguineous parents, had recurrent upper respiratory tract infections, atypical pneumonia, and cyclic episodes of anterior cervical lymphadenopathy accompanied by febrile illness from the age of 4 years. He received anti- inflammatory treatment. Neoplasia was excluded and he was referred to the immunologist at 7 years of age. Associated severe gastroesophageal reflux was confirmed and treated with prokinetic and pump inhibitors. In consultation with specialist, it was referred tonsillitis, otitis, sinusitis and fever for 3 months. At the physical examination, the patient presented a hard lymph node on the left side measuring 3 × 4 cm. Considering the complaints, we requested an immunological evaluation which identified IgG3 deficiency. The screening test for immunodeficiencies was requested (77 defects) and resulted negative). The DNA sample was assessed by exome sequencing and variant ChrX: 64,959,622 A > C (c1501A > C) was identified as homozygous in the MSN gene (OMIM'309845) located on the X chromosome. This variant in the MSN gene promotes the substitution of the amino acid aspartate at position 534 by alanine.
Conclusion: The authors present the first case with the mutation described and without evident hypogammaglobulinemia, characterized by recurrent lymph node enlargement. The position and region in which change occurred is highly conserved in several biological species. This variant is absent in healthy subjects tested and it has never been previously described in the literature.

PO-004

SAP Deficiency. A Case Report Mimicking Combined Immunodeficiency

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Introduction: X-linked lymphoproliferative syndrome type1 (XLP1) is a genetic disorder cause by deficiency of SAP protein. It is usually triggered by Epstein-Barr virus (EBV) infection that typical cause EBV- induced hemophagocytic-lymphohistiocytosis (HLH), B cell lymphomas, and dysgammaglobulinemia.
Case presentation: A 2 years-old male presented with sepsis and hepatitis. He had a history of Candida mucositis and diarrhea associated with neurologic symptoms (paresia). A contrast – enhanced compute tomography scan revealed imaging consistent with pulmonary abscesses. *Pseudmonona aureginosa* was detected on bronchoalveolar lavage and blood cultures. Labwork showed anemia, thrombocytopenia and hepatitis with a positive *Toxoplasma gondii* serology. He had a normal total lymphocyte count (6153/mm3) but a decreased level of CD4+ and naïve T cell (6.4 and 29 %, respectively). He had low levels of IgG (411 mg/dl) and IgE (<5 mg/dl) with B-cell lymphopenia (2.2 %) and a poor responses to Pneumococcal, Rubella, Measles and Chickenpox. NK cells were also low (1.6 %). Thus, a combined immunodeficiency was suspected. Complementary studies showed absence of NKT cells, and an EBV - PCR showed 3924 copies. Subsequent analysis revealed the lack of SAP expression by flow cytometry, and confirmation of XLP1 was made by sequentation of *SH2D1A* gen and the identification of a mutation (p.Met1Arg) in exon 1.
Discussion: Our SAP deficient patient presented with no typical symptoms at the time of diagnoses: He had no HLH criteria but he presented a combined immunodeficiency profile with hipogammaglobulinemia and T, B and NK cells lymphopenia instead.

Seletalisib is a selective PI3Kδ inhibitor (Allen et al., JPET 2017) which directly targets the underlying mechanism in APDS. Phase 1 clinical studies with seletalisib demonstrated a manageable safety and tolerability profile, displayed PK results supportive of once-daily dosing and evidence.

PO-006

Human STAT5B Mutations Cause Dysregulated Human Natural Killer Cell Maturation and Impaired Lytic Function

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Introduction: Natural Killer (NK) cells are critical innate effector cells whose development is dependent on the JAK-STAT pathway. NK cell deficiency can result in severe or refractory viral infections. Patients with STAT5b deficiency have autoimmunity and viral disease as a result of combined immune deficiency, which affects T-cell homeostasis and leads to natural killer (NK) cell impairment.
Objectives: In this study, we aimed to define the NK cell defects in two sisters with a homozygous single nucleotide deletion causing a mutation in the linker domain of *STAT5b* gene (c.1680delG; exon 13), leading to the loss of STAT5b expression.
Results: This alteration generated a non-functional $CD56^{bright}$ NK cell subset, characterized by low cytokine production. $CD56^{dim}$ NK cells from patients had decreased expression of perforin and CD16 and a higher frequency of cells expressing markers of immature NK cells: CD94, CD117, and interleukin (IL)-15Rα. Furthermore, we observed low NK cell numbers and impaired NK cell maturation in $Stat5b^{-/-}$ mice, underscoring a critical role for STAT5b in terminal NK cell maturation. Human $STAT5b^{-/-}$ NK cells had decreased cytolytic capacity, and fixed-cell microscopy of patient NK cells in conjugates with susceptible target

cells showed poor convergence of lytic granules to the microtubule-organizing center. This phenotype was accompanied by decreased expression of co-stimulatory and activating receptors, including CD11a, CD18, DNAM- 1, and NKp46. Interestingly, granule convergence and cytolytic function were partially restored after IL-2 stimulation.
Conclusions: Our results show that, in addition to the impaired terminal maturation of NK cells, human STAT5b mutations lead to impairments in early activation events in NK cell lytic synapse formation. Furthermore, we show that IL -2 rescued the cytolytic function of patient NK cells and restored lytic granule convergence. Our data gives further insight into the NK cell defect in STAT5b deficiency.

PO-007

Molecular Characterization of Five Patients with MHC Class II Deficiency Reveals Two New Mutations in the Trans-acting Regulator Factor *CIITA* and a Potential Founding Effect in the Colombian Population

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Introduction: Major histocompatibility class II (MHCII) deficiency (OMIM: 209920) is a rare autosomal recessive primary immunodeficiency (PID) characterized by early-onset extreme susceptibility to viral, bacterial, fungal and protozoal infections, and is almost invariably fatal unless treated with hematopoietic stem cell transplantation (HSCT). MHCII deficiency results from mutations in four different trans-acting regulatory factors (CIITA, RFXANK, RFX5, and RFXAP) required for expression of MHC-II molecules on the surface of antigen-presenting cells (APCs). We report the immunologic and molecular characterization of five Colombian patients affected with AR-MHCII deficiency.
Methods: All patients were diagnosed between 2008 and 2015. Medical records were reviewed and peripheral blood lymphocytes (PBL) and HLA-II expression in monocytes and B lymphocytes were determined by flow cytometry. *CIITA*, *RFXANK*, *RFX5*, and *RFXAP* were analyzed by Sanger sequencing in 3 patients and based on these results, exon-targeted sequencing was performed in the other 2 patients as well as in their parents and siblings when available.
Results: The cohort consisted of 3 females (P1, 4 and 5) and 2 males (P2 and 3) from 4 families: P1, P2 and P3 came from families F00165, F00829 and F00832, respectively, while P4 and 5 from family F00830 (siblings). Patients 1 to 4 exhibited a varied range of early onset-bacterial, viral and fungal infections and P1 and P4 died before the age of 1 year due to overwhelming CMV infections, and could not be transplanted. P2 developed CMV infection and was treated and transplanted at 7 months of age from an HLA-identical sibling but did not engraft, and a second HSCT from the same source did not engraft either and he died of overwhelming CMV infection 2 months later. P3 was diagnosed at the age 8 months old and received a HSCT from cord blood (CB) at 13 months old that was lost after 6 months post-transplant and is waiting a second transplant. P5 was diagnosed at 28 weeks of gestation and received CB-HSCT at 1 month of age and is alive and well. Flow cytometry of PBL in P1-4 revealed low % of lymphocytes but only in 2, low absolute numbers of CD3+ T cells while all had CD4 + T cells < 18 % and absolute numbers ranged from 149 to 606 cells/ul; CD4:CD8 ratio was <0.4. HLA expression in B lymphocytes and monocytes was < 0.1 % and < 6 %, respectively in all. Sanger sequencing in DNA from all patients revealed 2 new homozygous mutations in *CIITA*: C925T (R309X) in exon 9 in P1, P2 and P3, and C3379T (R1127W) in exon 19 in P4 and P5. In addition, both parents from families F00829 as well as from F00830 and the sibling from P4 were carriers of the mutation.
Conclusions: We report the first cases of MHC-II deficiency in Colombia. Remarkably, 3 patients with the same mutation in *CTIIA* came from geographically distant areas, suggesting a possible founder effect. HSCT remains as the only potential curable treatment with limited success.

Acknowledgements
Financial support: Estrategia de sostenibilidad 2016-2017 # ES84160114, Universidad de Antioquia.
Fundación FIP – Medellín, Colombia.

PO -008

Gene Therapy for P47^{-PHOX} Deficiency in Chronic Granulomatous Disease (CGD) Patients - pCCLChim Lentiviral Vector

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Introduction: Chronic Granulomatous Disease (CGD) is an inherited primary immunodeficiency disorder caused by defective components of the NADPH oxidase. CGD patients are susceptible to severe and recurrent infections. Mutations in p47^{-phox} NADPH oxidase component, coded by the *NCF1* gene, cause the second most common form of CGD.
Objective: We propose to use a lentiviral gene therapy strategy to restore the expression of the p47^{-phox} component.
Methods: We have made a lentiviral vector, pCCLChimp47 $^{-phox}$, that contains the chimeric cathepsin G/c -fes myeloid promoter and a codon optimized version of the human p47 $^{-phox}$ gene. We have tested the lentiviral vector in granulocytes obtained from p47^{-phox} deficient PLB985 cells, in monocyte-derived macrophages (MDM) from peripheral blood mononuclear cells of p47^{-phox} CGD patients and *in vivo* in a p47^{-phox} CGD deficient murine model.
Results: The lentiviral gene therapy efficiently restores p47^{-phox} expression and NADPH oxidase function in all models tested. Notedly, p47$^{-phox-/-}$ mice transplanted with gene therapy treated stem cells (bearing ~1 copy of vector) recovered an average of ~85 % functional granulocytes with levels of oxidase activity comparable to wild type. As expected, given the myeloid specificity of the chimeric promoter used, the majority of neutrophils (CD11b^{+}/Gr- 1^{high}) and a high percentage of monocytes (CD11b^{+}/Gr-1^{low}) were positive for p47^{-phox} protein while only a low percentage of B (B220^{+}) and T (CD3^{+}) cells expressed the transgene in the murine model.
Conclusion: Our study shows that the pCCLChimp47^{-phox} vector is a promising tool for the clinical application of p47^{-phox} CGD gene therapy.
Financial Support: FAPESP (process number: 2014/01962-3).

PO-009

Genome-Wide Approaches for the Genetic Dissection of Inborn Errors of Immunity in Colombian Patients

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Introduction: Primary Immunodeficiencies (PIDs) are inborn errors of immunity that result from mutations in over 300 genes involved in immune function in humans. The relatively recent advent of genome-wide (GW) approaches including genome-wide linkage (GWL) and genome/whole-exome sequencing (GES/WES), have accelerated dramatically the genetic dissection of many diseases underlying Mendelian traits in humans. These technologies represent a cost-effective and rapid first-line approach for the discovery of mutated genes, facilitating diagnosis and improving access to early treatment. We present an update of a joint international initiative aimed at the discovery of known and novel genes associated with PIDs, using WES and other GW approaches coupled to functional studies, to decipher the molecular basis of these diseases in Colombian patients.
Methods: Patients and relatives are being recruited through different research protocols approved by the ethics committee of the Universidad de Antioquia (UdeA) in Medellin. Peripheral Blood lymphocytes (PBLs) and/or EBV-transformed B cells from patients and controls were used as the source of DNA for genetic analyses. WES and/or Sanger sequencing are performed in patients and relatives and results are analyzed using "in house" pipelines of software to call for variants [Centro de Secuenciación Genómica UdeA (Medellin, Colombia), INSERM (Paris, France) and Rockefeller University (New York, USA)]; functional analyses are performed to confirm the causal relationship between the candidate genotype and the clinical phenotype. Each PID is presented according to the Classification of PIDs by the Expert Committee on PID of the International Union of Immunological Societies (IUIS).
Results: We have performed WES in 67 patients with the diagnosis of a PID and 26 of their relatives for a total of 93 exomes. Disease-causing genes have been identified in 14 of the 67 patients (21 %) and mutations are confirmed by Sanger sequencing in all. Their distribution is as follows: Combined ID with associated features: 1 patient (*ARPC1B*); Congenital defects of phagocyte number/function: 4 (*CYBB*) and 1 (*NCF4*) and defects in intrinsic and innate immunity: (*IL-12RB1*, *IFNGR1*, *STAT1*-GOF, *CARD9*). For all patients but one, functional testing has showed causal associations.
Conclusion: Using a GW approach coupled with functional analyses is allowed us to find mutations in in genes in 14 of patients with different PIDs. This represents a current rate of success of 21 % and what is being reported in the literature approaches now beyond 40 %; therefore, further implementation of additional tools and methodologies are being implemented to improve our rate of discovery. GW approaches are an invaluable tool to advance the diagnosis of monogenic diseases such as PID, enabling our patients to rapidly access to personalized treatment in Colombia.

PO-010

Mutations in PI3K110D Cause Impaired NK Cell Function Partially Rescued by Rapamycin Treatment

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Introduction: Human natural killer (NK) cells are critical for human host defense, and severe viral infection occurs in patients with impaired NK cell development or function. APDS1 occurs as a result of heterozygous gain-of-function mutations in PI3K110δ and leads to lymphadenopathy, lymphoid hyperplasia, Epstein-Barr virus (EBV) and cytomegalovirus (CMV) viremia, and sinopulmonary infections. While the effect of *PIK3CD* gain-of-function mutation on T cell and B cell phenotype and function are known, NK cell specific defects have not been previously described.
Objectives: The known role of NK cell function in the control of EBV and CMV prompted us to investigate the functional and phenotypic effect of PI3K110δ mutations on NK cell subsets and cytotoxic function.
Results: In our study of 10 patients with E525K and E1021K *PIK3CD* mutations, we found that patients with APDS1 had an altered NK cell developmental phenotype and profound cytotoxic dysfunction. Impaired NK cell cytotoxicity was due to decreased conjugate formation with susceptible target cells and abrogated activation of cell machinery required for target cell killing. These defects were partially restored following the initiation of treatment with rapamycin in three patients.
Conclusion: Here we describe novel NK cell functional deficiency due to PI3K110δ mutation, which is a likely contributor to the severe viremia observed in these patients. Rapamycin treatment partially restores NK cell function, providing further rationale for its use in this disease.

PO-013

Use of a NGS Panel for the Identification of Primary Immunodeficiencies

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Introduction: Diagnosis of Primary immunodeficiencies (PIDs) are growing around the world, definitive diagnosis consists in determining the type of mutation presented. Diagnosis of X–linked Agammaglobulinemia (XLA), Common Variable Immunodeficiency (CVID), Severe Combined Immunodeficiency (SCID) and Hyper– IgM syndrome are the most frequent diagnosis in our Research Unit. To date, we have identified several mutations by Sanger sequencing, however, it takes a long time to detect mutations in any of the genes studied. For this reason, the main objective of this work was to employ the new generation sequencing technologies to determine the mutations presented in *BTK* (XLA), *LRBA* (CVID), *IL2RG* (SCID) and *CD40LG* (HIGM).
Objective: To determine the type of mutation associated with a cohort of patients with clinical and laboratory diagnosis of XLA, LRBA deficiency, X–SCID and X–HIGM.
Results: The design of a sequencing panel that includes *BTK, LRBA, IL2RG* and *CD40LG* was performed by using StudioDesing® online tool provided by Illumina. This panel included all the exons and the splice sites. Amplicon size was 425 bp and it was obtained to sequence 96 samples. With this panel, we obtained sequencing results in 88 of 95 samples (92 %) and most of the exons were covered, with the exception for exon1 for *BTK*, exons 1 and 2 for *IL2RG* and exons 43 and 49 for LRBA. With this panel, we detect 10 patients with *LRBA* mutations, 29 individuals with BTK deficiency and 5 and 4 genetic defects for *CD40LG* and *IL2RG*, respectively. Most of the changes were missense mutations, however, nonsense, deletions, insertions and splice site mutations were also detected.
Conclusions: We detect in total 48 individuals with the genetic deficiencies suspected. However, we still do not know the genetic deficiency in 40 of the patients included in this panel, even though they showed clinical and laboratory data to suspect of the diagnosis studied. It is interesting to perform future studies to determine if the phenotype observed are due to related genetic deficiencies already described in the literature, or to determine if there are non–described deficiencies in this cohort of patients.
Acknowledgements: FOSSIS–CONACYT 161089; CB–CONACYT 154472 and 256471.

PO-014

Use of Next Generation Sequencing Panel for the Identification of Primary Immunodeficiencies

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Introduction: Diagnosis of Primary immunodeficiencies (PIDs) are growing around the world, definitive diagnosis consists in determining the type of mutation presented. Diagnosis of X-linked Agammaglobulinemia (XLA), Common Variable Immunodeficiency (CVID), Severe Combined Immunodeficiency (SCID) and Hyper-IgM syndrome are the most frequent diagnosis in our Research Unit. To date, we have identified several mutations by Sanger sequencing, however, it takes a long time to detect mutations in any of the genes studied. For this reason, the main objective of this work was to employ the new generation sequencing technologies to determine the mutations presented in *BTK* (XLA), *LRBA* (CVID), *IL2RG* (SCID) and *CD40LG* (HIGM).
Objective: To determine the type of mutation associated with a cohort of patients with clinical and laboratory diagnosis of XLA, LRBA deficiency, X-SCID and X-HIGM.
Results: The design of a sequencing panel that includes *BTK, LRBA, IL2RG* and *CD40LG* was performed by using StudioDesing® online tool provided by Illumina. This panel included all the exons and the splice sites. Amplicon size was 425 bp and it was obtained to sequence 96 samples. With this panel, we obtained sequencing results in 88 of 95 samples (92 %) and most of the exons were covered, with the exception for exon1 for *BTK*, exons 1 and 2 for *IL2RG* and exons 43 and 49 for LRBA. With this panel, we detect 10 patients with *LRBA* mutations, 29 individuals with BTK deficiency and 5 and 4 genetic defects for *CD40LG* and *IL2RG*, respectively. Most of the changes were missense mutations, however, nonsense, deletions, insertions and splice site mutations were also detected.
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Acknowledgements: FOSSIS-CONACYT 161089; CB-CONACYT 154472 and 256471.

PO-015

Analysis of the Correlation Between the Expression of BAFFR, Memory B Cell Populations and Clinical Manifestations in 82 Mexican Patients with Common Variable Immunodeficiency (CVID)

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Introduction: CVID includes many heterogeneous syndromes of unknown origin characterized by hypogammaglobulinemia and recurrent respiratory infection. The main problem is in the developed and differentiation in B cells, for this, patients have been classified according to the percentage of memory B cell. On the other hand, BAFF-BAFFR signaling promotes peripheral B cell survival and maturation.
Objectives: To 82 patients (49 women, 33 men) were correlated the expression of BAFFR, percentages memory B cells and clinical manifestation.

Results: Patients were grouped according to the Freiburg classification; group 1a = 27, group Ib = 27 and group II = 22. Group 1a had a significant reduction of its total B cells and an increase of transitional B cells ($p = 0.0002$, $p = 0.0007$; respectively). The three groups had a significant decrease compared to control ($n = 20$) in BAFFR expression ($p = 0.0001$, $p = 0.0001$ and $p = 0.0006$; respectively). The results show a positive correlation between total B cells and BAFFR expression ($r = 0.2746$, $p = 0.0281$) and a negative correlation between CD21low B cell and BAFFR expression ($r = 0.2980$, $p = 0.0271$). It was shown that the lower the BAFFR expression, the more severity of the disease ($p = 0.0262$; $r = 0.5371$).
Conclusion: In CVID the low expression of BAFFR result in severe B lymphopenia caused by the arrest of B cell development; proving that BAFFR is important for maintenace of B cell homeostasis.
Financing: CONACYT CB No.256471

PO-016

Autoimmunity and Malignancy in Common Variable Immunodeficiency

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Introduction: Common Variable immunodeficiency (CVID) is characterized by deficient immunoglobulin production, with recurrent respiratory and gastrointestinal tract infections.
Autoimmune diseases occur in approximately 20 % of patients; the age at diagnosis of autoimmunity is variable and may precede the primary immunodeficiency. Lymphomas are the most common form of malignancy in CVID.
Clinical case: Male 33 years old, with CVID, Chronic Diarrhea, Autoimmune Hypoparathyroidism/non-Hodgkin's lymphoma, Evans Syndrome, Bronchiectasis. Background of importance:
• Autoimmune hemolytic anemia diagnosed at age 14, Thrombocytopenic immune purpura integrated Evans syndrome.
• CVID, diagnosed at 20 years, according to the European Society of Immunodeficiencies criteria. With replacement therapy with human intravenous Gammaglobulin
• Bronchiectasis diagnosed in 2011 by High resolution thorax Tomography.
• Autoimmune hypoparathyroidism diagnosed in 2011
Current condition: At 31 years of age, started with intermittent diarrhea with up to 14 stools per day, occasional steatorrhoea with foamy stools; study protocol was initiated, with a colonoscopy with histopathological report of chronic inflammation, Lymphoid hyperplasia and extensive autolysis due to inadequate tissue fixation. Due to the suspicion of celiac disease, a gluten-free is started with improvement of the symptomatology, with only 2 stools per day of soft consistency. With current treatment with Loperamide for reason. Complete protocol Gastroenterology concluding Celiac disease, treatment with gluten elimination diet, with good evolution. However, it began 2 years later with abdominal distension, hematochezia, rectal bleeding, weight loss of 7 kg in one month, nocturnal diaphoresis; Panendoscopy is performed with biopsy, report of non-Hodgkin's lymphoma in ileum; is referred to the service of Oncology and treatment with chemotherapy is started; however, after the first cycle, dies by massive digestive tube bleeding.
Discussion: Common variable immunodeficiency is a complex group of disease that can converge autoimmunity, malignancy, in one patient, and that's an important thing that an immunologist have to investigated in these type of patients, because it's going to affect their prognosis, and these non infections complications, area associated with higher mortalitality, like in this patient.

References:
J Allergy Clin Immunol Pract. 2016; 4(1): 38–59; Current Opin Allergy Clin Immunol 2015;15:514-524; Autoimmunity reviews 2014;13:858-864

PO-017

Risk Factors for the Occurrence of Hearing Loss in Patients with Primary Antibody Deficiencies

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Background: Primary antibody deficiencies occupy half of the cases of primary immunodeficiencies. Acute medium otitis is the most frequent infection of the superior respiratory tract in them. Chronic medium otitis and hearing loss are the most common long-term complications. There's scarce information about hearing loss frequency as a complication in these patients.
Objectives: To know the risk factors for the occurrence of hearing loss and its severity in patients with primary antibody deficiencies.
Material and methods: Cross-sectional, analytic, case and control study design. Both sex patients, 4-65 years diagnosed with primary antibody deficiency according to the European Society of Immunodeficiencies were selected. Demographic and pathologic data from the patients was collected. Otoscopy, audiometry and statistical analysis was done.
Results: Fifty-one patients were studied, 17 cases (with hearing loss) and 34 controls (without hearing loss). From cases, 41 % males and 59 % females; controls, 73.5 % males and 26.5 % females. Mean age was 21 years. Thirty-three percent of the patients showed hearing loss, 47 % unilateral and 53 % bilateral. With respect to the type of hearing loss, 29 % conductive, 47 % sensorineural, and 23 % mixed; with respect to severity, mild in 35 %, 53 % moderate, and 12 % severe. Female sex confers higher risk for the occurrence of hearing loss ($p = 0.05$), with the rest of the studied variables (age, age at the time of diagnosis, time of delay of diagnosis, time of evolution since the diagnosis, acute medium otitis pre-and post- immunoglobulin treatment, and use of ototoxic drugs) with no significant statistical difference, although with a diagnosis delay >5 years, a higher risk for hearing loss was also found (OR 2.4).
Conclusions: This is the first study of this type in our country, and we found a significative number of patients with hearing loss, being this of great importance for the quality of life for the patient. We suggest the implementation of a complete audiologic evaluation at the time of diagnosis and follow-up to prevent severe complications in adults and in children long-term complications in language and learning.

PO - 018

Freiburg Classification and Clinical Manifestations in Adults Patients with Common Variable Immunodeficiency

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Introduction: The patients with common variable immunodeficiency (CVID) comprises a heterogeneous group with different causes of hypogammaglobulinemia predisposing to recurrent infections, a higher incidence of autoimmunity, enteropathy and malignancy. Although memory B cells are key players in humoral defense and their numbers are commonly reduced in these patients.

Objective: to establish classification by phenotypes of patients with CVID and its correlation with the clinical manifestations.
Methods: we studied 18 patients from a cohort, with diagnosis of CVID, of the Immunodeficiency Clinic of the Specialties Hospital of National Medical Center XXI Century. Flow cytometry was performed with determination of lymphocyte subpopulations with absolute and relative numbers, including: CD19, CD27 + IgM-IgD-, CD21 low. Patients were grouped according to the classification of Freiburg into 3 types: IA, IB, II, according to their values of IgM− IgD− CD27+ B cells, and CD21 low cells.
Results: 11 female and 7 male, average age of 42 years at the moment. Forty-four percent of patients with autoimmune hematological diseases, the most common immune thrombocytopenic purpura. Seven patients with CVID associated enteropathy. One with chronic myeloid leukemia, 1 with Non Hodgkin's Lymphoma and 3 with predominance of infectious processes. According to the Freiburg classification, 4 patients correspond to group IA, 4 to IB and 10 with group II. Seventy-five percent of patients with IA and IB groups had hematological autoimmune diseases compared to 20 % of those in group II. Forty percent of patients in group II had predominance of infections and 30 % of CVID-associated enteropathy. Four patients died, 2 due to massive lower gastrointestinal bleeding, 1 due to septic shock and one due to suicide.
Conclusions: The main utility of classifications, according to B cell subtypes, is to be able to find a marker, which identifies the genotype of the disease and with the prognosis. In this study, patients with less than 0.4 % of isotype-memory LB were associated with hematological autoimmunity, and those with more than 0.4 % of CD27 + IgM-IgD- showed greater frequency of enteropathy and predominance of infectious processes.
References:
J Allergy Clin Immunol Pract. 2016; 4(1): 38–59; J Allergy Clin Immunol. 2015 Jan;135(1):198-208; Clin Exp Immunol. 2012 Feb;167(2):275-81

PO - 019

Spleen-Portal Axis Abnormalities in Patients with Common Variable Immunodeficiency in a Tertiary Hospital in São Paulo, Brazil: Prevalence Analysis

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Introduction: Patients with common variable immunodeficiency (CVID) with spleen-portal axis abnormalities present higher mortality and specific clinical phenotype. The understanding of the prevalence, prognostic factors and pathophysiology of portal hypertension associated with liver disease in CVID is of fundamental importance for the adequate management of patients.
Objective: To describe the prevalence of spleen-portal axis abnormalities in patients with CVID.
Methods: Patients with a diagnosis of CVID according to criteria of the European Society for Immunodeficiencies were selected from the database of a tertiary hospital and divided into 3 groups: patients with portal hypertension (PH), isolated splenomegaly and control group (CVID without spleen- axis abnormalities). For the diagnosis of splenomegaly and PH, abdominal ultrasound and tomography were analyzed. Portal hypertension was defined according to clinical signs of this complication and portal vein diameter > 1.1 cm.
Results: A total of 109 patients were analyzed: 34 patients were diagnosed with PH, 19 patients presented with isolated splenomegaly, and 56 patients showed no spleen-axis abnormalities. Patients of HP group had the highest mean age (50 years, SD: 15). There was no statistically significant difference between mean age of onset of symptoms, mean age at diagnosis, disease time and time between onset of symptoms and diagnosis, in the 3 groups analyzed. Complications such as esophageal varices, gastric or perisplenic collateral circulation were present in approximately half of the patients and may also occur in patients with mild changes in liver laboratory data or platelets. Overall mortality in PH group was higher than in the other groups.
Conclusion: Portal hypertension appears to be an early finding in patients with CVID and incipient liver disease, and may be a marker of increased morbidity and mortality in these patients, which requires an individualized follow-up.

PO - 020

Evaluation of the Participation of LRBA in B Cell Receptor Signaling

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Introduction: LRBA is an intracellular protein expressed ubiquously, but increased expression in immune cells after activation has been observed. B cells increased it`s expression after several stimuli. The role of LRBA in T cells was demonstrated to be important for CTLA4 recycling, however, it´s role in B cells is still unknown. Mutations in *LRBA* are associated with common variable immunodeficiency (CVID), patients that suffers from hypogammaglobulinemia, B cell differentiation defects and autoimmunity, cells from *LRBA* deficient patients share defects on B-cell autophagy, activation, proliferation and apoptosis. In this project we attempt to identify if LRBA participate in the B cell receptor (BCR) signaling, since BCR mediates several of the cellular defects observed in *LRBA* deficiency.
Objective: To determine if *LRBA* knockout B cell lines exhibit functional defects when they are stimulated via BCR, compared with wild type cells, after BCR determination.
Material and methods: LRBA expression was evaluated in primary murine B cells after stimulation by flow cytometry. Raji cells are transfected through lipofectamin or by electroporation, with CRISPR-Cas9/LRBA plasmid to obtain knockout cells. LRBA-/-Raji cells are confirmed first by protein expression by Western Blot and by sequencing the exon 2, were the mutation is expected. Cells are stimulated via BCR with an anti-human IgM antibody, to functionally compare with Raji wild type. Functions to evaluate in this cell line are activation and proliferation, while apoptosis and autophagy will be evaluated in a pre-B cell line.
Results: LRBA expression in primary murine splenic B cells was observed to be inducible by LPS, with differential pattern across differentiation phases. We observed that there is a significant increased in LRBA levels in mature B-cells in comparison to transitional cells and such expression is induced after LPS stimulation in murine B cells. To study the role of LRBA in BCR signaling, we attempt to generate a mature B cell line that do not express LRBA, by now, two cell lines have been obtained using the lymphoblastoid derived from Burkitt lymphoma cell line, Raji, sequencing in this cell line indicates a missense change. This cell line is currently under study to determine if after BCR crosslinking, defects in cell activation could be observed.
Conclusions: We checked that LRBA is a inducible protein in primary murine B cells, and that expression seems to be greater in mature cells. Functional assays mediated by BCR are under development, to correlate if LRBA function through BCR.
Acknowledgements. CB-CONACYT 154472

PO - 021

Type and Location of Bronchiectasis in a Cohort of Adults with Common Variable Immunodeficiency

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Brackground: Bronchiectasis, are permanent dilatations of the bronchi. Its prevalence in patients with common variable immunodeficiency (CVID) is high, however there is little information regarding the type and location of the same; therefore the objective of this study is to know the type and location of bronchiectasis in a cohort of patients with CVID of third level of care.
Methods: It has been made a transversal, observational and descriptive study that included 32 adult patients with diagnosis of CVID according to the criteria of the European Society of Immunodeficiencies (ESID). All patients underwent high resolution pulmonary computed tomography (HRCT), which were interpreted by an expert radiologist. The frequency, type and location of bronchiectasis were reported using descriptive statistics.
Results: Thirty-two adult patients, ten men (31.25 %) and 22 women (68.7 %), were included. 40.6 % had bronchiectasis. Twenty-three percent had a lobe involvement, 15.3 % two lobes, 46.1 % 3 lobes and 15.3 % complete involvement of the parenchyma. The types of bronchiectasis were distributed as follows: tubular 38.4 %, varicose 23 % and cystic and tubular combinations 15.3 %, cystic and varicose 15.3 % and cystic, tubular and varicose 7.6 %.
Conclusions: The prevalence of bronchiectasis in patients with CVID varies from 16 to 70 %; in the studies, type, location and number of affected lobes are not described. Our results show that 40 % of the patients present bronchiectasis; frequently affect 3 lung lobes, located mainly in the right and middle lobe, the tubular type, is the most common. Their timely diagnosis and appropriate treatment can modify survival, reduce health costs and improve the quality of life.

PO - 022

Pulmonary Findings in Common Variable Immunodeficiency, not all Bronchiectasias

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Background: Variable common immunodeficiency (IDCV) is the most common primary symptomatic humoral immunodeficiency. Pulmonary complications occur in 27-34 %, may be infectious or non-infectious. Of the former, bronchiectasis is the most common cause up to 70 %. The most common noninfectious cause is pulmonary interstitial disease (PID) in 15-20 %, suggesting its presence in voided glass, bilateral septal thickening, parahilar and mediastinal lymphadenopathy.
Methodology: Retrospective study in patients with CVID according to ESID criteria. The population included both genders, older than 18 years who had high resolution chest X-ray (CCT), interpreted by the same expert radiologist. Patients with infectious process were excluded.
Results: We included 32 patients, 10 (31.2 %) men and 22 (68.7 %) women, mean age 42 ± 17 years. 40.6 % had bronchiectasis; other pulmonary findings were atelectasis, fibrosis, subsolid nodules, calcifying granulomas, and lymphadenopathy. In those without bronchiectasis (59.4 %), other manifestations were linear pathways of fibrosis, calcified granulomas, interstitial thickening, subsolid nodules, bulls and diaphragmatic elevation.
Conclusion: It has been reported that patients with CVID and PID have an average survival of 13.7 years vs. 28.8 years of those without PID. The tomographic findings suggesting PID suggest the need for pulmonary extension studies. Timely diagnosis is imperative, as these findings may be part of lymphocytic granulomatous lung disease, both of which require effective treatment, since they worsen the prognosis and quality of life of patients.

PO - 023

Anxiety Disorder in Patients with Immunodeficiency of Antibodies Treated with Human Intravenous Immunoglobulin

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Introduction: Immunodeficiencies (IDFs) of antibodies are a group of chronic diseases, the important feature of which is hypogammaglobulinemia with the need to replace intravenous human immunoglobulin (IVIg). In addition to recurrent infections, these FDI are associated with the increased prevalence of autoimmune, inflammatory and neoplastic diseases. Still, patients may acquire their own derogatory, anxious, and even depressive concept, generating much anguish and mental suffering. The literature shows that physicians should be alert to the mental health of patients with IDF to intervene both in their mortality and in morbidity and quality of life. Objective: To evaluate, through validated questionnaires, the symptoms of anxiety and depression in patients with IDF who undergo IVIG replacement monthly.
Method: A cross-sectional study using the Beck questionnaire applied to IDF patients receiving IVIg at a tertiary university hospital. Results: One hundred and one patients participated in the study. The mean age was 41.8 years, of which 54 % were female. Of the patients evaluated, 51 % have work activities at the moment and 36 % have some kind of hobby. The mean duration of illness was 15.2 years and treatment time was 10.8 years. Seventy-nine patients (77.4 %) were diagnosed with Common Variable Immunodeficiency (CVI). The analysis of the Beck questionnaires showed that 45 % presented symptoms compatible with depression, 6 % with severe depression. Sixty-three patients (61.8 %) already had or had psychiatric treatment.
Conclusion: During the follow-up of patients with IDF there is great concern about the underlying disease of patients with IDF and its complications, and that the possible symptoms of anxiety or depression may be masked and / or go undetected. Many factors can influence depression and anxiety and these can worsen the morbidity of patients with IDF. In this work, we conclude that the prevalence of mental disorders in patients with IDF is high, reinforcing the importance of the research of mental disorders and the multidisciplinary team in the treatment of patients with IDF.

PO - 024

Diagnosis of Selective Antibody Deficiency in a Patient with Type 1 Primary Ciliary Dyskinesia. Report of a Case

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The study of patientes with recurrent respiratory infection from early ages obliges to rule out structural and physiological respiratory alteratios but also primary immunodeficiencies, however, a simultaneous presentatios of both alteration is rarely suspected.
We present the case of a 3-years old male patient with severe recurrent respiratory infections who required several in-hospital treatment and mechanical ventilation since the age of 10 months. He was diagnosis with type 1 primary ciliary dyskinesia, cause he has unfavorable evolution, developed bronchiectasias and depletion of his pulmonary funtion. Consequently we began the search for other differential diagnoses: we performed lymphocyte subpopulation analyzes, serum total immunoglobulins measurements, subclases and antibody level against 14 serotypes of streptococcus pneumoniae, finding values of these below 0.5 ug/ml despite regulatory vaccination of the patient. The patient is currently under treatment of bronchodilatadors, inhaled steroids, pulmonar physiotherapy as well as immunomodulatory treatment with intravenose gammaglobulin.
In conclution, according to our review of the literature, this is the first reporto f a patient presenting primary ciliary dyskinesia concomitant with specific pneumococcal antibodies immunodeficiency. When observing a patients with reccurent respiratory infections and a unfavorable evolution we ought to keep an open mind and considering the possibility of atypical presentation of both entities, primary ciliary dyskinesia concomitant with specific antibodies immunodeficiency together. Allow to offer an integral treatment.

PO - 025

Is Mutation in LRRC8A Gene a Posible Cause of Hypogammaglobulemia?

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Introduction: The *leucine-rich repeat-containing 8* (LRRC8) is a protein expressed on T and B cells, required for B-cell development. There is one case report of a mutation of this gene that lead to B cell deficiency, producing congenital agammaglobulinemia. We report a family with mutation in LRRC8, but with Hypogammaglobulinemia.
Case presentation: Three-year-old girl without past medical history presents with recurrent fever and and upper and lower respiratory infection. Labs show: IgA: 30.35 mg/dl (58-311), IgG: 797.5 mg/dl (805-2421), IgM: 207.6 mg/dl (54-392), with normal T and B cell count. A diagnosis of hypogammaglobulinemia plus growing retardation was made, she had normal response to vaccines. Treatment with intravenous immunoglobulin G was started. A whole exome sequencing showed a variant heterozygous of the LRRC8A gene (NM_001127244), C.100G > A (p.Val34lle), not previously report in the literature. The mother is the carrier. The second girl, is a nine-year-old girl who presented with a history of recurrent upper and lower respiratory infection early in life. Labs show: IgA: 64 mg/dl(84-467), IgM: 148 mg/dl(91-451), IgG: 975 mg/dl (1042-2134), with normal T and B cells counts, with no response to polysaccharide vaccines. A diagnosis of common variable immune deficiency was made. Treatment with intravenous immunoglobulin G was started. Genetic studies are pending.
Discussion: Mutation in LRRC8 gene have only been linked with congenital agammaglobulinemia in a single case report. In this family report we found a new mutation in LRRC8A gene, that is linked with hypogammaglobulinemia in two pediatric patients. We believe that this new mutation could explain the presence of hypogammaglobulinemia instead of agammablobulinemia.

PO - 026

Common Variable Immunodeficiency and Huntington's Diseacasereport

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Introduction: This case report describes the occurrence of Huntington's Disease (HD) in a patient with Common Variable Immunodeficiency (CVI).
Case presentation: Young male, 21 years old, diagnosed with Common Immunodeficiency Variable at 11 years of age due to recurrent infections, had bronchiectasis as a sequel, Immunoglobulins: IgA 14.7 mg / dl, IgG 171.4 mg / dl, IgM 4 mg / dl. Monthly he used to use Intravenous Human Immunoglobulin. At the age of 20, he presented a depressive episode characterized by sadness, apathy, avolia, easy crying, insomnia, weight loss and loss of work function. During this period he began to use antidepressants, but without remission of symptoms. Over time he started with decreased visual acuity, diplopia, photophobia, horizontal nystagmus, amnesia for old events, chorea, episodes of constant hiccups, slowed pattern gait and short steps. Computed Tomography without significant changes. Neurological examination: No focal, motor or sensory deficits, without cervical stiffness, Hoffman's sign negative, normal tone, but with global hyperreflexia and increased bilateral flexor plantar skin area. The initial hypothesis was a Conversive Psychiatric Disorder and Severe Depressive Episode without psychotic symptoms. Over time the patient began to present frequent psychomotor agitation, difficulty in ambulation, difficulty in phonation, loss of sphincter control, difficulty in swallowing and dystonic postures. Magnetic Nuclear Image showed presence of pronounced diffuse atrophy of the brain parenchyma, preferentially affecting the cortex and nucleus of gray matter, associated with temporal lobe hypersignal; tests for Wilson's disease: negative; Cerebrospinal fluid: No specific changes; Genetic test for Huntington's disease: Positive. The patient developed clinical worsening and death
Discussion: It is known that the patients affected by CVI have, besides several immunological abnormalities, an increased incidence of autoimmune diseases and neoplasias. In the case in question the patient simultaneously presents two rare diseases to CVI and HD. HD is a hereditary neurodegenerative disease caused by the repeated expression of the CAG sequence in the gene of chromosome 4, gene responsible for some autoimmune and neoplastic diseases. Failure in this gene results in the formation of an abnormal protein that is toxic to neurons. Currently, there is no cure or treatment that can interrupt, minimize, or reverse the progression of the disease.

PO - 027

BTK Mutations Associated with Atypical X-Linked Agammaglobulinemia

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Introduction: X-linked agammaglobulinemia (XLA) is a disease were the patients are characterized by the absence of B cells in peripheral blood or lymphoid organs and absence of immunoglobulin. XLA patients are prone to recurrent bacterial infections on early childhood like conjunctivitis, otitis, sinusitis, skin infections, among others. In general, XLA patients are diagnosed within the first two years old; however, there are some reports in the literature where patients not show such phenotype, as diagnosis in teenager or adulthood life has been reported and they do not have severe complications despise they do not receive gammaglobulin treatment. Mutations *BTK* have been identified as the cause of this disease, however, at the moment there is not a correlation between the kind of mutations and atypical phenotype for XLA.
Objective: To determine defects in *BTK* and correlate the mutations found with the XLA atypical phenotype.
Results: In this work, we report five patients from four different families in whom, atypical XLA was observed. Atypical data in these patients included XLA diagnosis after 12 years old with no complications before diagnosis except for one of them. One patient with normal IgM levels and atypical infectious diseases, another one with normal IgG and IgA, the rest of the patients did not present immunoglobulins. Sequencing analysis of *BTK* showed that these patients with atypical manifestations carry mutations in PH, and SH2 domains, all of them were missense mutations, all of these mutations, except one correlated with detectable Btk expression, however, Btk degradation could be observed.
Conclusion: We find five mutations on atypical patients, most of them show detectable protein expression. The PH and SH2 domain were found to be affected, interestingly both domains serve as interaction domains with other proteins of with phospholipids from the plasma membrane, additionally one of the mutations detected are considered novel, as it has not been reported previously.
Acknowledgements: Carrillo-Tapia received a scolarship support by CONACYT. Authors thank financial support to proyects CB-CONACYT 154472 and FOSISS-CONACYT 161089.

PO - 028

X-Linked Agammaglobulinemia. Case Report

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Introduction: X-linked agammaglobulinemia (ALX) is a primary immunodeficiency characterized by the lack of development of B lymphocytes (LB), with low LB and low levels of immunoglobulins leading to recurrent and severe infections that begin between 3 - 6 months old. Infections (otitis, sinusitis, pneumonia) by encapsulated bacteria. The incidence 1/200000 live births. ALX is due to mutations in the BTK gene encoding Bruton's tyrosine kinase, on the X chromosome (Xq21.3-Xq22), which cause LB faults. Detection of mutations in BTK is necessary for definitive diagnosis and genetic counseling. Gamma globulin replacement therapy is indicated for life. CLINICAL CASES: Two clinical cases of ALX are described.

CASE 1	CASE 2
Male of 7 years, maternal uncle died of recurrent infections. I present at 3 m Rotavirus infection, at 5 m Urinary Tract Infection with recurrent episodes leading to Vesicostomy at 9 m and 2a6m Left nephrectomy; From 6 m Pneumonia to recurrence with hospitalization 3 times per year, Influenza (H1N1) to 2a Meningitis and Vasculitis to 4a with treatment in PICU; Osseoarticular sepsis at 4a, 2 occasions hospital treatment; Juvenile Rheumatoid Arthritis, Amebiasis and Giardiasis at 6a. Complementary tests: low IgG, IgM, IgA, normal IgE, LT within normal parameters, absence of LB. Molecular study: Presence of the p.gly419arg mutation in exon 14 of the BTK gene.	Male of 6 years, has complete vaccines and Prevenar (2 doses). From the 6 m of life, the patient had pneumonia and suppurative otitis media, requiring hospitalization 3 to 5 times a year with the use of broad-spectrum antibiotics. All the cultures reported S. pneumoniae; 1 year ago received treatment for TB. Complementary tests: low IgG, IgM, IgA, normal IgE; LT normal parameters; LB under. Molecular study: presence of the p.Arg562Trp mutation in exon 17 of the BTK gene.

At the moment both patients receive monthly intravenous gammaglobulin.
Discussion: It is important that we suspect, reach the definitive diagnosis and initiate early treatment; Isolation is not necessary, infections should be prevented.

PO - 029

LRBA Deficiency in Mexican Patients with Common Variable Immunodeficiency

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Introduction: Common Variable Immunodeficiency Disorders (CVID) are the most common primary immunodeficiencies disorders (PIDs), (Schouwenburg, 2015), they are characterized by recurrent infections, low serum levels of IgG, low IgA and/or IgM and poor specific antibody responses (Conley, 2009). The incidence of autoimmune disease in CVID patients may approach 20 % of cases (Xiao, 2014). By genetic studies in families with CVID were found distinct homozygous mutations in the gene encoding

LRBA (López-Herrera, 2012). Affected individuals present a variety of clinical symptoms including early-onset hypogammaglobulinemia, recurrent infections, autoimmunity, and chronic diarrhea (Agahammondi, 2017).
Objective: The aim of this work, was to explore the frequency of LRBA deficiency in a cohort of 34 patients with clinical diagnosis of CVID, most of which, consanguinity is unknown.
Results: A sequencing panel for four genes, including *LRBA*, was established using Studio Design tool from Illumina. Within the cohort of patients with CVID we included 34 that present clinical manifestations compatible with LRBA deficiency, additionally, protein expression was found to be absent or reduced. Among the patients with LRBA deficiency we identified missense mutations, four of them has not been reported and are located between con A like domain and WDL domain, and one with an insertion of 14 bp that was analyzed by Sanger sequencing. Additionally, we suspect of deletions in additional patients, such deletions are under study.
Conclusion: Nine of the patients analyzed with CVID presented mutations in LRBA. The rest of the patients without expression of LRBA might have deletions that need to be analyzed by Sanger sequencing.
Acknowledgements: This work was realized in Cinvestav and was supported by FUMENIP A.C. and Conacyt#161089 and 154472.

PO - 030

Transient Hypogammaglobulinemia of Infancy (THI): Clinical and Immunologic Features of 23 Patients

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Introduction: Immaturity of the immune system is the main cause of high incidence of infections in infants and toddlers. Transient hypogammaglobulinemia of infancy (THI) is characterized by a delay in normalization of immunoglobulins, especially IgG and IgA. Physiologically, hypogammaglobulinemia occurs between 3 and 6 months of life. THI is defined when this type of hypogammaglobulinemia last longer than expected. It's a retrospective diagnosis, confirmed when immunoglobulin levels normalize around 4 years of age.
Objective: To assess clinical and laboratorial features of children with THI followed on our clinic, as well as disease outcome and necessary treatment. Methods: Retrospective analysis of 23 patients charts.
Results: Sixty-one percent of the patients were male, and the main infection was respiratory (otitis and pneumonias). Mean age of onset of symptom was 9 months. Six patients (26 %) had severe infections that required hospitalization in intensive care unit and 11 patients (42 %) used prophylatic antibiotics and/or IGIV. Mean age of normalization of the immunoglobulin levels was 44 months (3,6 years).
Conclusion: THGI is a benign disease, but almost half of the patients in our study needed some kind of prophylatic treatment.

PO - 031

HIV Infection in a Patient with Hypogammaglobulinemia, Evolving with Severe Opportunistic Infections: Report of Two Cases

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Introduction: immunodeficiencies predominantly occur in antibodies to recurrent synopulmonary infections, chronic or recurrent diarrhea, autoimmunity, neoplasms, inflammatory diseases, and allergies. The increase in the frequency or severity of infections, or even the occurrence of opportunistic infections in these patients when they are in regular replacement of human immunoglobulin, should alert to the association with cellular comimunodeficiency.
Objective: Present two cases of patients with hypogammaglobulinemia in monthly replacement of intravenous immunoglobulin (IVIg) who evolved with acquired human immunodeficiency syndrome **Cases:** Patient 33 year old woman, followed by variable immunodeficiency (CVI) since 2000, with serum IgG levels of 18 mg/dL, CD4 + and normal CD8 + and negative serology for infectious agents. It presented good therapeutic response to IVIg replacement, except for the persistence of recurrent sinusitis. From 2006, there was a general state of decline with asthenia and progressive weight loss (up to BMI = 14 kg/m²). In February 2007, she was hospitalized with fever, painful hepatomegaly and cytomegalovirus (CMV) perineal skin ulcers; weakly positive serology for HIV, viral load above 750,000 copies/mm3; CMV retinitis, *M. avium*-complex positive blood culture and esophageal candidiasis, pancytopenia, pancreatitis and cholestasis. It had CD4 + = 15 cells/mm3 and inversion of the CD4/CD8 ratio (0.14). He reported sexual contact with HIV + individuals in 2004. An antiretroviral regimen and treatment of opportunistic infections were started, with clinical and laboratorial improvement. The patient died in 2015 due to massive pulmonary embolism following bone fracture. Patient 2: male, 64 years old with Systemic Lupus Erythematosus and antiphospholipid syndrome, with hypogammaglobulinemia secondary to the use of immunosuppressants (diagnoses in 2015). Initiated IVIg replacement in May 2016. In October 2016, he started infection, fever, oral moniliasis and unexplained weight loss. Immunochromatographic test for HIV with positive result, and CD4 + count = 425 cells/mm3. Initiated antiretroviral treatment, with control of opportunistic infections.
Conclusion: the presence of severe opportunistic infections, a marked decrease in CD4 count, and significant clinical worsening in patients undergoing regular replacement of IVIG or IgGI may be evidence of HIV infection. This diagnosis may require, in these cases, PCR testing even in the presence of negative serology.

PO - 032

Evolution of Patients with Hypogammaglobulinemia Secondary to the Use of Rituximab Accompanied in a Tertiary Outpatient Clinic

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Introduction: Rituximab (RTM) is a specific monoclonal antibody directed to B cells (anti-CD20). It is used to treat lymphoproliferative disorders and selected autoimmune disorders. Prolonged B cell depletion is associated with the risk of adverse effects, including hypogammaglobulinemia, increased risk of infections, failure to develop immune responses after vaccination and neutropenia. Objective: To evaluate the evolution of patients with hypogammaglobulinemia secondary to the use of RTM in the Clinical Immunology and Allergy Service of HC FMUSP.
Method: Retrospective study with review of medical records and laboratory exams of nine patients who underwent MTR and presented hypogammaglobulinemia in the years 2004 to 2017. Results: In our sample, all patients who progressed to hypogammaglobulinemia were receiving lymphomas. There is no immunoglobulin dosage record prior to treatment. Of the 9 cases, mean age was 52 years (4 men and 5 women), 2 lost follow-up,

and 1 of them also presented neutropenia. Seventeen patients who continued in follow-up required IVIG replacement, due to infectious exacerbations, mainly pneumonia and sinusitis. The mean serum IgG dosage at the time of onset of IVIG replacement was 491 g / dL. The mean time between the first dose of RTM and the need for IVIg replacement ranged from 2 to 8 years, with an average of 5 years. The IgA dosage was used as a parameter for the recovery of hypogammaglobulinemia, and it was observed that only 1 of the 7 patients presented recovery of the condition up to the moment.
Conclusion: Given the data, we considered the immunoglobulin dosage to be important before initiating RTM treatment and periodically, in order to indicate the replacement of IVIg or IgSC in a timely manner avoiding complications such as potentially serious infections.

PO - 033

Neuroendocrine Tumor in a Child with Common Variable Immunodeficiency

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Introduction: CVID is the most frequent severe primary humoral deficiency, characterized by low titles of IgG and IgA and/or IgM, defects in antibodies production, after excluded other causes of hypogammaglobinemia. Digestive neoplasms are described in adults with CVID, but are almost not described in children.
Case report: A 4-year-old boy had more than two pneumonias per year. The diagnostic hypothesis was a primary antibody deficiency. Serum Igs titles were: IgA < 7(113-248), IgM 144 (65-134), IgG 230 (739-1475) mg/dL, CD4/CD8 = 0,45, normal Btk. Were excluded other causes of hypogammaglobinemia and done the diagnosis of CVID. The immunoglobulin reposition took to a clinical improvement. At 8 years, he developed an epigastrium's pain. The endoscopy showed duodenal polyp and dysplastic tubular adenoma. Annual endoscopic was indicated. At 9 years, the endoscopy showed duodenal polyps and tubular duodenal adenoma. A colonoscopy showed tubule-villous adenoma, with soft and moderate colon atypia and rectal tubular adenomas, removed by endoscopy. At 10 years, he had diarrhea and abdominal pain. Tomography showed colon and rectus pneumatosis. Five months later, he had constipation; colonoscopy showed a tumor mass. In the surgery were found neuroendocrine intestinal tumor and metastasis in the liver, omentum, and costal gratins. The tumor could not be removed due to its size. Despite parenteral nutrition and two cycles of chemotherapy, the patient died.
Conclusions: The pneumonias caused by low titles of IgG were resolved after immunoglobulin reposition. The patient evolved with a rapidly growing neuroendocrine tumor. We believe that is also important to investigate digestive tumors in children patients with CVID, to enable early therapy.

PO - 034

Selective IgA Deficiency in Children: is it Really a Benign Disease?

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Introduction: Selective IgA deficiency (SIgAD) is the most common primary immunodeficiency. Although the majority of patients are asymptomatic, some may present with allergies, autoimmunities, recurrent infections, neoplasia or progress to Common Variable Immunodeficiency (CVID).
Objective: To evaluate the frequency of allergies, autoimmune manifestations, neoplasia and progression to CVID in children and adolescents with SIgAD.
Methods: Retrospective analysis of medical records of patients diagnosed with SIgAD followed at Allergy and Immunology Clinic of Instituto da Criança - FMUSP from 2016 to 2017. SIgAD was defined as the presence of serum IgA levels persistently lower than 7 mg/dL in children older than 4 years with exclusion of other immunologic abnormalities.
Results: We included 38 patients (20 M) aged 4-20 years (median 15.3 years). The median age at diagnosis was 6.41y (4 – 14y) and the median time of follow-up was 8.5y (4mo – 18y3mo). A single female patient developed CVID at the age of 18. Autoimmunities were diagnosed in 23.7 % of the patients (9/38): Hashimoto´s thyroiditis $n = 3$, Graves' disease $n = 1$; unspecified thyroiditis $n = 1$; type I Diabetes Mellitus $n = 1$; Juvenile Idiopathic Arthritis $n = 1$; Vitiligo $n = 1$; Systemic Lupus Erythematosus (SLE) $n = 1$ and celiac disease $n = 1$; one female patient had Hashimoto thyroiditis and SLE. The median age of the diagnosis of autoimmunities was 6.9 years (2-14 years). Isolated antinuclear antibodies (ANA) were found in 5 patients. Neoplasia occurred in 7.9 % of patients (3/38): Hodgkin's lymphoma ($n = 1$) and histiocytosis ($n = 2$). The patient with Hodgkin's lymphoma also had Hashimoto's thyroiditis and SLE. Food allergy was absent in our cohort. Asthma was present in 52.6 % (20/38), allergic rhinitis in 73.7 % (28/38) and eczema in 21.0 % (8/38). Short stature was evidenced in 3 patients and precocious puberty in 2. No deaths were reported.
Discussion: Although known as frequently asymptomatic, in our cohort of SigAD patients more than 70 % were allergic. Despite studying mainly children, we found a high prevalence of autoimmunity and neoplasia. This demonstrates that complications were neither uncommon nor always mild. Early diagnosis and close monitoring since childhood are critical to improve prognosis.

PO - 035

Chronic Diarrhea in Common Variable Imunodefficiency (CVID): Treatment with Oral Immunoglobulin

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Rationale: Gastrointestinal manifestations in CVID are usually not controlled with intravenous immunoglobulin (IVIG).
Methods: We report two cases of successful oral IVIG treatment of CVID-associated chronic diarrhea.
Results: Case 1: 8y/o boy, had several admissions for pneumonia and diarrhea, one in pediatric ICU. Aditionally, he had recurrent otitis media, chronic rhinosinusitis and bronchiectasis. At the age of 1: IgG 273 mg/dL, IgA and IgM undetectable, no BTK deficiency. IVIG was introduced right after the diagnosis. Because of persistent chronic diarrhea and severe malnutrition, oral IVIG (5 g/month) was initiated and after 2 months, the diarrhea ceased, remaining so after 16 months of use. Case 2: 36 y/o woman

diagnosed with CVID in 1998, laboratory tests: IgG 253 mg/dL, IgA 37 mg/dL and IgM 16 mg/mL. Chest CT showing bronchiectasis. She began to receive IVIG right after the diagnosis and remained stable, with occasional use of antibiotics for rhinosinusitis. By the age of 34, she started with persistent diarrhea, > 20 episodes/day, weight loss (10 pounds) and impairment of daily activities. Stool culture did not show any pathogenic bacteria. Oral IVIG was initiated (5 g/month) with complete resolution of diarrhea. After 6 months of treatment, she remained with no diarrhea.
Conclusions: Oral IVIG demonstrated benefit in CVID-associated chronic refractory diarrhea. Further controlled studies are needed to confirm the optimal dose and mechanisms of such route of administration of IVIG.

PO - 036

74 CVID Clinical Presentation in Two Immunology Centers in Argentina

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Introduction: Common variable immunodeficiency (CVID) is a heterogeneous group of primary immunodeficiencies characterized by hypogammaglobulinemia and poor to absent specific antibody response. The onset of symptoms may be at any age, CVID is the most frequent symptomatic antibody deficiency in adulthood.
Results: In our center we registered 96p CVID and we performed retrospective study of 74p with CVID. 36p are woman and 38p are men. Taking into account the age at the diagnosis of our patients, we sort out them in 3 group (G) is, G1:32p (43 %) < 10 years (y), G2:17p (23 %)10yto20y and G3: 25p (34 %) >20y. Based on their clinical presentation, we divided p in two groups, CVIDi: those who had only infections and CVIDr: those who presented immune dysregulation like: autoimmunity, lymphadenopathy, granulomatous disease, interstitial lung disease and enteropathy.

Group (G)	Patients (P)	CVIDi	CVIDr
G1	32p	26p (81 %)	6p (19 %)
G2	17p	7p (41 %)	10p(59 %)
G3	25p	13p (52 %)	12p (48 %)

Dysregulation manifestations are; G1: lymphadenopathy 4p, autoimmunity 7p, interstitial lung disease1p. G2: lymphadenopathy 2p, autoimmunity 8p.G3: lymphadenopathy 6p, autoimmunity 6p.In p who only had infections, 21p (28 %) presented bronchiectasis at the moment of the diagnosis. Nowadays 54p are in current monitoring under immunoglobulin replacement therapy: 36p with intravenous gammaglobulin (gg) and 18p use subcutaneous gg with adequate IgG levels in blood. Follow up was lost in 12p and 8p died.
Conclusion: Even though CVID patients are susceptible to recurrent infections, some patients could associate other clinical complications including autoimmune or inflammatory disease or granulomas at the diagnosis. In our cohort, children present more infections at diagnose than older patients, who have more immune dysregulation manifestations, that cannot be prevent with immunoglobulin therapy. Many patients have already had organ damage at diagnose.

PO - 037

X – Linked Agammaglobulinemia (XLA) Diagnosis in Adult Life

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Introduction: XLA is a humoral disorder caused by gene mutation in Bruton’s tyrosine kinase (BTK), an enzyme which plays a critical role in B cell maduration, leading to reduced levels of B cells in peripheral blood and lymphoid organs, and severe hypogammaglobulinemia. The incidence ranges from 1/100000 to 1/400000 newborns. The mean age at diagnosis is around 3.5 years old. Symptoms present early in life, when levels of maternal IgG fall. Affected males suffer from recurrent pyogenic and fungal infections, involving respiratory tract mainly. The diagnosis is confirmed by genetic analysis.
Case report: A 35-year-old man presented at our hospital, after developing septicemia secondary to abdominal infection. At the age of 8, he experienced pneumonia and other upper respiratory tract infections. He is the third son of non-consanguineous parents. Family history reveals autoimmunity in some members of his mother’s family. He had one brother, died aged 15, with a long history of severe infections before his first year of life. After his death, the mother isolated our patient to protect him.
Immunologic evaluation revealed severe hypogammaglobulinemia (0.1 g%), with low levels of IgG (93 mg/dl), IgA (9 mg/dl), IgM (34 mg/dl), and 0.1 % $CD19^{+}/CD20^{+}$ (6 B cells). Imaging studies verified the presence of bronchiectasis and liver enlargement. The probable diagnosis was XLA, so BTK direct gene sequencing was made, revealing the presence of a mutation c.1684C > T (pArg562Trp) which confirmed the diagnosis. Meanwhile, he started Ig replacement therapy and antibiotic prophylaxis, with clinical improvement. He has started psychological support to re-integrate himself into social activities.
Conclusions: Mutations in some domains of BTK gene determine phenotypic expression of XLA. According to literature, 1672 mutations have been described. There is a link between genotype and phenotype developing into a different range of severity. However, in some members of the same family this does not happen, as in our case report. This fact is called phenotypic heterogeneity, and it supports the idea that epigenetical factors and other modifying genes, influence the clinical presentation. As a rule, XLA patients are diagnosed in childhood, but we have to keep in mind that this PID can also be diagnosed in adult life.

PO - 038

Use of IV/SC Immunoglobulin in Secondary Hypogamaglobulinemia: Cases Report

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Introduction: Secondary hypogammaglobulinemia is a common cause of immunodeficiency after certain treatments such as chemotherapy and

anti-CD20. Replacement treatment with Immunoglobulin is not well elucidated
Objective: To describe the clinical and immunological features of patients (p) with hypogamaglobulinemia secondary to Immunosupressive drugs, who required treatment with IV/SC immunoglobulin (Ig).
Methods: Patient`s available data were collected. Hypogammaglobulinemia was defined as IgG-IgA-IgM serum levels < -2 SD for age.
Results: Ten patients (1male/9 female) were included. Causes of hypogammaglobulinemia identified were: chemotherapy 7p (3p with solid tumor; 4p with acute lymphoblastic leukemia) and anti-CD20 3p (1p with lupus and nephrotic syndrome, 1p with Pompe disease and 1p was a baby whose mother received anti-CD20 during pregnancy) Mean age at diagnosis of hypogammaglobulinemia was 5,3y (r: 0,23-14,87y) Mean values of serum IgG were 2,97 g/l (r: 2,01-4,4) IgA 0,25 gr/l (r: 0,12-0,4) IgM 0,30 gr/l (r: 0,06-0,54). Igs were determined routinely in patients under treatment with antiCD20. In those receiving chemotherapy, Igs were performed because of infections (pneumonia in 2p, fungal infection in 1p and sepsis in 5p) 1p started treatment with SCIg and 1p with IVIg. 2/9p choosed to switch to SCIg. Serum levels of Igs were performed every 3 months. In the follow up 1p with nephrotic syndrome recovered normal values of IgG after 18 months of replacement treatment and 1p with solid tumor after 2y. Both patients stopped SCIg with good outcome. In 3p infections were documented while receiving IV/SCIg (bronchitis, celulitis, fungal infection). No adverse effects were registered. 9p are alive and well after 2,7y (r: 0,5-4,9) of follow up. 1p with histiocytosis died because of his illness.
Conclusion: Secondary immunodeficiency could be associated with severe infections. Replacement treatment with IV/SCIg in patients with secondary hypogammaglobulinemia was used to prevent infections in our cohort, with good outcome and tolerance.

PO - 039

Immunology Phenotype in a Cohort of CVID Pediatric and Adults Patients

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Introduction: Common Variable Immunodeficiency (CVID) is characterized by hypogammaglobulinemia, defective antibody responses and recurrent infections. It is associated with an increased susceptibility to autoimmune disorders, lymphoproliferation, granulomas and malignancies. It´s usually diagnosed in second/third decade of life, but a proportion of children with hypogammaglobulinemia develop CVID.
Objective: to describe immunological features of a cohort of CVID patients.
Results: In our centers we registered 94 CVID patients (ESID criteria). Laboratory data was collected retrospectively from medical recordsof 62 patients with CVID, male: 29/female: 33 According to the age at diagnosis and taking into account the distribution of our value reference, we divide patients in 2 groups: **G1** (4-11 years) n = 20, **G2** (>11 years) n = 45. We analyzed lymphocytes subsets (Median %), CD3: G1/G2 73/72; CD4: G1/G2 38/36, CD8: G1/G2 33/33, CD56 G1/G2 8/11, CD19: G1/G2 15/13. B compartment (Bc) (n: 52): Immature /transitional (TBL), IgM$^+$memory (mIgM), class switched memory (Sm), CD21Low, TCD4 compartment (n:33): naïve (nTCD4) and memory (mTCD4) were compared with age-matched normal values. Statistical analysis was performed with Mann–Whitney test. Values with a P value <0.05 were considered significant

		mIgM	Sm	TBL	CD21L	nTCD4	mTCD4
Median %	GI	7	7	12,5	4,6	54	42,5
GII	10	4	5	8	39	59,9	
p	GI	0,02*	0,004*	0,26	0.12	0.384	0.032*
GII	0,20	0.001*	0.18	0.03*	0.005*	0.0002*	

*p <0.05
Conclusion: Phenotypic defects in T and B cells are commonly found in pediatric and adult patients with CVID. Our cohort show this impairment. The more prominent defect in TCD4 compartement found in G2 could explain clinical manifestations as lymphoprolipheration, dysregulation and malignancy described in these patients.

PO - 40

Common Variable Immunodeficiency vs Hypogammaglobulinemic Patients

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Hypogammaglobulinemic patients with recurrent infections who do not full fill CVID diagnostic criteria are classified as IgG deficient (HIgG). These patients constitute a diagnostic dilemma Objective: to compare clinical and immunological phenotypes in a cohort of patients to differentiate these two PIDs.
Results: In 28 CVID and 11 HIgG we determined the clinical phenotypes and performed flow cytometry immunophenotyping of B-cell and T-cell patterns: B compartment (Bc): Immature /transitional (TBL), IgM$^+$memory (mIgM), class switched memory(Sm), CD21Low. TCD4 compartment: naïve (nTCD4) and memory mTCD4) Clinical phenotypes: CVID and HIgG have recurrent respiratory infections and all patients were treated with immunoglobulin replacement therapy. No infectious complications: CVID: 39 % HGV: 9 %. Immunological Phenotypes: IgG at diagnosis: CVID (n: 42) 349 mg/dl vs. HGD (n: 23): 551 mg/dl (p: 0, 0004) B compartment: CVID (n.28) vs. HIgG (n:12): median: mIgM: 6,5 vs. 8,0 % (p:0,49); Sm: 4,5 vs. 9.0 % (p:0.02); TBL: 10 vs. 10 (p: 0,35); CD21Low: 8,3 vs. 2.0 % (p: 0,005). T compartment: CVID (n:20) vs. HIgG (n:9): nTCD4: 37,9 vs. 54 % (p:0,01); mTCD4: 60,5 vs. 42,2 % (p:0,02). Switched memory B-cell and CD21Low was more severely affected in CVID that HGD. Regarding T compartment CVID showed significant decrease naïve T CD4 with expansion memory T CD4.
Conclusion: Both CVID and HIgG are similar regarding to infectious complications, but CVID group presents more frequently no infectious compromise. Laboratory evaluation is really useful to differentiate these groups inasmuch as immunoglobulins levels and distribution of B and T cell compartments are significantly different.

PO - 041

Pediatric Patients with Phenotype of Common Variable Immunodeficiency: Follow-Up

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Introduction: Common Variable Immunodeficiency (CVID) may present at any time of life, although the 2 major peaks of onset are childhood (5

and 10 years of age) and the third decade. Several published articles report that 20 % of patients were under the age of 12 years.
Objective: to evaluate the clinical and immunological features of a group of pediatric patients with CVID and their follow up.
Results: The study population comprised 27 individuals with CVID diagnosed during childhood (4-11 yr). We evaluated serum IgA, IgM and B-cell compartment: Immature /transitional, IgM^{+}memory, class switched memory. The patients were followed up for an average of 7 years. 23/27 remained CVID. 4/27 increased IgA and IgM levels and normalized their class switched memory cells. 2/4 suspended gammaglobulin treatment, one of them is under antibiotics prophylaxis and both have normal globulins. Both are asymptomatic nowadays and under antibody function reevaluation. The other 2 are still under gammaglobulin replacement therapy and they are also in good clinic condition without any intercurrence.
Conclusions: Follow up of pediatric patients with CVID phenotype is really important given the fact that some of them can finally behave as late transient hipogamma deficient patients, and some others can turn around to other humoral immunodeficiencies. IgA, IgM and B lymphocyte subpopulations monitoring could allowed us to proper reclassificate this patients.

PO - 042

Hyper IgM Syndrome: Case Report

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F.S.C., male, 17 years old, born and raised in Osasco. Patient treated at the Immunology department in Darcy Vargas Hospital in intravenous immunoglobulin (IVIg) replacement since December 2014. Previously healthy, at 8 years old, he developed an acute abdomen. Diagnosed with Burkitt's lymphoma (immunohistochemistry: CD20, bcl-6 and CD10 positive). Classified as intermediate risk. Chemotherapy protocol initiated with cyclophosphamide, vincristine, prednisone, methotrexate, cytarabine and decadron. Control evaluation evidenced two abdominal masses > 8 cm, reclassified as high risk. Modified chemotherapy protocol, initiated cytarabine and etoposide. Mass reduced little, configuring therapeutic failure. Infected, he evolved with septic shock. Abdomen CT showed splenic and retroperitoneal masses, and hepatic nodules. He underwent splenectomy and mass resection. Initiated protocol with Rituximab, ifosfamide, carboplatin, etoposide, methotrexate, cytarabine and decadron, finishing treatment after 6 months. He presented convulsions, initiating phenobarbital, replaced by carbamazepine and currently oxcarbazepina. One year after finished chemotherapy, he developed recurrent sinopulmonary infections and, 5 years later, evolved to pneumonia progressing to septic shock. Anti-HIV-negative, IgG: 127, IgM: 748, IgA: 6.3, CD3: 1750, CD4: 922, CD8: 795, CD19: 830, CD56/16: 307, C3: 115, C4: 16.9, CH50: <60; Serology for rubella and CMV reagents. We made hypothesis of hyper IgM syndrome and started IVIg replacement with infections controlled. Dosage of CD40 / CD40-L showed little reduction compared to healthy control. Genetic study of the most common exons linked to hyper IgM syndrome showed no mutations.
Primary immunodeficiencies are associated with the onset of neoplasms and autoimmunity. The use of Rituximab, associated or not to chemotherapy in Burkitt's lymphoma, can trigger acquired hypogammaglobulinemia with normal or decreased IgM levels. Many cases of Hyper IgM Syndrome present inconclusive genetic study.

PO - 043

Tomographic Pulmonary Progress in Patients with Antibody Defects

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Introduction: The most common primary immunodeficiencies are the antibody defects, which are characterized by defective antibody production. Clinically, affected individuals are susceptible to infections, mainly respiratory. Therefore, radiologic evaluation of lungs is important and shows a variety of pulmonary findings, including air trapping, bronchial wall thickening, bronchiectasis, ground glass opacities, parenchymal consolidation, pulmonary nodules and fibrosis. As treatment, these patients should receive intravenous immunoglobulin (IVIG), which reduces the risk of infections and may change their clinical course.
Objectives: Assess pulmonary progress in patients with antibody defects, all of them in use of IVIG replacement therapy, through computed tomography (CT).
Results: In this study, we analyzed 94 patients, 49 female (52 %). The age range of subjects was 18 to 79 years, with a mean age of 45. The average age at diagnosis was 31 years and patients have about 12 years of disease follow-up.
The first CT analyzed already had some abnormalities in 88.2 % of the patients. The most frequent radiologic findings were pulmonary nodules (61,6 %), then wall thickening (54,6 %) and bronchiectasis (39,5 %). About the bronchiectasis, 73.5 % were observed in the lower lobe, 38.2 % in the middle lobe and 20.6 % in the upper lobe. The mean time between the two CTs analyzed was 4.6 years. Regarding the last CT, 94.7 % of the patients had abnormalities. In the last CT the main findings were: pulmonary nodules (66.2 %), wall thickening (53.26 %) and bronchiectasis (41.3 %). Bronchiectasis can already be identified on first CT in 66 % of the patients with X-Linked agammaglobulinemia (XLA) and this number goes up to 83 % on the last chest CT. While Common Variable Immunodeficiency subjects had 31 and 36 % of bronchiectasis, respectively on the first and last CT.
Conclusion: Most of the patients already present some CT abnormalities at diagnosis and, despite of the treatment, during our study, there was still an increase in the CT findings. Bronchiectasis, which may be the tomographic alteration with more clinical repercussion, presents a high frequency since the first CT, affecting 40 % of the patients and this number is still higher in subjects with XLA, reaching 80 %.

PO - 044

Selective IgG3 Subclass Deficiency in a Patient with Severe Asthma and Allergic Bronchopulmonary Aspergillosis

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Introduction: IgG3 comprising 4-8 % of all serum IgG, it is the most susceptible IgG to the proteolytic digestion, it is an excellent activator of the complement system and have affinity for protein antigens, further it have highly affinity to Fc receptor on macrophages, therefore, IgG3 its important for antibody mediated phagocytosis. Selective IgG3 subclass deficiency increases susceptibility to infections, almost all published studies are in children

and in our knowledge, the association between IgG3 deficiency and allergic broncho-pulmonary aspergillosis (ABPA) has not been reported.
Clinical Presentation: Fifty-one years old man from Jalisco, México. No familiar background for immunodeficiency. On 2012 he started with cough, chest tightness, wheezing and shortness of breath, he was hospitali-zed 16 times, the symptoms were increasing until he had dyspnea at rest and cough with expectora-tion all day long and daily night symptoms. He was diagnosed with severe asthma and the treatment was performed with oral steroids in many times, high dose inhaled steroids, theophylline and monte-lukast.
Laboratory test results: Hb: 17.4 g/dl, leucocyte 11,200 cel/ul, lymphocytes 4,100 cel/ul, monocytes 890/ul, eosinophils 1060 cel/ul, basophils 40 cel/ul, IgG: 890 mg/dl, IgA: 330 mg/dl, IgM: 96.5 mg/dl, IgE: 928 mg/dl, ESR: 5 mm/hr, pANCA: negative, cANCA: negative, PCR: <3.19 mg/l. BAAR, PCR for mycobacterial and my-cological culture in sputum were negative. Skin prick test was positive for *Aspergillus fumigatus*, *Candida* and *Fusarium*. Antibody response to pneumococcal polysaccharides antigens was grater than 50 %. IgG subclasses were measured with only IgG3 diminished (84 mg/dl). First spirometry test with FEV1: 50 %, and post-bronchodilator FEV1: 62 %. TAC with maxilar and ethmoidal sinusitis. He started treatment with intravenous immunoglobulin, biweekly subcutaneous omalizumab, oral itra-conazole, high dose inhaled steroids and long action B2 agonist, after this the improvement was noto-rious.
Conclusion: Selective IgG3 subclass deficiency in adults is poorly studied and the majority of reports in the litera-ture associate this disease with upper respiratory tract infections. In our knowledge this is the first case report for a patient with ABPA and elective IgG3 subclass defi-ciency, this support the recommendation that selective IgG3 subclass deficiency should be conside-red in adults with recurrent upper respiratory tract infections with or without allergic rhinitis and asth-ma, and therefore IgG subclasses should be analyzed even when total IgG levels are normal.

PO - 045

Neonate with Agamaglobulinemia Due to Improper Treatment of Common Variable Immunodeficiency During Pregnancy

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Introduction: Common Variable Immunodeficiency (CVID) is a disease characterized by low levels of serum immunoglobulins and increased susceptibility to infections. Diagnostic criteria includes: recurrent infections, age over 4 years, reduced levels of IgG, IgA and / or IgM, absence of isohemagglutinins and/or vaccine response, exclusion of secondary causes of hypogammaglobulinemia. Due to the unclear genetic nature of this immunodeficiency, a clear pattern of heredity is not defined. Treatment usually consists of intravenous infusion of immunoglobulin every 3-4 weeks at the initial dose of 400- 600 mg/kg to keep the serum IgG levels above 500 mg/dL. Placental transfer of IgG antibodies is an important mechanism that provides protection for the newborn while the humoral response is inefficient. This mechanism results in serum levels of neonatal IgG equivalent to maternal levels and with the same patterns of antigen recognition.
Case presentation: Female, 21 years old, diagnosed with common variable immunodeficiency since 2015. She is followed up in a service of Allergy and Immunology, where she receives intravenous immunoglobulin (IVIG) 30 g (630 mg/kg) every 4 weeks. However, the patient is not adherent to the treatment and had presented last infusion on January 2016. During this period she became pregnant and only seeked for medical evaluation in January 2017 due to pneumonia, when she was treated with intravenous antibiotics and IVIG. She had spent more than a year without receiving IVIG. She gave birth to a healthy child on may 2017, after 40 weeks of gestation, normal birth, without complications. At this moment, the patient had IgG levels of 90 mg/dl. The newborn had IgG at birth of 153 mg/dL, IgA <6.5 mg/dL and IgM 22.7 mg/dL, decided to initiate IVIG and currently she receives human immunoglobulin 1.4 g (430 mg / kg) every 4 weeks. Mother and child are now adherent to treatment.
Discussion: It is of great importance that a pregnant woman with CVID presents serum immunoglobulin levels within normal range in order to allow an adequate passage of IgG to the fetus through the placenta. We observed in this case that the poor adherence of the patient caused IgG levels with replacement need in the child, which will probably last for at least 6 months (average time for the child to develop an effective humoral system). We emphasize the importance and necessity of treating patients with common variable immunodeficiency, especially in cases such as gestation.
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PO - 046

Hypogammaglobulinemia in Patients with Chronic Diarrhea: Cause or Consequence?

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Introduction: Common Variable Immunodeficiency (CVID) manifests itself in several different ways, sometimes disguising proper diagnosis, as it presents broad and non specifc symptons.
Case presentation: R.R.S., 55 years old, came to the Emergency Room (ER), in March 2017 with a history of diarrhea (12 to 14 episodes a day) and vomiting. The patient, who had been self medicating for eight months with loperamide, reported important weight loss and a decrease in her overall wellbeing. First examination showed she was dehydrated and underweighted. She was admitted to the Clinical Gastroenterology Service (CGS) for treatment and investigation. Several hypothesis were discarded: neoplasm, inflammatory, infectious diseases, drug related and celiac diseases. Further examination requested by the Allergy and Immunology Service revealed normocytic anemia, reactive protein C 20,32; regular kidney and liver functions as well as regular electrolyctes; IgG 266; IgM 25; IgA 217 and IgE 9,1. Parallel to Intravenous Immunoglobulin (IVIG) replacement, CGS also introduced immunosuppressant steroids, thus

diminishing the number of daily bowel movements. After 5 days, the patient did not present any further episodes of diarrhea, being discharged while weaning the steroids and prophylactics antibiotics. She returned to the ER at a later date, with new exams (IgA 193; IgM 65; IgG 512) and received a last infusion of Intravenous Immunoglobulin.
Discussion: CVID is the deficiency of the most common primary antibody. It is not related to gender and it peaks during the 1st and 3rd decades of life. Our patient represents a case of chronic secondary diarrhea to CVID with no recurrent bacterial infection. Nonetheless, she did present other standard criteria for diagnosis, such as being more than 4 years old, have low serum IgG level and the exclusion of underlying causes. The presence of infection, in spite of being common, may not be present in CVID. IVIG may be an effective treatment, and responsiveness to it is a good indicator towards a precise diagnosis. Lastly, it must be taken into consideration that CVID sometimes leads to the compromising of the gastrointestinal system, thus, patients that present chronic diarrhea not related to known causes, as well as hypogammaglobulinemia, should have primary immunodeficiency as a plausible diagnosis hypothesis.

PO - 047

Is Patau Syndrome Associated with Humoral Immunodeficiency? Case Reports

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Introduction: Patau syndrome is a rare chromosomal disorder (1:5,000 to 1:20,000 live births) generally defined as trisomy 13. The patients with this syndrome mainly present a spectrum of malformations including oral, facial, ocular, central nervous system, limb, fingers, lung-cardiac system, uro-genital involvement and others. We report the occurrence of humoral immunodeficiency in two patients with Patau syndrome.
Case reports: Patients are 14 and 10 years old, male, both referred to clinical immunology service due to recurrent respiratory infections. A relevant condition of the primary immunodeficiencies, Bruton agammaglobulinemia or X-linked agammaglobulinemia (XLA) is defined by the lack or deficiency in concentrations of all types of immunoglobulins and low mature circulating B cells. It results in severe humoral deficiency in which patients frequently develop bacterial, fungal and protozoan infections. One of the patients reported has XLA and receiving prophylactic intravenous gammaglobulin. The second one has normal immunoglobulins with impaired response to polysaccharides.
Discussion: We emphasize the possibility of a predisposing primary immunodeficiency leading to recurrent infections concomitant with Patau syndrome diagnosis.

PO - 049

Analysis of Regulatory T Cells and Their Correlation with Memory B and T Cells and Autoimmune Manifestations in Patients with Common Variable Immunodeficiency (CVID)

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Introduction: Common Variable Immunodeficiency (CVID) is a heterogeneous Group of primary antibody deficiencies, which is defined by marked reduction of serum IgG, IgA and/or IgM levels and recurrent bacterial infections. One group of patients are associated with defects in T cells and regulatory T cells (Tregs) resulting in recurrent viral infections and early-onset autoimmune disease.
Objectives: In 28 patients, we analyzed wheter there is a correlation Treg cells and memory subpopulation in T and B cells, as well as autoimmune manifestations.
Results: Twenty-eight patients (17 women and 11 men, mean age 23 years) were studied, 10 patients with autoimmunity (35 %, thrombocytopenic purpura). Patients with CVID and autoimmunity expressed less Treg CD127 low, Treg (FOXP3+) compared to controls ($p = 0.0002$, $p = 0.0005$, respectively). Patients with autoimmunity have fewer total B cells but more innate CD21 B cells than patients without autoimmunity ($p = 0.0075$, $p = 0.0488$). There is also a correlation between more expression of CD4+ CD45RO T cells and less Treg ($r = 0.7$ $p = 0.018$).
Conclusions: Our results showed that 35 % of patients with CVID have autoimmunity and low Treg expression. Research in this area might provide noteworthy data to better understand immune dysfunctions and dysregulations related to CVID condition.
Financing: Conacyt FOSSIS No. 161089 and CB No. 256471

PO - 050

Effect of Bay 41-2272 on Human Neutrophils

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Neutrophils are the first line of cellular innate immune defense against pathogens. Previous studies reported that BAY 41-2272, a guanylate cyclase agonist, induced monocyte/macrophage priming and/or activation. Aiming to identify new immunomodulators to treat cell dysfunctions, we investigated the effects and mechanisms involved in neutrophil activation by BAY 41-2272.

Human neutrophils were treated with BAY 41-2272 (3.0 and 30.0 μM) to evaluate superoxide anion (O2-), cGMP, cAMP, IL-8 and hydrogen peroxide (H2O2) production. Neutrophil chemotaxis and LIVE/DEAD Fixable Dead Cell assay was evaluated too.

PMNs treated whit BAY 41-2272 (0,3 μM; 3 μM and 30.0 μM) with subsequent activation with 50 nM of phorbol-myristate-acetate (PMA) blocked the superoxide anion (O2-), IL-8 and DHR production for doses 3,0 and 30 μM of BAY 41-2272 when compared whit neutrophils plus PMA treatment (**Figure 1 A,B,C**). BAY 41-2272 did not kill the neutrophils and inhibited its migration (**Figure 1 D,E**). cAMP production was observed but cGMP production was not seen (**Figure 1 F,G**). We also evaluated the production of IL-8 in patients with Behçet disease, a chronic inflammatory disease, and we saw an inhibition of IL-8 production for doses 3 and 30 μM of BAY 41-2272 when compared with patients neutrophils plus PMA treatment. After the BAY 41-2272 treatment the levels of IL-8 of Behçet´s patients decreased to the levels of the healthy controls (**Figure 2**).

Figure 1 – BAY 41-2272 inhibited immune functions of neutrophils through cAMP dependent and cGMP independent pathway.

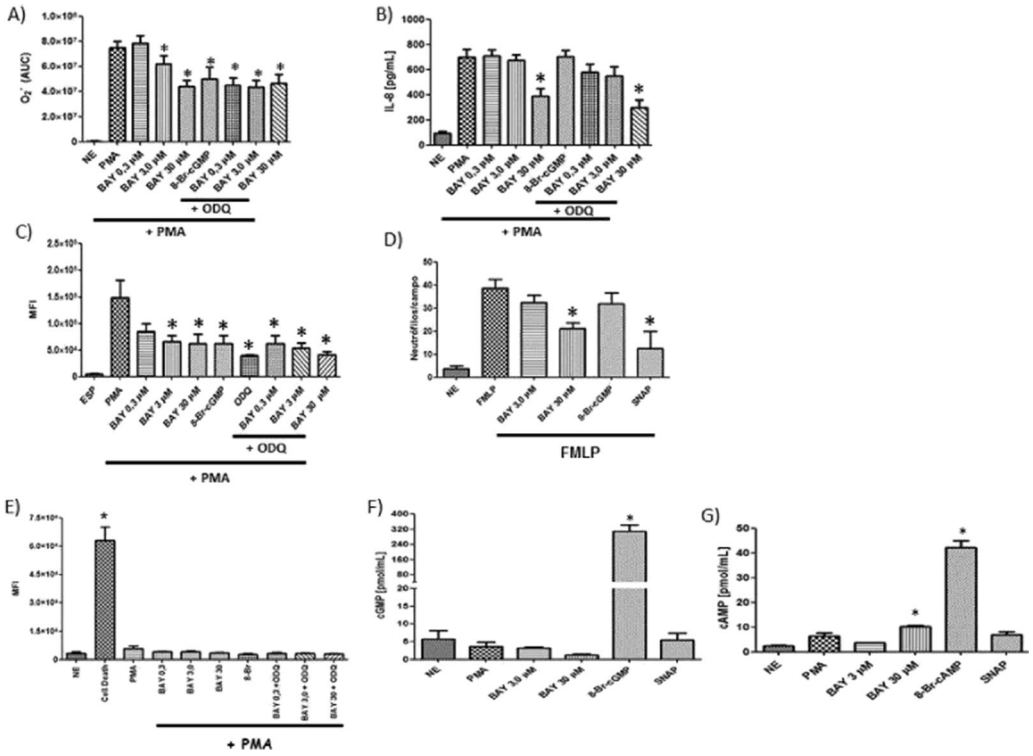

Figure 1: Effect of BAY 41-2272 on human neutrophils. Human neutrophils were treated with BAY 41-2272 in doses of 0.3, 3.0, 30.0 μM, ODQ 10.0 μM (sGC inhibitor), 100 μM 8-Br-cGMP (sGC agonist), 10 μM SNAP plus PMA 50nM. **A)** O_2 (n = 8); **B)** IL-8 (n = 12); **C)** DHR (n = 8); **D)** Necrosis after treatment whit BAY 41-2272 by flow cytometry (n = 4); **E)** Assayed for chemotactic response (n = 8); **F)** cGMP (n = 3); **G)** cAMP. (n = healthy volunteers, in duplicate for neutrophils). *$p < 0.05$, compared with PMA/FMLP expression by one-way ANOVA followed by Tukey´s test.

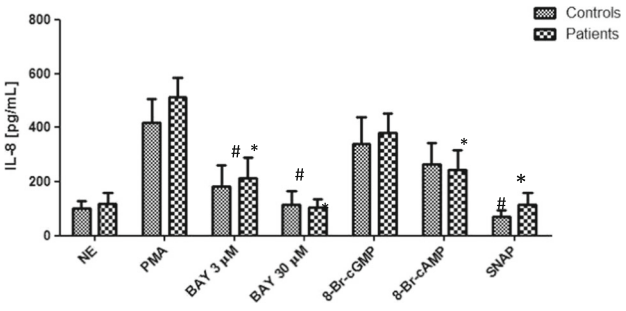

Figure 2 – BAY 41-2272 inhibited IL-8 production of patients with Behçet disease.

Figure 2: IL-8 production in Behçet patients neutrophils after priming whit BAY 41-2272 and PMA 50 nM treatment. Human neutrophils were treated with BAY 41-2272 in doses of 3.0, 30.0 μM, 100 μM 8- Br-cGMP, 10 μM 8-Br-cAMP and 10 μM SNAP plus PMA 50nM. Healthy volunteers and patients, in duplicate for neutrophils. (n = 7 healthy volunteers and n = 7 Behçet patients, in duplicate for neutrophils). $^{\#}p < 0.05$, compared whit PMA of healthy controls and $^{*}p < 0.05$, compared with PMA of Behçet patients by one-way ANOVA followed by Tukey´s test. Conclusion: BAY 41-2272 acts in the pre-activation of human PMNs, inhibiting the potential effect of PMA on the oxidative burst and the production of superoxide anion and IL-8, probably through a cAMP dependent and cGMP independent pathway, becoming an important focus of study as a modulator of neutrophil activation.

PO - 051

Novel Mutation in the gene TNFAIP3 in Autoinflammatory Syndrome Familial Behcet-like

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Introduction: Autoinflamatory disease is a group of diseases recently describe that begins with periodic fever but it has been growing and now more than 30 diseases had been included. All of them characterize by systemic inflammation. The A20 Haploinsuficiency is Behçet's disease-like disorder, or autoinflammatory syndrome familial Behcet-like, it is caused by a mutation in TNFAIP3 (tumor necrosis factor–induced protein 3; also known as A20).
Case report: A girl of 12 years old girl, without relevant background. Since 2 years of age, she started with a fever up to 40 ° C, irregular, lasting 6 days and resting for 1 week, sometimes with aphtas and adenopathy, treated as tonsillitis and pharyngitis with multiple cycles of oral antibiotics. Due to the persistent of the symptoms, it was considered as PFAPA, she was taken to tonsillectomy at the age of 3. The reappearance of the symptoms. It was discarded infections, autoimmunity, lymphoproliferation disease. At 6 years old the symptoms disappear until the age of 11 years old. Then she started with migratory myalgias and arthralgias, progression to abdominal pain, headache. It restores periods of fever of the same characteristics to the initials, including afthas. The musculoskeletal pains were intensified with limitation upon to limitation for walking with peripheral neuropathy. It was calculated PRINTO score being positive for the 3 possibilities of recurrent fever. With normal humoral and cellular immunity, we as her treating doctors, run out again autoimmune pathology. Genetic studies show TNFAIP3 mutation gen c.440_441del (p.Leu147GInfs*7) compatible with A20 Haploinsufficiency; this is a novel mutation for this disease. We started treatment with colchicine with good evolution, and resolution of all symptoms.
Comments: the diagnosis of autoinflmatory disease is always a challenge, it is very important to know or learn about them. A20 Haploinsufficiency is a new described disease, leads to a strong proinflammatory state, which leads to significantly increased levels of proinflammatory cytokines (IL-1β, TNF, IL-6, IL-18 and IL-17), and it can present as Behct´s syndrome-like. Genetics studies are a helpful test to clarify the diagnosis in this entity. Colchicine is the first line treatment but if it is not symptom resolution some reports had used biologic treatment. Fortunately in our patient we had resolution of sympotoms with first line treatment.

PO - 052

A Case Report of a Novel Compound Heterozygous Mutation in a Brazilian Patient with Deficiency of IL1RA (DIRA)

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Introduction: Autoinflammatory diseases (AID) are a group of rare disorders recently described. DIRA is a neonatal AID that presents very early in infancy with marked skin and bone involvement. Here we reported the case of a Brazilian DIRA patient with a new compound heterozygous mutation, its clinical response to canakinumab.
Case presentation: A 7-year-old Brazilian child experienced since very early in life with severe episodes of recurrent osteomyelitis, associated with skin rash and systemic inflammation without respiratory distress syndrome. The first episode was during the fourth month of life and always was treated as infective osteomyelitis Just at the age of 7 years he was sent to our department as primary immunodeficiency but the clinical phenotype rule out this diagnosis and DIRA was suspected. The Genomic DNA was extracted and a sanger sequencing was performed, demonstrating the presence of two yet described mutations in *IL1RN* but found for the first time in compound heterozygosis: p.Ile74_Pro78del and p.Gln48Thr. Canakinumab was initially started as 2 mg/kg every 4 weeks without good disease control (15 kg – 75 mg of canakinumab). The doses were increased to 4 mg/kg every 4 weeks and an excellent control of skin and bone disease was achieved. However in the 5, 6 and 7th doses vomiting and diarrhea immediately after Ilaris shot was experienced and overdoses was suspected and we tapered the doses to 150 mg every 6 weeks with control of disease and side effects.
Discussion: Bone autoinflammatory disorders are a group of inflammatory diseases caused by the unprovoked activation of the innate immune system leading to bone inflammatory process mediated mainly by constitutive overproduction of interleukin 1-β.DIRA is potentially fatal, and may be confused with neonatal sepsis. Biologic drugs, such as Anakinra and Canakunimab, raised down mortality of DIRA patients, mainly related to systemic inflammatory response syndrome (SIRS) in early life, or interstitial lung disease in childhood. Till this moment just one report using canakinumab to treat DIRA is published without long outcomes.

PO - 053

IL-10 Receptor Mutations: a Series of Cases

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Introduction: Very early onset inflammatory bowel disease (VEOIBD) is a unique disease entity with a complex genetic susceptibility. Gene sequencing

techniques have revealed various monogenetic mutations contributing to the pathogenesis of VEOIBD, including interleukin 10 (IL-10) and IL-10 receptor (IL-10R) mutations. The objective of this abstract is to present 3 clinical cases of IL10-receptor mutation admitted on our outpatient clinic.
Case presentation: Case 1:LMM, a 3-year-old girl, presented with bloody diarrhea, recurrent fever and failure to thrive since 3 months old. On her first evaluation, rectovestibular fistula was observed, requiring surgical intervention and protective colostomy at 9 months. The colonoscopy and biopsy showed intense chronic ulcerative colitis. Immunoglobulins were above 97th percentile for age, and complete blood count (CBC), lymphocyte profile and dihydrorhodamin tests (DHR) were normal. Azathioprine, oral steroids and exclusive enteral nutrition (EEN) were initiated. Despite this treatment, the patient maintained multiple infections and bloody diarrhea. Case 2:LM, a 9-month-old girl (case #1 sibling) presented with bloody diarrhea and anal fistula since 3 months old. Immunoglobulin levels were increased. CBC, lymphocyte numbers and DHR were normal. Due to positive family history and similar clinical picture, azathioprine and EEN were initiated very early on. Despite that, patient persisted with multiple local infections and GI tract bleeding. Case 3:SCSL, currently 5 years and 9 months, presented with oral ulcer at one month old. After two months, she initiated with anal fistulae and fissures, followed by multiple local infections. Colonoscopy and biopsy demonstrated erosive panproctocolitis. Laboratory investigation revealed no abnormalities. Azathioprine, mesalazine and infliximab were administrated, with favorable response: the fistulae were completely healed and normal height/weight gain were achieved. All three patients underwent genetic sequencing, and mutations in the gene encoding the IL10-receptor were found. Patients 1 and 2 are currently waiting for a compatible donor for a HSCT, and the disease remains clinically active. Patient 3 has achieved partial clinical remission and is not listed for HSCT as of now.
Discussion: Due to the broad spectrum of this extremely rare mutation, a correct diagnosis is frequently a challenge and often delayed. Accurate genetic assessment is required to treat properly these patients.

PO - 054

Lymphoproliferative Disorder with Hypogammaglobulinemia: an Unusual Presentation of 22q11.2 Deletion Syndrome

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Introduction: 22q11.2 deletion syndrome (22q11.2DS) is the most common human microdeletion. It is known to have a heterogeneous presentation that includes multiple congenital anomalies, and immunodeficiency is one of the most striking features. Usually it is characterized by T cell lymphopenia, B cell dysfunction and autoimmunity.
Case Presentation: second child from healthy and non-consanguineous couple was born preterm (BW-2800 g; BL-45 cm). The child was healthy until 8mo, when started to present diarrhea, acute otitis, sinopulmonary and urinary tract infections. At 3yo presented splenomegaly and knee luxation. At 5yo was splenectomized. Infections worsened with need of intravenous antibiotic therapy and developed multiple lymphonodomegaly and nodules in thyroid, kidneys and pelvic region. Cervical node biopsy was negative for malignancy. The child complains of arthralgia and leg pain, besides many episodes of spontaneous patellar luxation. At 15yo was admitted at intensive care unit due to thrombocytopenic thrombotic purpura and a Clinical Genetics appointment was required. Physical exam revealed short stature, facial dysmorphisms (flat faces, proptosis, hypertelorism, long palpebral fissures, tubular nose, high palate, simplified ears), joint hypermobility, digitalized thumb, soft skin with stretch marks. Thyroid function, parathyroid hormone, electrolytes were normal. Anemia, moderate leukocytosis, thrombocytopenia, elevation of serum C-reactive protein and erythrocyte sedimentation rate were observed. Immunological investigation showed low levels of IgG: 373 mg/dL and IgA: < 50 mg/dL and normal levels of IgM: 196.6 mg/dL, high absolute values of TCD3+ lymphocytes (10.090 cells/mm3), TCD4+ (6.946 cel/mm3), TCD8+ (3213 cells/mm3), B (1.608 cells/mm3), NK (891 cells/mm3) cells and normal levels of C3, C4 and vaccine response. Indirect antiglobulin test was positive. Antinuclear Antibody and other autoantibodies were negative. 22q11.2DS was suspected and MLPA (Multiplex ligation-dependent probe amplification) confirmed the 3 Mb 22q11.2DS.
Discussion: Immunodeficiency affects up to 75 % of 22q11.2DS patients. Classical presentation includes recurrent infections, poor response to vaccines, IgA deficiency, atopy and autoimmune diseases. This patient presents a distinct phenotype with recurrent infections, multiple lymphonodomegaly, lymphocytosis (T, B and NK) and autoimmune hemolytic anemia, suggesting an immune dysregulation disorder.
Support: FAPESP and CNPq

PO - 055

Molecular Diagnosis in a Patient with Immune Dysregulation Disorder: Higher Cost-Effectiveness Yield of Whole Exome Sequencing

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Introduction: A specific group of Primary immunodeficiencies (PIDs) entitled "diseases of immune dysregulation" develops through mutation in genes with critical roles in the regulation of immune responses and immunological tolerance. These patients develop autoimmune and/or inflammatory disorders as a result of their impaired immunity. Our aim in presenting this case report is to emphasize the high genetic heterogeneity associated to this group of PID highlighting the diagnosis power of new generation sequencing strategies.
Case presentation: Male patient, now being 6 years old, born from non-consanguineous parents and without family history of PID. At 2 months of age begun with autoimmune anemia, thrombocytopenia, neutropenia, splenomegaly and with abdominal lymphadenopathies. Despite not evident double negative T cell expansion, suspicion of ALPS was considered. In agreement with no mutations found in *FAS* gene (nor germline neither somatic), immunological evaluation revealed a plasma FasL > 300 pg/ml with normal lymphocyte apoptosis assay in vitro (via Fas). Then, mutations in *FASLG* gene were ruled out. Mutations in *RAG1* and *RAG2* were also excluded despite a mild T- cell and NK lymphopenia with reduced number of naive T cell counts, along with normal lymphocyte proliferation to mitogens, while slightly decreased to antigens. Later he presented benign polyclonal B-cell lymphoproliferation (lymphadenopathy, splenomegaly, polyclonal B-cell lymphocytosis) and absence of peripheral natural killer T cells. Despite no evidence of EBV or CMV infections and normal SAP expression, *SH2D1A* and *BIRC4* genes were analyzed without pathogenic findings. Similarly, no germline gain of function mutations in *STAT3* were identified.

Finally, whole exome sequencing combined with analysis of PID-associated genes revealed a heterozygous variant in caspase recruitment domain 11 (*CARD11*) gene able to explain in the light of current knowledge, the patient's clinical picture. This gain of function mutation triggers a disorder referred as B cell expansion with NFkB and T cell anergy (BENTA).
Conclusion: Sequencing gene by gene is four times more expensive than massive exome sequencing combined with targeted gene analysis. Furthermore, it must be considered the time elapsed until the patient reached a definitive diagnosis. This case clearly illustrates the high cost-effective impact of new generation sequencing strategies in diagnosing patients with immune dysregulation.

PO - 056

Successful Treatment of Autoimmune Polyendocrinopathy Candidiasis Ectodermal Distrophy (APECED) Syndrome with Rituximab and Mycophenolate Mofetil

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Introduction: Autoimmune polyendocrinopathy, candidiasis and ectodermal distrophy (APECED) syndrome is a rare primary immunodeficiency disorder caused by a deficiency of the AIRE gene, characterized by chronic mucocutaneous candidiasis and multiple autoimmune phenomena due to a failure in central tolerance. While the endocrine manifestations remain the most frequently described, nonendocrine organ involvement has been increasingly reported. Although this syndrome is of known autoimmune origin, immune modulation therapy has not yet been protocolized.
Case presentation: We describe the case of an 8 year old female patient with APECED syndrome with multi organ involvement, both endocrine (thyroid, parathyroid, pancreatic, adrenal) as well as nonendocrine (megaloblastic anemia, enteritis, and nephrocalcinosis) who presented with acute renal failure and adrenal failure, and consequently multiple and severe electrolytic disorders which led finally to an episode of cardiac arrest. With the suspicion of an autoimmune tubulopathy, rituximab and mycophenolate mofetil immunotherapy was started, with marked improvement of renal, adrenal, pancreatic, intestinal and thyroid function.
Discussion: APECED syndrome can present with multiple complications due to autoimmunity (including rare cases of autoimmune tubulopathy). Even though it has not yet been standardized, our case (as the other few cases reported so far) supports the idea that immune therapy targeted to both T and B lymphocytes could be of benefit in these patients. Furthermore, it also raises the question of whether it should be initiated precociously, before organ damage develops.

PO - 057

NEMO: Description of an Atypical Clinical Case

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Introduction: The Inhibitor of Kappa Light Polypeptide Gene Enhancer in B-Cells Kinase gene (IKBKG), also known as NF-kappa B Essential Modulator (NEMO), is located on the X chromosome and encodes the regulatory scaffold subunit of the inhibitor of kappa B kinase gamma (IKKγ) of the IKK complex. Upon activation, the IKK complex phosphorylates the inhibitor of kappa B (IKB), leading to its degradation and thereby facilitating nuclear translocation of NF-kB and transcription of genes involved in inflammation, immunity and cell survival. Hypomorphic mutations in the IKBKG gene, which results in different forms of anhidrotic ectodermal dysplasia with immunodeficiency, have been described.
Case presentation: N.B.M., 6-year-old boy, born from non-consanguineous parents. At age 3 months, he presented with anemia, persistent thrombocytopenia, elevated liver enzymes and erythema nodosum. At 5 months, he had an episode of idiopathic subdural hemorrhage, and started with persistent fever accompanied by hepatosplenomegaly and disseminated lymphonodomegaly, as well as persistent anemia and increased serum inflammatory markers. By then, oral corticosteroids were introduced. In addition, the patient had four episodes of pneumonia. The initial investigation suggested unspecified autoinflammatory disease, hypogammaglobulinemia (IgA 21 mg/dL, IgM 38 mg/dL and IgG 290 mg/dL), lymphocyte counts below the 10th percentile for age with 2 % of B cells. Cyclosporine was initiated when he was 2 years old, but discontinued after 2 years. Genetic testing showed no mutations in PSMB4, PSMB8, PSMB9, NLRP3, SAMHD1 and LRBA, NOMID. A novel germline mutation arising of splicing regulatory elements in the NEMO gene, IKBKG, was found. It's a *de novo* synonymous exonic splicing silencer. It leads to the expression of a NEMO isoform lacking the domain coded by exon 5, termed NEMO - . . Currently, he is receiving monthly intravenous immunoglobulin and continuous oral corticosteroid therapy.
Discussion: This NEMO patient exhibit autoinflammatory disease characterized by panniculitis, transaminitisand type I Interferonopathy but lack significant primary immunodeficiency, broadening the spectrum of disease attributed to NEMO mutation.

PO - 058

Aberrant NK Cell Phenotype in a Patient with CD25 Deficiency

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Introduction: Human IL-2 receptor α chain deficiency (CD25 deficiency), caused by mutation in the *IL2RA* gene, is a combined immunodeficiency characterized by invasive viral and bacterial sinopulmonary infections, as well as lymphoproliferation and severe multi organ autoimmune disorders.
Aim: To describe the NK cell phenotype in a patient with CD25 deficiency.
Material and methods: whole fresh blood and peripheral mononuclear cells from a patient with CD25 deficiency were analysed by flow cytometry in different opportunities. IFN-γ production by NK cells was measured after rIL-12/IL-15/IL-18 stimulation. Degranulation assay was performed using K562 target cells. Proliferation was assessed by CFSE dilution.
Results: the patient had normal absolute counts of NK cells with severe impairment of $CD56^{dim}/CD56^{bright}$ ratio. About 50 % of NK cells had a $CD56^{++}CD16^{+}$ phenotype not seen in healthy donors (HD). $CD56^{Dim}$ cells express 100 % of CD62L CD62L. $CD56^{bright}$ cells showed high levels of perforin and granzime B as usually seen in $CD56^{dim}$ cells of HD. $CD56^{bright}$ cells produced about half percentage of IFN-γ than HD cells. These cells had high degranulation capacity. $CD56^{dim}$ cells displayed proliferative capacity when stimulated with rIL15 + rIL2.

Discussion: the patient's NK cell phenotype showed that the expression of the IL-2 receptor α chain appears to be necessary for normal NK cells development and that the aberrant phenotype of NK cells may play a role in the pathophysiology of viral infections patients with CD25 deficiency.
Comment: the importance of extensively study our patient's cells gives us the possibility to dissect different aspects of the biology of immune system.

PO - 059

Chronic Mucocutaneous Candidiasis (CMC) Associated with Gain-of-Function (GOF) of STAT 1: Case Report

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Introduction: GOF mutations in the signal transducer and activator of transcription 1 (*STAT1*) result in unbalanced STAT signaling and cause immune dysregulation and immunodeficiency. The latter is often characterized by susceptibility to recurrent *Candida* infections, resulting in the clinical picture of CMC. It presents heterogeneously both in clinical manifestations and genetic background. However, studies so far emphasize the key role of T helper 17 (Th17) cells and the impaired function of their cytokines interleukin 17 (IL-17) and interleukin 22 (IL-22). These cytokines have been shown to be essential for mucocutaneous anti-fungal host defense.
Case presentation: H. C. S., a 24-year-old male, with recurrent oral candidiasis resistant to standard treatment since one year old. Family history is unknown, once the patient is adopted. His infection backgrounds include several recurrent otitis media, as well as a herpes zoster episode by the age of three, and erysipela at 8 years old. The initial investigation showed hypergammaglobulinemia (IgA 183 mg/dL / IgG 1972 mg/ dL/ IgM 167 mg/dL), with normal B and T lymphocytes. Due to drug abuse, he presented with low vitamin B12 level and, as a consequence, pancytopenia (Hemoglobin 7.1 g/dl; platelets 38000; CD3:926 mm^3; CD4:382 mm^3). After replacement of vitamin B12, the blood cells accounts were normalized. Due to his digestive symptoms, an endoscopy was performed, which identified esophageal moniliasis, distal erosive esophagitis and intense pangastritis. Genetic sequencing identified STAT 1 GOF mutation – position c.800C > CT:p.267A > A/V. The patient is currently using oral nystatin, without improvement.
Discussion: Due to the high frequency of STAT 1 mutations in patients suffering from CMC, it is proposed to perform the genetic sequencing of *STAT 1* in individuals presenting susceptibility to recurrent Candida infections.

PO - 060

Report of Four Cases of Activated PI3 Kinase Delta Syndrome

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Introduction: Activated PI3 Kinase Delta Syndrome (APDS) is a combined immunodeficiency, with autosomal dominant inheritance leading to a gain-of-function in PIK3 gene, characterized by variable B and T cell lymphopenia, hypogammaglobulinemia with increased IgM serum levels and susceptibility to viral infections and autoimmunity. We present four clinical cases of APDS followed in our outpatient clinic. We describe four patients, two of them siblings, currently ages 9 to 33 years, and no history of consanguineous parents. All presented with recurrent upper and/or lower airways infections and three of them with diarrhea chronic diarrhea as the onset symptoms. Other manifestations were bronchiolitis obliterans, hypothyroidism, membranoproliferative glomerulonephritis, varicella zoster encephalitis and septic shock. The onset of symptoms ranged from 2 months to 9 years. Laboratory findings on initial evaluation by Clinical Immunology service were lymphopenia, hypogammaglobulinemia, elevated IgM levels and poor antibody response to polysacharides Laboratory tests excluded chronic granulomatous disease, CD40-ligand deficiency and AID deficiency. All four patients are currently on monthly IVIG replacement therapy, although some of them still present with recurrent episodes of upper airways infection or diarrhea. They underwent genetic sequencing and missense mutation in the PIK3CD gene (exon 24 /C.3061G > A) was found, this mutation leads to amino acid change (p.E1021K) in the C-lobe domain of the PI3 kinase p110-delta protein.
Discussion: These series of cases demonstrate the broad phenotypic spectrum of APDS, from recurrent sinopulmonary and viral infections to autoimmune manifestations. Therefore, correct diagnosis and proper treatment of these patients is challenging.

PO - 061

Autoimmunity and Lymphoproliferative Syndrome and Related Disorders in Two Centers in Argentina

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Introduction: Autoimmune lymphoproliferative syndrome (ALPS) and ALPS related disorders are characterized by lymphoproliferation and autoimmune cytopenias. Different genes are implicates, however in approximately 30 % of patients it is no possible to identify a gene defect.
Objective: To describe the diverse clinical presentation of 8 patients with ALPS or ALPS related disorders followed in two centers in Argentina.
Results: Retrospective analysis of 8 patients with lymphoproliferation, autoimmunity and infections. P1: Boy,13yo, thrombocytopenia and splenomegaly. Partial response to steroids. DNT 4,3 %. FAS mutation. Good outcome with mycophenolate mofetil (MMF). P2: Male, bacterial infections, at 8 years old splenomegaly that required splenectomy, abdominal adenomegalies and thrombocytopenia that improved with steroids. DNT14%. FAS mutation. P3: Girl, recurrent effusive otitis, at 2 years old presented splenomegaly, disseminated adenopathies and anemia. Severe hypogammaglobulinemia, soluble FAS ligand > 500 pg/ml, B12 vitamin 1520 ng/l, DNT 12 %, impaired apoptosis. FAS mutation. Good response to steroids and subcutaneous immunoglobulin (SCIG). P4: 3 month old girl with BCGitis, hepatosplenomegaly (HEM) and adquired CMV infection. With tuberculostatic and ganciclovir the infections improved but not the HEM and added anemia and thrombocytopenia. Hypergammaglobulinemia, T lymphopenia and normal DNT. Abnormal apoptosis. NRAS mutation. P5: Girl, 7 months, severe pancytopenia and HEM. Leukocytosis and hypergammaglobulinemia. Steroids, IV gammaglobulin (IVIG) and sirolimus. Died with severe bleedings. NRAS mutation. P6: Male, 19 years old, severe thrombocytopenia and cervical adenopaties. Good response to IVIG but relapsed after a few weeks. He received rituximab, sirolimus and MMF but always relapsed. In 2016 he started with weekly SCIG with good response. P7: Man, at 32 years old chronic enlargement of cervical lymph nodes, no infectious hepatitis and unspecific arthritis with positive ANA. Hidroxicloroquin and steroids. He developed unilateral amaurosis and a SNC biopsy revealed lymphocyte infiltrate in cavernous sinuses with elevated IgG4. DNT 5,8 %. Good response to sirolimus. P8: Boy 1yo, splenomegaly,

cervical adenomegalies and pancytopenia. With IV steroids anemia and thrombocytopenia improved but neutropenia remained. He received MMF, IVIG, and sirolimus but no response. Good resolution with rituximab. DNT in peripheral blood 12 % and in bone marrow 4,3 %. In the last 3 patients no mutation was found yet.
Conclusion: Patients with ALPS and ALPS related disorders present a very variable clinical picture, also the laboratory findings change during the evolution and sometimes not all diagnostic criteria are present at the beginning of the symptoms. We believe that with a high clinical suspicion it is essential to start treatment promptly and try to arrive to a molecular diagnosis.

PO - 062

A Novel Mutation of Chediak-Higash Syndrome

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Introduction: Chediak-Higashi syndrome (CHS) is a rare autosomal recessive immunodeficiency disease characterized by frequent infections, hypopigmentation, progressive neurologic deterioration and hemophagocytic lymphohistiocytosis (HLH), known as the accelerated phase.(1) This syndrome is a lysosomal storage disorder caused by mutations in the lysosomal trafficking regulator (LYST), which encodes the CHS1/LYST protein.(2)
Case Presentation: The aim of this study is to report a case of Chediak–Higashi syndrome in a 3 year-old girl born to consanguineous parents, who presented the accelerated phase of the disease. Despite the treatment of accelerated phase, the girl had no remission, and evaluated with death before undergoing to allogenic stem cell transplantation. A mutation at p.Glu3292Stop in LYST gene was detected with Next Generation Sequencing. This is a novel mutation that isn't described yet.
Discussion: CHS is a rare disease with a varied spectrum of clinical presentation and investigation findings. The prognosis of the accelerated phase is poor. HSCT is the only curative treatment for hematological and immunological disorders. We emphasize the need for early diagnosis on basis of characteristic clinical findings and diagnostic laboratory examinations, which leads to early transplantation before development of the accelerated phase.
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PO - 063

Vasculitis and Chronic *Salmonella* Infection in IL-12RB1 Deficiency: a Diagnostic and Therapeutic Challenge

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Introduction: Interleukin-12 receptorβ1 (IL-12Rβ1) deficiency is an autosomal recessive disorder that causes recurrent and severe disease by mycobacteria and *Salmonella*. Vasculitis has been reported as a manifestation of the disease.
Case 1: Eight year-old female, only child of non-consanguineous family, endogamic region. BCG vaccine at birth without abnormal reaction. Started at 18 months old with Henoch-Schönlein purpura. Three months later she had two episodes of lower gastrointestinal bleeding, angiography showed findings compatlble with polyarteritis nodosa. Prednisone and immunosuppressant were started. Intestinal salmonellosis with positive stool culture was documented and two years later sepsis due to *Salmonella enteritidis* group D. She was considered as a *Salmonella* carrier, receiving ciprofloxacin prophylaxis. Two months later had a cerebral abscess due to *Salmonella enteritidis.* The functional IL12 gamma IFN axis was abnormal, homozygous mutation in IL-12Rβ1gene, in exon 12 was found p.Arg486X/ p.Arg486X, both parents are carriers. Currently on therapy with interferon gamma and cotrimoxazole profilaxis and has remained clinically stable.
Case 2: A seven year-old female, non-consanguineous family, 3 healthy siblings. Started at 7 months old with axillary lymphadenitis after application of BCG vaccine and was treated with dicloxacillin and antituberculous drugs.. She was was hospitalized because of persistent fever, and the diagnosis of salmonellosis was made. Two months later she had Henoch Schönlein purpura. One month later had reactivation of salmonellosis, lymphadenitis and vasculitis. Cervical adenopathy positive for *Salmonella* and leukocytoclastic vasculitis in skin biopsy. Functional IL12 gamma IFN axis was abnormal, heterozygous mutation in IL-12Rβ1 gene was found. Despite treatment with imukin and ciprofloxacin, she relapsed on four occasions, cholecystectomy was performed. A month later she presented seizures and a MRI suggestive of vasculitis. Because of recurrence of *salmonella* sepsis, autoimmunity with hemolytic anemia and vasculitis with CNS involvement, was decided to add GGIV, hydroxychloroquine and steroids to treatment. Currently stable
Discussion: It is important to individualize treatment in patients with autoimmunity and susceptibility to infections. Our cases presented cutaneous and abdominal vasculitis with chronic and recurrent *salmonella* infection due to an underlying PID. A conservative approach in terms of immunosuppressant drugs and the regular use of IVIG is suggested.

PO - 064

Autoimmune Manifestations in a Group of Adult Patients with Primary Immunodeficiencies in Hospital Alejandro Posadas, Buenos Aires, Argentina

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Introduction: Primary immunodeficiencies are a group of inherited defects of the immune system with at least 300 diferent entities currently known. Patients with Primary immunodeficiencies can present with, or develop during the course of their life, a susceptibility to recurrent and chronic infection along with autoimmune, allergic, inflammatory, and/or proliferative disorders.
Objective: We aimed to determine the incidence of autoimmunity in primary immunodeficiencies in adult patients with active follow-up at the Hospital Alejandro Posadas, and compare our results with published studies.
Methods: We have screened 101 cases of Primary immunodeficiencies in adult patients diagnosed in our center and those who were transitioned from the pediatric immunology center, now in active tracking in Hospital Alejandro Posadas, searching for the occurrence of autoimmunity/ inflammation.

Results: We found one or more autoimmune disease in 35 of our 101 patients (34,6 %), with predominance of autoimmune cytopenia (12 patients, 34,28 %) and inflammatory bowel disease (12 patients, 34,28 %), followed by Hashimoto (5 patients 14,28 %), Systemic Lupus Erythematosus (4 patients, 11,4 %), autoimmune atrophic gastritis (4 patients, 11,4 %) autoimmune hepatitis (3 pacients, 8,5 %), lymphocytic interstitial pneumonia (3 patients, 8,5 %), rheumatoid arthritis (2 patients, 5,7 %), Vitiligo (2 patients, 5,7 %), nephritis (2 patients, 5,7 %), vasculitis (2 patients, 5,7 %) and thrombophilia, myasthenia gravis, type 1 diabetes, eosinophilic pneumonia (1 patient 2,8 % for each). In this review, 19 patients (54 %) were first diagnosed with an autoimmune disease. The greatest association with autoimmunity was found for common variable immunodeficiency patients.
Conclusions: Our results provide similar information to literature reports and confirm that autoimmune and inflammatory diseases are much more frequent in Primary Immunodefience patients than in the general population.

PO - 065

Autoimmune Lymphoproliferative Syndrome Case Report

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Introduction: Autoimmune lymphoproliferative syndrome (ALPS) is a rare inherited disorder of apoptosis, most commonly due to mutations in the FAS (TNFRSF6) gene. It presents massive enlargement of the lymphoid organs, autoimmune cytopenias and a predisposition to develop lymphoid malignancies.
Case report: We describe a case of a 7-year-old boy with splenomegaly, autoimmune haemolytic anemia and thrombocytopenia since first year of life and extend investigation - viral etiologies and hematological diseases and treatment with corticosteroids without improvement before the suspect of ALPS. He was referred to IMIP to investigate ALPS at 4-year-old and screening tests obtained elevated vitamin B12 (1932 pg/mL) and double-negative T cells circulating ($CD3^+TCR\alpha\beta^+CD4^-CD8^-$ 8,7 %). Mutation analyses for the ALPS-related genes (FAS, FASL, CASP10) c.586_596del:p.Q196X12 FAS gene. Established treatment with corticosterois and mycophenolate mofetil (MMF) but he remained treatment refractory significantly enlarged spleen, anemia and thrombocytopenia and sirolimus (rapamycin) was started in a dose of 2,5 mg/m^2. Evolved with reduction disease manifestations.
Discussion: ALPS is a rare disorder, but should be suspected and ruled out in children presenting with chronic and refractory cytopenias associated with nonmalignant lymphoproliferation. Management of ALPS varies significantly with patients requiring long-term immunosuppressive therapies. Mycophenolate mofetil and Sirolimus are the best-studied and most effective corticosteroid-therapy for ALPS. Here in, we describe a patient with better response to sirolimus versus MMF. Recent data supports sirolimus as effective therapy in patients with ALPS and relapsed/refractory autoimmune cytopenias.

PO - 066

Sideroblastic Anemia, Immunodeficiency, Fever and Developmental Delay (SIFD) Referred as Leukemia Cutis

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Introduction: The number of primary immuodeficiencies described has increased over the years counting more than 300. A new autoinflammatory disease has been recently described, that presentes with systemic inflammation in context of congenial sideroblastic anemia associated with B-cell immunodeficiency, periodic fevers and developmental delay, caused by mutations in TRNT1. This is the first report of SIFD presenting with skin lesions resembling leukemia cutis.
Case report: A 6 month old girl of a nonconsaguineous family, was referred with recurrent fever, most of the times unrelated to infection. She was a premature baby, 34 weeks, 2.140 g, with laryngomalacia. Intensive Care was necessary for 14 days due to respiratory distress. Extended neonatal screening was normal. Umbilical cord fall occurred after 20 days. Fever was reported after each vaccination. Local reaction was reported after each immunization. Cutaneous lesions were previously diagnosed as insect bite and skin biopsy was reported as leukemia cutis. The patient was referred to Oncology in order to exclude leukemia. The following infections were diagnosed: paniculitis, herpes stomatitis, tonsilitis, lobar pneumonia, viral tracheitis due to *Metapneumovirus*. Recurrent high fever episodes associated with anemia occurred in the first year and blood transfusion was done during acute episodes (3-6 months old). Severe failure to thrive and delay on neurological development was also present. No hearing loss was confirmed. Acute phase proteins were persistently elevated (CRP, Ferritin). Immunoglobulin levels were: IgG = 147 mg/dL, IgA = 14 mg/dL, IgM 24,2 mg/dL and CD19: 17.4 %. Molecular diagnosis was performed after whole exome sequencing (WES):*TRNT1 NM_182916 c.495_498del, p.F167Tfs*9*heterozygous mutation and *TRNT1 NM_182916 c.1246A > G, p.K416E* heterozygous mutation.
Discussion: We report a patient with severe anemia, recurrent fever, elevated inflammatory markers, hypogammaglobulinemia and developmental delay who had skin lesions and was first diagnosed with leukemia cutis. WES revealed compound heretozygous loss-of-function mutations in TRNT1 causing SIFD. This is the first report of a patient with SIFD in Latin America and points to the difficulty of making an early diagnosis in these patients.

PO - 067

Pyoderma Gangrenous in a Patient with Wiskott-Aldrich Syndrome

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Introduction: Wiskott- Aldrich syndrome (WAS) is an X-linked disorder caused by a mutation in the gene that encodes the Wiskott-Aldrich protein (WASp). Classical WAS is characterized by microthrombocytopenia, recurrent infections, extensive eczema and increasead susceptibility to autoimmunity and/or malignancy. Pyoderma gangrenous (PG) is an uncommon neutrophilic dermatosis that presents as an inflammatory and ulcerative disorder of the skin, with unclear reasons for the development of the inflammatory process. However, findings suggest that immune system dysregulation may contribute to PG. We report herein a case of aggressive PG in a patient with mutation in the WASp gene.
Case presentation: 8 year-old boy with a phenotypic diagnosis of classical WAS at the age of 4 presenting eczema and

thrombocytopenia. At 2 years of follow up, he developed painful large ulcerated violaceous skin lesions, whose histopathological skin biopsy was compatible with PG. Started prednisone and dapsone with unsatisfactory control. Persisted with new lesions and recurrent sterile subcutaneous abscess. Conducted pulse therapy with methylprednisolone wtih relative improvement, being indicated the use of anti-interleukin -1 with excellent clinical response. Genetic analysis revealed a mutation identified in the WAS gene - deletion causing a premature stop codon and the production of a truncated protein (Del AT - p.Ile238Trp fsX21).
Discussion: This report extends the clinical spectrum and highlights unusual manifestations (PG) in a patient with WAS and off-label indications for IL-1 blocking therapies as neutrophil-dominant skin disease such as in this patient.

PO - 068

Cytotoxic T Lymphocyte Antigen-4 (CTLA4) Haploinsufficiency with no Hypogammaglobulinemia: Case Report

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Background: CTLA4 molecule (CD152) plays an important role in the peripheral tolerance mechanism. Activation of T lymphocytes (LT) is given by means of two main signals: the binding between T cell receptor (TCR) and Major Histocompatibility Complex with the antigen and, the second, the interaction of CD28 molecule on LT's surface and molecules of B7 family (CD80 and CD86), expressed on the surface of antigen-presenting cells (APCs). Under certain conditions, APCs express CTL4 molecule that has higher affinity to CD28 than B7 molecules (CD86 and CD80). However, CTLA4 has an inhibitory action on LT, inducing its apoptosis. Mutation in CTLA4 leads to loss of function and lymphocyte infiltration in several organs. We report a patient with CTLA4 mutation and his clinical spectrum.
Case Report: EMA, 9 years old, caucasian, Santo André - SP, non consanguineous parents, presented failure to thrive and microcytic anemia since 9 months old. At 5 years old, he developed petequiae, bruising and jaundice with the diagnosis of Evans Syndrome. The patient evolved with diarrhea, intermittent arthralgia and recurrent mouth ulcers. At 8 years old, he presented severe dehydration, electrolytic disturb and seizures. The following year, he had pancreatitis and drug-induced hepatitis. Due to the intestinal manifestations, he was submitted to several studies and lymphocyte infiltration was reported in intestinal mucosa. The following therapies has been prescribed: blood transfusions at the begining of the symptoms, intravenous immunoglobulins, glúten free diet, mesalazin and azathyoprin, with no clinical improvement. Partial response was observed with corticosteroids regarding diarrhea but side effects as cushingoid face and fracture of lumbar vertebrae occurred. Considering clinical manifestations, gene sequencing for CTLA4 was performed and showed a heterozygous mutation c.443A > C leading to p.Q148P, a novel mutation that predict to be pathogenic.
Discussion: CTLA4 is a potent inhibitor of T -cell proliferation and its loss of function leads to lymphocyte infiltration as seen in intestinal tissue of our patient. B cell exhaustion was also reported associated with hypogammaglobulinemia and our patient did not develop antibody. We emphasize the phenotypic variability of CTLA4 mutation.

PO - 069

Hepatic Disease in Ataxia-Telangiectasia, Diagnosed In Institutonacional de Pediatría in Mexico City

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Introduction: Ataxia telangiectasia (AT) is a condition with great morbidity and with multisystemic expression[1]. The main features are neurological and immunological symptoms, although the digestive system involvement has been described, but the liver disease is almost anecdotal. Dysphagia, low weight gain have been documented, but reports of hepatic impairment are rare. We describe patients with diagnosis of AT in which the hepatic condition was documented, to know more about this association is important to obtain a timely treatment.
Objectives: To describe the clinical and biochemical characteristics of patients with AT and liver disease, from January 1997 to April 2017. As well as describing the histopathological results in patients with AT.
Results: We reviewed 177 records of patients diagnosed with Ataxia, using ICD-10: Ataxia, unspecified, Hereditary ataxia unspecified, Cerebellar ataxia with defective DNA repair, from January 1997 to April 2017. Of these, 30 met the operational definition of AT (17 %). The most frequent age at diagnosis was 2 years (33.3 %, with 10 cases), the least frequent age at diagnosis was of 11, 6 and 10 years, with one case for each (10 %). We found 12 men (40 %) and 18 women (60 %). Of the 33 records of patients diagnosed with AT, 6 patients had hepatic disease (20 %) of the 30 patients. In these patients were performed an evaluation to find the etiology of this feature. Autoimmune and infectious liver disease were rule out, we found negative autoimmunity markers like AntiLKM antibodies, smooth anti-tumor antibodies and neutrophil anti-cytoplasmic antibodies in the 6 patients. Hepatic biopsy was performed in one patient, with a report of moderate chronic hepatitis with mild portal fibrosis and liver steatosis. The adyuvant therapy in this patients were human immunoglobulin, ursodeoxycholic acid, omega – 3 fatty acid, without improvement of liver disease.
Conclusion: Liver disease is common in AT, it is possible, as reported[2], the progression of a steatohepatitis is rapid. Hepatic impairment should be evaluated, in all AT patients. Hepatic biopsy, is an option for a more specific diagnosis of liver disease, but we suggested that liver disease is a intrinsic feature of this primary immunodeficiency.
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PO - 070

Recurrent Infections and Chronic Inflammation: What Should we Suspect?

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Mevalonate kinase deficiency or hyper-IgD syndrome is a hereditary autoinflammatory syndrome caused by mutations in the mevalonate kinase gene
13-year-old boy, born to non-consanguineous parent and no family history of primary immunodeficiency. Admitted at 7 days of life because of bronquiolitis- pneumonia and severe anemia requiring antibiotics and red blood transfusion. After that he presented several neumonia episodes with recurrent obstructive component. Since 7 months of age had intermittent episodes of bloody diarrhea and abdominal pain without microbiological findings. At 9 months of age had viral meningitis and anemia. At 10 month of age was admitted because prolonged fever, leukocytosis, cervical adenitis, bronchitis and anemia. At 17 month of age was re admitted because of fever, conjunctivitis, exantema, chronic anemia, failure to drive and poliadenopathies and hepatoesplenomegalia were found at physical examination.
Impetiginized chickenpox was observed at 3 years old.
He continued with, enlarged generalized adenopathy and hepatosplenomegaly observed by CT Scan. Malignancies were ruled out in several times. Plastic peritonitis was observed by surgery and reactive hyperplasia folicular in cervical and abdominal lymph node. Displasic red blood cells and hemophagocitosis were findings on bone marrow aspiration. Given past medical history of developmental delay, short stature and dysmorphic features (coarse fascies) mucopolysaccharides were ruled out.
At 12 years of age presented a Streptococcal sepsis with mild right pleural effusion required IUC, during the antibiotic treatment and improvement of illness presented fever, adenitis, pharyngitis autolimited.
Laboratory investigations revealed white blood cells, CRP and ESR were strongly elevated despite improvement of febrile episode. Autoinmunity and viral cause were ruled out.
Immunological test showed policlonal hipergammaglobulinemia and mild T-B-NK Lymphopenia, expanded total double negative cells,high levels of HLA DR -CD3 and low memory and post switched B cells were found Normal antigen response as well as B12 vitamin levels were detected. Homozygous variant on MVK c709A > T p T237S by NGS was found and confirmed by Sanger technique
He begun with Anti-IL 1 treatment (Canakinumab) a year ago with very good response.
Recurrent infections is not common situation in autoinflammatory síndrome and next generation sequencing is an importat diagnostic tool in this very complex presentation

PO - 071

Hypertrophic Osteoarthritis and Liver Disease in APDS Patient – Case Report

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Introduction: Hypertrophic osteoarthritis (HOA) is characterized by polyarthritis with digital clubbing and periosteal reaction. The secondary form is commonly associated with pulmonary diseases but has been also described in other conditions including cholestatic liver diseases.
Case Report: Here we describe a 9 year-old boy with gain of function mutation (GOF) in p110 delta catalytic subunit of the PIK3CD (APDS) in whom E1021K mutation was identified. Besides some common clinical manifestations described in this syndrome, he also presented, at the age of 5, primary sclerosing cholangitis. He doesn't have pulmonary compromise. At the age 7, he presented what we thought to be polyarthritis of the ankles, wrists and interphalangeal joints. A treatment with low dose of prednisone (1 mg/kg/day) was started with a satisfactory outcome, but the symptoms relapsed when corticotherapy was discontinued. No response to IVIG in immunomodulatory doses. He also presented with digital clubbing on the hands and foot. A course of anti-TNF alpha was tried, but fails. The X-ray of the bone revealed periosteal reaction and the diagnosis of hypertrophic osteoarthritis was made.
Discussion: Here we described a young boy with E1021K mutation with gain of function in p110 delta catalytic subunit of the PIK3CD (APDS). Regarding to his clinical presentation, as described in the literature he presents with respiratory recurrent infections and lymphoproliferation. During the progression of the disease he developed an important digital clubbing. This sign is frequently associated with pulmonary or cardiac disease, but different from the majority of the cases with APDS, our patient didn't have a progressive or important pulmonary disease. Otherwise, an association of polyarthritis with digital clubbing and periosteal reaction occurs in hypertrophic osteoarthritis (HOA), a condition that can be primary or secondary. Regarding the last one, it is commonly associated with pulmonary diseases but has been also described in other conditions including cholestatic liver diseases. In our patient, the hypertrophic osteoarthritis seems to be related with hepatic disease. Although no case of hypertrophic osteoarthritis has been reported in a child with APDS before, this condition should be reminded in those patients with polyarthritis, digital clubbing and lung or hepatic diseases.

PO - 072

Impaired Net Formation in CD40L-Deficient Patients

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Introduction: Neutrophils are the most abundant cell type in human circulation and are the first line of defense against pathogens at sites of infection. Recent studies have shown that neutrophil extracellular traps (NETs) form an extracellular structure able to neutralize virulence factors and destroy microorganisms. Patients with X-linked Hyper-IgM syndrome (X-HIGM), a rare immunodeficiency caused by mutations in the gene encoding the molecule CD40 ligand (CD40L), are highly susceptible to infections with elevated incidence of opportunistic infections caused by fungi.
Objectives: Since neutrophil responses are important to control fungal infection and studies indicate the influence of the CD40-CD40L interaction on granulopoiesis, we proposed to investigate whether the increased susceptibility to infections in CD40Ldeficient patients could be related to failure in NET formation.
Results: NET formation against PMA stimulus was decreased in CD40L-deficient patients compared to healthy subjects. ROS generation against PMA was similar between the investigated groups, although CD40L-deficient patients were not able to increase the production of ROS after treatment with IFN-γ as observed on healthy individuals. Evaluation of neutrophils' maturation stage indicates the presence of immature peripheral neutrophils in CD40Ldeficient patients.
Conclusion: The results indicate that CD40L-deficient patients present a failure in NET generation in response to PMA, likely related to incomplete neutrophil maturation. This study contributes to expand the knowledge on the immunopathology of CD40L deficiency and contributes to elucidate the mechanisms involved in increased susceptibility to infections in CD40L-deficient patients. In addition, our findings bring new perspectives for the understanding of CD40-CD40L interaction and its function in the immune response.
Keywords: Neutrophils. NETs. X-HIGM. CD40L deficiency.

PO - 073

IFNγ Induced STAT1 Phosphorilation (P-STAT1) and TH17 Cells in Patients Evaluated for STAT1 Mutation: Analysis of Their Value as Screening Tests

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Introduction: Autosomal dominant Stat1 mutations with Gain of function (STAT1 GOF) have been established as a cause of Chronic Mucocutaneous Candidiasis. Laboratory studies that facilitate both the recognition of these defects and the evaluation of the protein function, in candidate patients, included the degree of phosphorilation (p) of STAT1 proteins after IFNγ and/or IFNα stimulation and % of TH17.
Objective: To present the results of IFNγ induced p-STAT1 functional assays measured by flow cytometry in 10 patients (Pts) with confirmed heterozygous mutation in STAT1 (mut-STAT1) and 7 Pts studied for STAT1 defects but without mutations (non-STAT1) as well as percentages of Th17 cells in order to evaluate the value of this parameters for the mutational analysis orientation.
Results: Among mut-STAT1 Pts, 6 showed higher levels of IFNg induced p-STAT1 on monocytes measured as mean fluorescence intensity (MFI) compared with normal controls (NC) (mean( )MFI:238 r:147-313 vs108 r:76-183) while 2 had slightly augmented (MFI:141 r:88-194 vs130 r:76-184) and 1 were similarly phosphorilated (MFI:159 vs 158). One Pt had less % of phosphorilation than NC (65 vs 98 %) indicating a defective function of STAT1. In 8 Pts with augmented levels of p-STAT1, the increased was related to higher levels of STAT1 protein than NC (MFI: 746 vs 348). p-Stat1 levels were normalized calculating the ratio between p-STAT1 MFI and SAT1 MFI. Considering this ratio, only in two Pts the p-STAT1 levels remains higher then NC while in 4 were lower and in 3 similar. In 7 Pts without confirmed mutation in STAT1 the increased in p-STAT1 was also observed (MFI:224 r:154-283 vs 170 r:117-230) and had the same link with STAT1 levels. Regarding Th17, in 9 mut-STAT1 Pts had lower % (% :0.25 r:0.01-0.57) compared with non-STAT1 (% :0.6 r:0.1-1.2) and NC (% :0.64 r:0.25-1.03).
Conclusion: IFNγ induced p-STAT1 level should be interpreted considering the amount of STAT1 protein and the ratio between both. Considering that higher levels of p-STAT1 in mut-STAT1 pts were also observed in pts without mutation, the value of this test for defining a possible STAT1GOF is limited at least under our assay conditions. % of Th17 was low in all mut-STAT1 Pts and its evaluation in combination with the levels of p-STAT1 might improve the selection of candidate patients for *STAT1* gene analysis.

PO - 074

Primary Immunodeficiency Casuistic in a Low Complexity Care Pediatric Hospital

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Introduction: The Primary Immunodeficiencies are a heterogeneous group of more than 200 diseases caused by genetic defects of one or more components of the immune system. As a consequence of these defects, patients with primary immunodeficiency have a higher susceptibility to infections, caused by virus, bacteria, fungus, or protozoan, with variable severities (1), besides of immune disregulation, auto-immunity, aberrant inflammatory response, and malignity. Early diagnosis enables, in some cases, specific treatment, decreasing mortality and morbidity, and providing an improvement in the quality of life of patients and their families.
Objectives: Document the incidence of Primary Immunodeficiency and report its cases at the Hospital Municipal da Criança e do Adolescente de Guarulhos (HMCA) and its clinical presentation, in São Paulo, Brazil – a low complexity care hospital and a municipal pediatric specialty clinic – during the period from September of 2016 to April of 2017, when the Allergy and Immunology clinic started consultation. With the report of these cases we would like to alert pediatricians about the need for a great clarification regarding the warning signs of Primary Immunodeficiencies, since the majority of the cases are followed up by general pediatricians who should be able to carry out an initial investigation.
Results: The HMCA is the only pediatric public hospital of the Guarulhos city – São Paulo operating on free demand nowadays. The number of daily consults at the Emergency Department is, in average, 350 children and adolescents. Five percent of them are admitted to the hospital as inpatients. The pediatric population consulted during the study period was of 1,671 admitted patients (786 girls and 885 boys), and 267 patients from the specialty clinic (142 girls and 125 boys). The team diagnosed 5 cases of Primary Immunodeficiency, 3 males and 2 females, age ranging from 1 to 18 months. One of them had the diagnosis of Severe Combined Immunodeficiency, and the other 4, transient hypogammaglobulinemia of infancy.
Discussion: The Primary Immunodeficiency incidence varies in different countries, due to the different conditions of access to health services. There is no reliable data about the incidence of Primary Immunodeficiency in Brazil. The data collection could improve with the implementation of specific neonatal screening, which includes T-cell Receptor Excision Circles (TREC) and Kappa deleting Recombination Excision Circles (KREC), associated with the clinical suspicion in the pediatric practice. It would decrease the number of complications and consequent admissions, apart from sequels and early death. The trained pediatrician is a gear capable of connecting clinical suspicion to a complex diagnosis, thereby determining a change in the natural history of a patient, who will have the certainty of a specialized follow up and even a change in his life expectancy.

PO - 76

Chronic Mucocutaneous Candidiasis. About a Case

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Introduction: Chronic mucocutaneous candidiasis (CMC) is a rare heterogeneous primary immunodeficiency; with an incidence of 1/10,000 live births, characterized by an ineffective response to Candida infection[1]. The clinical presentation is limited to the skin, mucous membranes and nails, sometimes other organs; is associated with auto immunities and endocrinopathies. Several immunological defects were detected in IL-17 and its receptors, mutations in the signal transducer factor and transcription activator (STAT1) and defects in the IL-12 interferon gamma[2]
Clinical Case: Male of 13 years of age, non-consanguineous parents, paternal uncle died at the 6 years due to infections. It is a product of 5th pregnancy, at the 3rd month of gestation the mother presented pharmacodermia by Penicillin, was born by eutocic birth, weight 3200gr, received exclusive breastfeeding for 6 months; From 6 months of life I present mucosal mycosis receiving treatment with Nystatin in multiple opportunities (every month); From the age of 3 years has white scaly plaques on the head, chest and alterations in nails, since the age of 5 years receives treatment with Griseofulvin. Complementary tests: metabolic

defect in neutrophil function (NBT test), decrease in CD4-CD8. Molecular study with direct sequencing of the coding region of the STAT1 gene, reports R274W mutation in heterozygous state. Currently the patient receives transfer factor and presents improvement of mycotic lesions.
Discussion: The management of patients with CMC is multidisciplinary and is based on the treatment of infectious diseases secondary to immunological deficit; one the options for the treatment of CMC is the transfer factor or dialyzable leukocyte extract with which clinical improvement of the patients was reported, as in the presented case.
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PO - 077

The First Documented Case of MSMD in El Salvador

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Introduction: In the recent years, the field of PID has grown thanks to the development of the genetics. One of these new PID is the Mendelian Susceptibility to Micobacterial Infections (MSMD) a group of genetics problems in the IL-12/IFN-gamma axis that include mutations in the receptors/intracellular mediators for both citokines. (Fig. 1) A specific group of MSMD, the IL-12Rß1 deficiency is an emergent diagnosis in patients with Mycobacterial Infections with non-satisfactory evolutions. To 2011 about 200 families in all the world had been identified as carriers.
Case report: A one year old male was admitted to our hospital with clinical history of fever, failure to thrive and an axillar mass. He received a usual, a BCG dose at birth. A excisional biopsy was performed with an initial diagnosis of Histiocytosis. However, the CT scan of thorax and abdomen revealed multiples ganglionar masses. The AFB testing was positive from gastric samples (gastric aspirate procedure) and the diagnosis of Mycobacterial infection was consistent. An initial course of Isoniazide, Rifampicine, Pirazinamide and Etambutol for 9 months was instead. In the evolution colonies of M. bovis was isolated and the bacilloscopy remain positives beyond the end of the initial treatment. A second course of treatment was initiated on the next two months, this time adding Streptomicine with poor results after a year. The case was aborded by the National Program of Tuberculosis and the PCR study revealed Mycobacterium bovis with high susceptibility to first and second grade drugs (Fig 2). The new strategy include Isoniazide, Rifampicine, Etambutol, Amikacine, Ofloxacine and Etionamide; but a PID was suspected and an immunologic abordage was solicited. Initially the Immunoglobulins and the Citometry for linfocitic subpopulations didn´t revealed any abnormality. The case was presented to the experts of INSERM and blood samples of the patient and his family were analized to indentify any IL-12/IFN-γ axis defect. The exome-sequencing technique revealed a specific mutation in the exome 3 that codifies to ß-chain of IL12-R (Fig. 3) and the immunologic implication is a non-functional receptor. The recommendation of INSERM team was the application of IFN-γ scheme to improve the clinical results, however this drug is not available in El Salvador and finally the patient was deceased
Discusion: Patients with IL-12 receptor beta-chain defects have increased susceptibility to mycobacterial infections and in addition to Salmonella and some fungi (Candida principally) and should receive as part of their exogenous IFN-γ (Imukin®) treatment to control Their infections. This was the first documented case of this disease in El Salvador, but new patients are being approached under the same suspicion. The presence of unusually difficult mycobacterial infections to treat despite good bacterial susceptibility to first-degree drugs should alert the medical team to the likelihood of this new nosological entity.

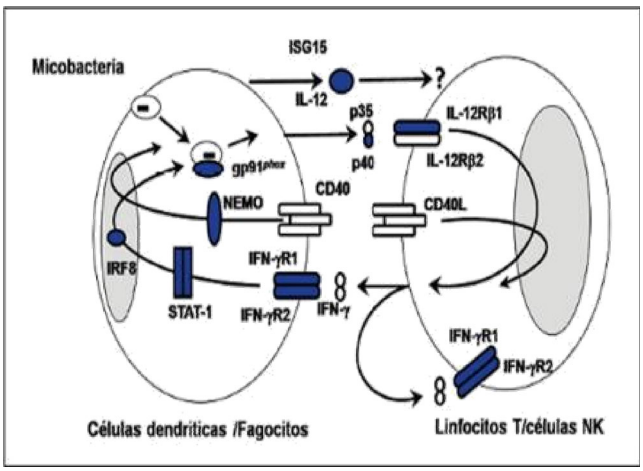

FIG. 1 The sites of all possible defects in MSMD


Edad: 1 año
Aislado No. 568027
Médico Responsable: Sin información
Fecha de recepción de la cepa: 18 de Octubre de 2012
Fecha de emisión final de resultado: 19 de Diciembre de 2012

RESULTADOS*

Identificado por PCR como *M. bovis*
Pruebas de sensibilidad:

FÁRMACO DE PRIMERA LÍNEA: Método BACTEC MGIT-960

Fármaco	Resultado	Concentración µg/mL
Estreptomicina	S	1.0
Isoniazida	S	0.1
Rifampicina	S	1.0
Etambutol	S	5.0
Pirazinamida	R	100.0

Interpretación
S: Susceptible
R: Resistente

Este resultado se refiere únicamente a la muestra recibida
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FÁRMACO DE SEGUNDA LÍNEA: Método de las proporciones en medio Middlebrook 7H10 enriquecido con OADC al 10%

Fármaco	Resultado	Concentración µg/mL
INH alta	S	≤ 1.0
INH baja	S	≤ 0.2
Rifampicina	S	≤ 1.0
Amikacina	S	≤ 4.0
Kanamicina	S	≤ 5.0
Capreomicina	S	≤ 10.0
Ofloxacina	S	≤ 2.0
Levofloxacina	S	≤ 1.0
Etionamida	S	≤ 5.0

* Los resultados de las pruebas de susceptibilidad en el laboratorio son sólo sugerentes de lo que pasa realmente in vivo

FIG 2. The results of PCR that revealed M. bovis in the patient

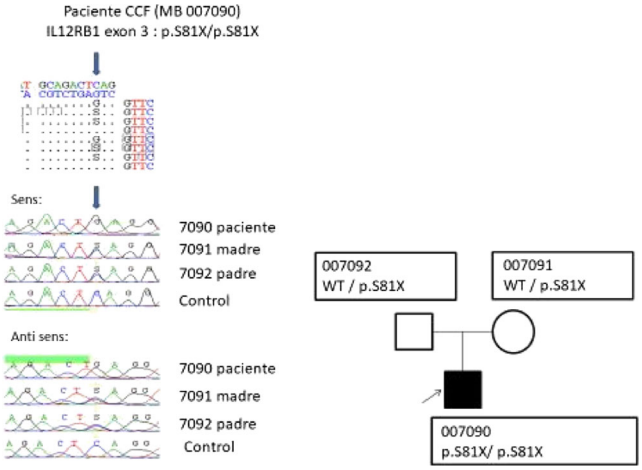

FIG. 3 The exome sequencing revealed the recesive autosomic defect of IL12RB1 exon 3 (S81X/S81X)

PO - 078

Clinical, Laboratory and Genetic Finds in Patients with Chronic Granulomatous Disease

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Introduction: Chronic Granulomatous Disease (CGD) is a primary immunodeficiency which is product of defect in nicotine adenine dinucleotide phosphate oxidase complex. It is characterized by recurrent bacterial and fungal infections.
Case presentation: Three case reports of CGD are described; two are young-adults sisters, whose parents are second cousins. Recurrent furunculosis was the first symptom observed in the oldest sister at age of 8 months(m) and lymphadenomegaly in the other at 3 m. Both presented intermittent dermatological infections. The oldest sister (case 1), diagnosed at 14y, had hepatic-pulmonary abscesses, corneal ulcer and tuberculosis, whilst the youngest one (case 2), diagnosed at 12y, presented more dermatological manifestations, and pneumonia (PMN). The last case is a 10-year-old male with no history of consanguinity. He started with prolonged fever due to pulmonary infection at 8-month-old, being diagnosed with CGD at 2y10m. He presented two severe episodes of PNM; other manifestations were pustules and fever. All patients are currently using prophylactic antibiotics and antifungals. Laboratory findings were superoxide anion: spontaneous mononuclear 1,170 / PMA 0.275 for the case 1 and 0.05 / PMA 0.65 for case 3; the dihydrorhodamine test: neutrophils 43.93 / PMA 43.95 for the case 2. Mutation (c. 87 88del.GT/ p.V25fsX51) on exon 2 of the gene NCF1 was identified in sister's cases. In third case, the sequencing of the CYBB gene detected the C537R mutation (exon 13).
Conclusion: There are clinical and genetic heterogeneity presented in CGD as demonstrated by the studied cases, with similar cutaneous and pulmonary affections, however with different severities.

PO - 079

Severe Infection by *Candida sp* and *Mycobacterium Tuberculosis* in a Patient with Functional Alteration of Signal Transducer and Activator of Transcription (STAT1)

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Introduction: Germline mutations of the STAT1 gene underlies susceptibility to 3 types of infectious diseases: Mendelian susceptibility to mycobacterial diseases (MSMD), Chronic Mucocutaneous Candidiasis (CMC) and Viral Infections. Gain-of-Function (GOF) mutations are associated with CMC through upregulation of cytokines that inhibit IL-17. Loss-of-Function (LOF) mutations are associated with MSMD through alterations in the cellular response to Interferon gamma (IFNγ).
Case presentation: Female of 34 years old with familiar history of consanguinity, 2 sisters with hypothyroidism and one of them with cerebral tumor. She started at 9 months of age with oral, cutaneous and genital candidiasis, oral herpes, onychomycosis, sinusitis and otitis media; all of these were severe and recurrent. She has presented autoimmune manifestations as vitiligo, hemolytic anemia and antiphospholipid syndrome. No clinical manifestations of endocrinopathology. Laboratory: Skin culture: *Rhodotorula rubra, Trichosporon beigelii, Cryptococcus uniguttulatus, Candida sp.* IgG 2560 mg / dl, IgA 291 mg / dl, IgM 167 mg / dl, IgE 18 IU / ml, IgG1: 1400 ng / 100 ul, IgG2 293 ng / 100 ul, IgG3: 120 ng / 100 ul, IgG4:6.9 ng/100 ul, CD4 456 cell / ul, CD8 264 cell / ul, CD19 68 cel / ul, C3 129 mg / dl, C4 15 mg / dl. In 2011, determination of STAT 1 mutation was performed with gain of the function (genotype WT / T288A). On January of 2017 she presented intestinal perforation secondary to mesenteric abscess in terminal ileum that required right hemicolectomy, with histopathological report of chronic lymphadenitis with granulomas and caseous necrosis and positive Ziehl Nielsen for Mycobacteria. In addition, positive blood PCR was determined for Ebstein Bar Virus and received acyclovir. At the momento, she continuous with voriconazole, isoniazid, pyrazinamicide, rifampicin and ethambutol.
Discussion: Chronic mucocutaneous candidiasis is an entity in which multiple associations should be researched such as autoimmunity, endocrine diseases and other infectious processes. STAT1 is a transcription factor of the Interferon alpha, beta and gamma receptors, it is necessary to discard other infectious processes such as intracellular bacteria and viruses. As we know our patient has a genetic defect on STAT 1, we can provide close monitoring, detection of complications and proper management. The relevance of this case is that only 6 % of patients who have CMC by GOF present mycobacterial infections, which makes it a challenge to establish the complete functionality of STAT1 in the immune response.

PO - 080

Correlation Between Gene Mutation and Neutrophil Functional Phenotype to Define Molecular Analysis of Patient with Unknown Mutation

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Introduction: Neutrophils are key cells in host defense. Some Primary Immunodeficiencies (PID) patients present mutations that directly affect

effector mechanisms of these cells, such as NADPH oxidase system genes. However, mutations in proteins involved with cell migration or cytokine signaling can also impair neutrophil response.
Objectives: The aim of this study is to evaluate function of neutrophils from PID patients with different mutations and the correlation between neutrophil response pattern and genetic variations.
Results: We analyzed complete blood cont (CBC), immunoglobulin levels and neutrophil function from healthy donors (n = 10) and four PID patients: p1, patient with CYBB mutation (Chronic Granulomatous Disease, CGD); p2, patient with mutation in Interferon gamma receptor 1 gene; p3, patient with mutation in CD18 gene; and p4, patient with unknown mutation. All patients had normal CBC numbers and immunoglobulin levels and, as main manifestation, severe and/or persistent *C. albicans* infections. For oxidative burst by DHR assay, all patients responded to PMA (90nM), excepted DGC patient. However, when stimulated with *C. albicans* (2: 1), neutrophils from all patients presented failures in H2O2 production. In relation to phagocytosis to Zymosan (10:1) and *C. albicans* (2:1), evaluated by phase contrast microscopy, p2 and p3 showed a decrease in phagocytic potential. However, neutrophils from all patients failed to eliminate C. albicans (2: 1). Regarding NETosis, evaluated by fluorescence microscopy, patients presented different levels of failure when stimulated with PMA (150nM) or *C. albinas* (2:1). DGC patient and p4 produced less than 25 % NETs when compared to healthy controls. P2 presented less than 30 % NETs compared to the controls, whereas p4 generated NETs in the presence of PMA, but this potential was reduced (65.5 % of the controls) in presence of *C. albicans*. We did not find correlation between these data and white blood cell count or Igs levels. However, correlations between functional data from p1, p2 and p3 neutrophils enabled us to suggest signaling failures in *C. albicans*-dependent NETosis, which will be confirmed through molecular biology.
Conclusion: Our results allowed an initial correlation between neutrophils function and possible genetic alterations for a patient with unknown mutation. Increasing sample number and including new data (mutations, phenotypes) we will be able to propose a prediction model to facilitate the diagnosis of PID patients and reduces costs with inadequate laboratorial tests.

PO - 081

MCM10 is Required for Human NK Cell Maturation and Homeostasis

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Introduction: Human natural killer (NK) cells play a critical role in the control of viral infection and malignancy. The importance of NK cells is underscored by cases of isolated NK cell deficiency that arise from monogenic causes of impaired NK cell terminal maturation. Mature human NK cells in peripheral blood are characterized as $CD56^{bright}$ and $CD56^{dim}$, with each subset possessing unique phenotypic and functional properties. These subsets likely represent discrete stages of differentiation, with the $CD56^{bright}$ subset thought to be the direct precursor of the $CD56^{dim}$ subset. As such, requirements for NK cell development can be informed by monogenic disorders that lead to impaired maturation as reflected by aberrant representation of peripheral blood NK cell subsets. Using whole-exome sequencing, we have identified deleterious compound heterozygous mutations in minichromosome maintenance complex 10 (*MCM10*) in a boy with fatal susceptibility to cytomegalovirus. As with previously described mutations in the eukaryotic DNA helicase complex members *GINS1* and *MCM4,* the frequency of NK cells in the patient with *MCM10* mutations was greatly reduced and peripheral blood NK cells were primarily of the immature, $CD56^{bright}$ subset.
Objectives: We sought to define the requirement for MCM10 in human NK cell development and homeostasis.
Results: Using CRISPR-Cas9, we modeled hypomorphic *MCM10* mutation in a human NK cell line. This led to decreased proliferation and cell cycle arrest, chromosome segregation defects, and increased induction of DNA damage repair pathways. To specifically address the role of MCM10 in NK cell development, we performed CRISP-Cas9 gene editing of MCM10 in healthy donor $CD34^{+}$ hematopoietic stem cells. MCM10-deficient NK cells had impaired terminal maturation following in vitro differentiation from CD34+ HSC compared to mock-edited controls.
Conclusion: Our results define MCM10 deficiency as a novel NKD and demonstrate a critical role for MCM10 in human NK cell homeostasis and maturation.

PO - 082

Bloch Sulzberger Syndrome and IKBKG Gene Mutation

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Case Presentation: A 2 year old female patient, non-consanguineous parents, was referred to evaluate imune response due to recurrent furunculosis (> 100 lesions in the last year). At 2 days of life, bullous lesions developed that evolved to warts. Pyodermitis was treated with antibiotics. At 2 months of age, she was treated with topical corticosteroid and at 6 months of age, the lesions improved. After the eruption of conical teeth, genetic studies were performed. Molecular study revealed mutation of the IKBKG / NEMO gene with deletion of exons 4-10, with the diagnosis of Pigmentary Incontinence (Bloch Sulzberger Syndrome).
Discussion: Pigmentary Incontinence (PI or Bloch Sulzberger Syndrome) is a rare hereditary multisystemic genodermatosis of dominant X-linked character, usually lethal in males. It affects the skin in all patients, but also other ectodermal tissues comprising teeth, hair and nails, eyes and central nervous system (CNS). The severity of the disease is related to neurological and / or ocular insufficiency. PI is caused by mutation of the IKBKG / NEMO gene in Xq28. The exclusion of exons 4 to10 accounts for about

80 % of cases (familial and sporadic). This gene encodes for the NF-kB pathway, involved in many fundamental physiological and pathological functions, including cell survival. It is important to remember the immune impairment associated with this broad mutation.
Comment: Although it is uncommon, the pigmentary incontinence should be remembered among the differential diagnoses of vesicle and verrucous lesions in childhood, mainly due to the immunodeficiencies that may be associated with the possibility of poor prognosis related to neuropathological involvement.

PO - 083

X-Linked SCID: Diagnosis can be Early

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Introduction: Primary immunodeficiencies (PIDs) affect the development and/or function of the immune system, are rare diseases, but it is a major health problem occurring frequently comparable to leukemia. SCID is one of them and considered a pediatric emergency. Transplantation of hematopoietic stem cells is curative, provided the diagnosis is made early. The present case report aims at alerting the importance of the knowledge of these cases, through the implantation of the diagnostic tests as soon as possible in the life of the child, in order to obtain a favorable outcome for these patients.
Case presentation: Boy, 3 months old, with family history suggestive of primary immunodeficiency, received vaccination for BCG, hepatitis B virus and Polio, without any reactions at the time. He was admitted for immunological screening and performed following exams: T-lymphocytes, immunoglobulins, TREC and KREC and serologies for HIV and CMV. Values below p10 and p3 were present for all lymphocytes and immunoglobulins, respectively, absent TREC and non-reactive serologies, confirming the diagnosis of severe combined immunodeficiency (SCID). During hospitalization, he developed reactions to BCG vaccine, it was introduced Isoniazid - treatment dose. He was followed up on an outpatient basis, enrolled in National registry of bone marrow receptors and accepted for gene therapy at St. Jude Hospital - USA, where he is currently awaiting treatment.
Discussion: SCID is the most serious PID, leading to profound deficiency in cellular and humoral immune functions. At birth these patients are healthy but are susceptible to serious infections caused by common agents or live attenuated vaccines and, when left untreated, they die. Despite the curative treatment of the disease, late diagnosis makes it impossible to perform. The quantification of TREC and KREC molecules has been implemented in several countries in Europe and the USA, allowing these children to be diagnosed soon after birth and the necessary interventions performed early. Currently, the University Hospital of Taubaté (HUT) is part of the hospitals that incorporated these techniques with new borns. This is an attempt to prove the existence of these cases and to reinforce the importance of implanting these exams throughout the country.
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PO - 084

The Use of the Lysate of Mycobacterial (LM) and Purified Protein (PPD) to the Diagnosis of Patients with Mendelian Susceptibility to Mycobacterial Disease (MSMD)

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Introduction: Patients with primary immunodeficiency (PID) have an increased susceptibility to mycobacterial infections. The elimination of this infection depends mainly on the success of the interaction between macrophages and infected T lymphocytes. Patients with Mendelian Susceptibility to Mycobacterial Disease (MSMD) present severe and recurrent infections due to impaired signaling on the IFN-γ/IL-12 axis. In these patients, BCG vaccines and non-tuberculous environmental mycobacteria can cause severe disease. At moment, mutations in five genes have been described that lead to MSMD; among them IFNGR1 and IFNGR2, which encodes the two chains of the IFN-γ receptor; STAT1, a transcription factor; IL12B, which encodes the p40 subunit of IL-12; and IL12RB1, which encodes the IL-12 receptor β 1 chain expressed in NK and T cells and the IRF8 gene.
Objectives: Our aim was evaluated the IFN-γ/IL-12 axis of patients with clinical history suggestive of MSMD using mycobacteria lysate (LM) and purified protein (PPD) by ELISA assay.
Results: In 2016, 43 samples of patients with a clinical history suggestive of MSMD arrived in our laboratory, 6 of them presented alterations of the IL-12/IFN axis when compare with healthy controls. The age of the diagnosis of male patients ranged from 2 to 16 years. The only two female patients diagnosed were 36 and 40 years old. The clinical history was heterogeneous: 4 had lymph node hyperplasia, 2 pneumonia, 1 colitis, 1 *Herpes zoster*; another had a urinary tract infection and 1 BCGitis. The pathogens isolated were the *M. tuberculosis*, *M. abscessus*, *M. gordonae*, *M. genavense* and *M. konsossi* species found in 5 different patients. Statistical analysis of the IFN-γ/IL-12 axis evaluation was shown to be

significant in IFN dosing with LM and LM + IL-12 ($p < 0.0012$) as with PPD and PPD + IL-12 ($p < 0.010$). In the IL-12 dosage the results of samples with LM and PPD did not show statistical significance. The statistical difference was observed in the samples with interferon gamma; LM + IFN ($p < 0.010$) and PPD + IFN ($p < 0.020$). The genetic diagnosis will be performed.
Conclusion: The evaluation of the IL-12/IFN axis with LM and PPD allowed the diagnosis of 6 patients with MSMD.

PO - 085

G-CSF Therapy in a Child with Autosomal Dominant Chronic Mucocutaneous Candidiasis (AD-CMC) and Auto-immune Hepatitis Caused by STAT-1 Gain-of-Function (GOF) Mutation

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Introduction: AD-CMC caused by GOF mutation in STAT1 is a rare and severe primary immunodeficiency that is characterized by fungal mucocutaneous infection, autoimmune phenomena, and oropharyngeal and esophageal cancer in some patients (1).GOF mutations in STAT1 with increased production of IFN-g and impaired IL-17 immunity were found in most patients with AD-CMC (2). Evidence showed that G-CSF treatment improved clinical symptoms and partially restored the underlying Th17 defect in a patient with AD -CMC, suggesting G- CSF as valid immunotherapy in this deficiency. However there are controversies in the literature (3, 4).
Case Presentation: Considering the importance as a potential therapeutic advance, we evaluated the effect of G -CSF treatment in a 5 year-old girl with AD-CMC caused by STAT1 GOF mutation associated with autoimmune hepatitis. Despite use of Filgrastim 5mcg/kg twice weekly subcutaneously, the patient did not improve of fungal mucocutaneous infection. Measurements of the Candida-specific Th17 response both before and after treatment for 6 months, demonstrated reduced production of IL-17 by mononuclear cells. The patient was receiving Cysclosporine 3 mg/kg/day for autoimmune hepatitis during the therapy with G-CSF.
Discussion: In our patient with AD-CMC GOF STAT1 mutation, we could not confirm the beneficial effects of G-CSF. Maybe this lack of effect can be due to the immunosuppression caused by Cyclosporine.
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PO - 086

Serratia Marcescens Osteomyelitis as a Clinical Presentation of Chronic Granulomatous Disease

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Chronic granulomatous disease is a rare, primary immunodeficiency disorder characterized by a defect in oxidative metabolism in phagocytes and recurrent bacterial and fungal infections. We report a case in a 1- years-old children admitted with osteomyelitis due to Serratia marcescens. After 4 months in the second hospitalization There is evidence of positive CPR for Mycobacterium spp. non tuberculous CSF. CGD is characterized by severe and recurrent infections typically involve the lung (pneumonia), lymph nodes (lymphadenitis), liver (abscess), bone (osteomyelitis), and skin (abscesses or cellulitis); granulomas typically involve the genitourinary system (bladder) and gastrointestinal tract. Major advances have occurred in the diagnosis and treatment of this disease, with the potential for gene therapy or stem cell transplantation looming on the horizon. Then the diagnosis early and suspicious of primary immunodeficiency is important to improve the prognosis.
Case presentation: Male patient of 1 years with a prenatal history: 5 controls, no complications. Natales: delivery eutocico, gestational age: 39 weeks weight birth: 3240. Apgar 9-9. Postnatal: Exclusive breastfeeding up to 5 months. No previous hospitalizations. Patient presents fever and increase of volume of the left foot reason for which goes to the Hospital. On examination it looks like thinned (9 kg), mild pallor, and whitish lesions in oral cavity. Not lymph nodes, no hepatosplenomegaly. Connected with the environment. Start treatment with oxacillin and clindamycin. Blood count: Hemoglobin: 7.6 hematocrit: 31.4 plaqueta:217000 leukocytes: 15110 segmented: 60 % Abastonados: 12 % lymphocytes: 25 %. CPR: 8. Negative blood cultures. Remains febrile after two weeks of treatment so it is decided to change coverage to Vancomycin and ceftriaxone prior crop wound secretion. The result of cultivation was Serratia Marcescens sensitive to imipenen. Bone scan: hipercaptante area during early and late compatible with osteomyelitis in left foot. Study of PID s decided by the evolution of the disease. Dosage of immunoglobulins and lymphocyte population within normal values. However, the Test positive dihydrorhodamine. Study of direct sequencing of genomic DNA. Presence of the mutation p.Trp361Arg in exon 9 of CYBB gene. This result is compatible with the diagnosis of disease chronic granulomatous linked to chromosome X.
Discussion: Chronic granulomatous disease (CGD) is a genetically heterogeneous condition characterized by recurrent, life-threatening bacterial and fungal infections and granuloma formation. CGD is caused by defects in the phagocyte nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, which constitutes the phagocyte oxidase (phox). These genetic defects result in the inability of phagocytes (neutrophils, monocytes, and macrophages) to destroy certain microbes.
CGD may present at any time from infancy to late adulthood, but the majority of patients are diagnosed as toddlers and children before the age of five years. In several series, the median age at diagnosis was 2.5 to 3 years of age. Patients with CGD usually present with recurrent or severe infections caused by bacteria or fungi. Other presenting features include growth failure, abnormal wound healing, diarrhea, and infected dermatitis. The organisms that infect patients with CGD are catalase producing for example: *S. aureus*, *Serratia*, *Klebsiella*, *Aspergillus*, and *Burkholderia*. This patient symptoms were targeted in the left foot and the crop which came a rare germ: Serratia Marcescens which makes us think of a primary immunodeficiency. Patients with CGD commonly experience growth retardation. Failure to thrive is a frequent presenting symptom in young children. Although bone marrow transplantation is an attractive option for the definitive cure of CGD, survival without bone marrow transplantation is roughly comparable. In contrast to mortality, the morbidity of recurrent infections and hyperinflammation remains a major issue in CGD with at least one severe infection every 3–4 years/ patient and recurrent inflammatory bowel disease in onethird of patients.

PO - 087

Allogeneic Hematopoietic Stem Cell Transplantation for Chronic Granulomatous Disease: the Experience in a Single-Centre in Argentina

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Introduction: Chronic granulomatous disease (CGD) is the most prevalent disorder of the phagocyte function, leading to significant morbidity and mortality. Since the results published by Güngör et al., hematopoietic stem cell transplantation (HSCT) remains the only recommended curative therapy for this disease, as gene therapy is still experimental and not available in Latin America.
Objective: To report the recent outcomes of a single-centre experience regarding HSCT in CGD.
Results: There are 69 confirmed cases of CGD in our centre since 1987 (67 X-linked and 2 autosomal recessive, diagnosed through dihydrorhodamine (DHR) test and/or genetic analysis). Of these, 5 patients with X-linked CGD (without inflammatory manifestations) were selected to undergo allogeneic HSCT. The first patient had a lung infection by *Penicillium* and was in a poor clinical condition prior to HSCT, which was performed in 2010 with a matched related donor (MRD), using a reduced intensity conditioning. DHR test after HSCT was similar to the donor; however, he died at +50 days due to fungal lung infection, viral reactivation and multi-organ failure. Four other HSCT have been performed so far since 2016 (3 with a matched unrelated donor (MUD) and 1 with MRD) to 4 stable patients, in good clinical conditions, with a myeloablative conditioning (MAC). One of these HSCT was only done recently (currently +3 days), so no follow-up or DHR test can be reported yet. As for the other 3 patients: 2 of them had Cytomegalovirus reactivation after HSCT, which could be controlled with antiviral medication. Graft-versus-host disease occurred in the 3 patients. Oxidative capacity was recovered in all 3 of them, and they remain alive after 1-13 months of follow-up.
Conclusions: In our cohort, a good clinical condition prior to HSCT was associated with a greater survival. Also, MAC could be an alternative for centres where busulfan AUC is unavailable.

PO - 088

Congenital Neutropenia a Case Report

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Phaphagocytic neutrophil granulocytes are amog the first immune cell active at sites of infection, forming an important first-line defense agains invading microorganisms, constitute 50-70 % of human blood leukocytes, they are produced in bone marrow from myeloid progenitor cells. Inherited quantitative neutrophil disorders are termed Congenital neutropenia (CN), classified by absolute neutrophil count (ANC) in peripheral blood into mild, moderate or severe. The estimated overall incidence is 10-15 mio births.
Patients with CN suffer from recurrent infections with bacteria and fungi, causing cellulits, pneumonia or sepsis, and oral aphtosis, paradontosis, or tooth loss, In same cases, CN may predispose to myelodysplastic syndrome or acute leukemia. Case presentation: ARA,
Brazilian female eight years old referred by an assistant pediatrician due to cellulites in face, chronic periodontal disease, reports of recurrent canker sores, as well as recurrent cutaneous abscesses from one year of life. Non-consanguineous parents, single daughter, aunt has recurrent canker sores. Physical examination: regular general condition, febrile, right hemi swelling, gum hypertrophy, oral thrush. During the hospitalization, serial hemograms were performed, which showed severe neutropenia. During outpatient follow-up, a multigene panel was developed for phagocyte defects.
Laboratory assessment during eight weeks evidenced severe neutropenia, average cento e noventa e seis neutrophilis. Medulogram: maturation arrest at the promyelocyte stage. Panel of congenital neutropenia: autossomal-dominat heterozygous mutation of Elane (encoding neutrophil elastase). Discussion: Case report and clinical-laboratory-genetic description of a child with eight years of life with recurrent coetaneous abscesses, cellulitis, oral thrush and chronic periodontal disease.
Congenital neutropenia with autossomal-dominat heterozygous mutation of Elane, accouting for 50 % of all severe CN cases. Elane deficiency is responsible for neutropenia severe CN type 1 (SCN), have chronic profound neutropenia. After diagnosis of SCN, the patient is administering myeloid-specific G-CSF subcutaneousty 10 μg/kg/day three times per week, with increase of total neutrophils and improvement of symptoms associated with neutropenia. Patient is followed up at the immunology outpatient clinic.

PO - 089

Functional Evaluation of Phagocytes in the Post-Transplantation of Hematopoietic Stem Cells in a Patient with Chronic Granulomatous Disease

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Introduction: Chronic Granulomatous Disease (CGD) is a primary immunodeficiency that presents recurrent infections due to dysfunction of the NADPH oxidase system in phagocytic cells. Hematopoietic stem cell transplantation (HSCT) can be performed with intention to cure CGD, showing survival rates up to 95 % and graft failure up to 20 %. The increase in graft resistance in CGD patients may be related to hyperactivation of the immune response, history of recurrent infections and dysfunction of organs resulting from previous infections.
Case presentation: Male patient was hospitalized in the first month of life to treat pneumonia and had a second episode at 4 months of age. Due to recurrent pneumonia and history of recurrent infections in male relatives, dihydrorhodamine (DHR) test was performed. DHR showed result consistent with CGD. The mother was identified as a carrier based on DHR test, confirming the hypothesis of X-linked CGD. After diagnosis the patient presented with pneumonias and perianal abscess caused by *Klebsiella pneumoniae.* These infections occurred despite the daily use of antibiotics, antifungals and subcutaneous administration of interferon-γ. After 14 months of diagnosis, he underwent haploidentical HSCT. Besides conventional molecular VNTR exam, we perform serial DHR tests to monitor transplantation which showed no functional recovery up to 3 months after HSCT. The patient continued using prophylactic medications but maintained monthly infections. At 2 years of age, he received a non-related umbilical cord HSCT. At the molecular level, this patient had a VNTR with engraftment and this was compatible with the functional recovery of the cells. By DHR, functional reconstitution of the NADPH system was observed since 50 days after HSCT. Besides a successful engraftment the patient presented fungal infection in the central nervous system and cytomegalovirus reactivation, which lead him to death after 2 months of HSCT.
Discussion: HSCT is important as being an alternative of cure for CGD patients. In addition to chimerism tests and other evidence of graft attachment, the DHR was useful in monitoring the recovery of the NADPH system. The DHR technique is a simple and low cost test to follow functional recovery of phagocytic cells after HSCT. Unfortunately, our patient developed recurrent infection for 2 years until receiving the HSCT and probably this contributed to the reactivation of the post-transplant infectious condition and evolution to death.

PO - 090

Activated Phosphoinositide 3-Kinase Syndrome (APDS): a Diagnosis to be Aware of

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Introduction: Recent discoveries have broadened the spectrum of clinical manifestations of primary immunodeficiency diseases (PIDD). Less common presentations can be challenging and delay diagnosis. We report 3 patients to illustrate the clinical and laboratorial presentation of a newly described combined immunodeficiency.
Case presentation: Patient 1 - 10yo male, medical history of chronic hepatosplenomegaly, peripheral lymphadenopathy, hemolytic anemia, and recurrent sinopulmonary infections. He had persistent low CD4 count (CD4 459 < p10), hypogamaglobulinemia with IgA 17, IgG 436, IgM 76, and chronic diarrhea. He is under IVIG replacement and prophylactic antibiotic. Currently his infections are under control and he has mild anemia. Patient 2 – 11yo female, medical history of recurrent sinopulmonary infections with bronchiectasis, splenomegaly, chronic and severe anemia leading to splenectomy, and chronic diarrhea refractory to corticosteroids. She is under IVIG replacement and sirolimus. Patient 3 – 16yo male, medical history of chronic sinopulmonary infections, chronic EBV, hepatosplenomegaly, and peripheral lymphadenopathy. Persistent low CD4 and CD19 counts, high IgM levels. (IgA 66,6/IgG 764/IgM 644,3/ CD3 2061/CD4 435/CD8 1561/CD19 91/ NK91). He meets diagnostic criteria for systemic lupus erythematosus (anemia/thrombocytopenia/pericarditis/positive anti-nuclear and anti-dsDNA antibodies/proteinuria) and recently had a hemorrhagic stroke. He's currently on daily steroids (prednisolone 30 mg q.d.), hydroxychloroquine and prophylactic antibiotic. Exome sequencing of all 3 patients revealed a pathogenic variant in the PIK3CD gene (p.E1021K), a common mutation associated with activated phosphoinositide 3-kinase syndrome (APDS).
Discussion: APDS is a combined primary immunodeficiency described in 2013. Ever since, there is an increasing number of patients being identified worldwide. It is characterized by recurrent sinopulmonary infections, bronchiectasis, chronic viral infections, lymphoid hyperplasia and autoimmunity, among other manifestations. CD4 lymphocyte counts and immunoglobulin levels are usually low. Awareness of this disease might help earlier diagnosis and allow better treatment options. Severe cases may require HSCT and promising targeted therapies are under research.

PO - 091

STAT1 Gain-of-Function Mutation in Patient with Visceral Leishmaniasis and Secondary Hemophagocytic Lymphohystiocitosis

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Introduction: STAT1 gain-of-function (GOF) mutations were initially thought to be associated only with Chronic Mucocutaneous Candidiasis. However, subsequent reports have show that STAT1 GOF can lead to infections by *Histoplasma capsulatum*, *Coccidiodes immitis* and other intracellular organisms. We report here the only case we are aware of disseminated leishmaniasis caused by a GOF STAT1 mutation.
Case Presentation: 4 year-old boy presenting with low grade fever and severe astenia for 2 weeks, with hepatoesplenomegaly, pancitopenia and liver failure, evolving to shock and respiratory distress. A bone marrow aspirate showed a hypocellular bone marrow, with hemophagocytosis and the presence of Leishmania. The cultures were negative to mycobacteria, fungi e bacteria. He was treated with lipossomal amphotericin and the HLH-2004 protocol was initiated (without etoposide). After 8 weeks, the patient was still in serious condition with fever, anemia, thrombocytopenia, elevated ferritin and splenic nodules. A diagnostic splenectomy was performed, which showed macrophagic activation with nodular spleen necrosis secondary to the visceral leishmaniosis. Death occurred on the second week after splenectomy, by an overhelming infection. DNA sequencing showed a STAT1 p.R274Q mutation known to have a gain-of-function effect.

PO - 092

Glucose-6-Phosphate Dehydrogenase Deficiency and Recurrent Staphylococcal Infection

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Introduction: Glucose-6-phosphate dehydrogenase (G6PD) is a key enzyme of pentose-phosphate pathway that leads to the production of coenzyme nicotinamide adenine dinucleotide phosphate (NADPH) and has an antioxidant role. G6PD deficiency is an X-linked, hereditary genetic defect due to mutations in the G6PD gene. The most frequent clinical manifestations of G6PD deficiency are neonatal jaundice and hemolytic anemia. Patients with severe enzyme deficiency may have impaired phagocyte NADPH oxidase activity and defective production of reactive oxygen species (ROS) and increased susceptibility to infection.
Case Presentation: A 23-year-old male nonconsanguineous black family was referred to evaluate primary immunodeficiency disease (PID) by recurrent staphylococcal infection disease. He had invasive staphylococcal infection - meningitis at age 3 years, abscess and sepsis at age 4 years and abscess and sepsis at age 15 years old with admission Intensive Care Unit and tracheostomy. Laboratory data screening PID were normal. Chronic Granulomatous Disease was thought and dihydrorhodamine (DHR) test performed with ION > 80. Two qualitative assays G6PD were positive for deficiency. G6PD activity assay were not possible. Discussion: Dysfunction of phagocytes is a relevant risk factor for staphylococcal infection. Chronic granulomatous disease (CGD) is the most common defective phagocyte NADPH oxidase enzyme and was ruled out in our patient. Recent data published (Siler et al) studied severe G6PD deficiency and susceptibility infection, it as can be a phenocopy of CGD. Determining the level of G6PD enzyme activity and analysis of reactive oxygen species production were recommended in such patients as herein described.

PO - 093

Primary Immunodeficiency Diseases Treated with Hematopoietic Stem Cell Transplant: a 10-Year Patient Registry From a Referral Center of for Primary Immunodeficiency in Brazil

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Introduction: Primary immunodeficiency diseases (PIDs) are disorders resulting mostly from inherited defects of the immune system. The

prevalence of primary immunodeficiency is estimated at approximately 1 in 2000 live births, and more than 300 distinct disorders have been identified. The management of patients with PID begins with early identification and diagnosis. Hematopoietic stem cell transplant (HSCT) is a potentially curative treatment for lifethreatening PID.
Objective: Report outcomes of HSCT in PID.
Methods: A retrospective study of all patients with PID underwent to bone marrow transplant at Hospital de Clínicas de Porto Alegre for PIDs from 2007 to 2017.
Results: 18 HSCT were performed in 16 children with various types of PIDs. Two patients were submitted to a second transplant due to secondary engraftment failure. Disease distribution: 5 Hyper-IgM Syndrome, 3 Wiskott-Aldrich, 3 Leukocyte Adhesion Deficiency, 2 Chronic Granulomatous Disease, 2 Severe Combined Immunodeficiency, 1 Chediak-Higashi, 1 Severe Chronic Neutropenia, 1 Griscelli Syndrome. Eleven (61 %) are male and 7(39 %) female with a median age at transplant of 50 months. According to donor type, 8 received HLA-matched unrelated, 3 received HLA-matched related, 3 received haploidentical, 1 received HLA-mismatched unrelated and in 3 patients the source was umbilical cord. Eleven (61 %) received reduced intensity conditioning and 7(39 %) myeloablative conditioning. Acute graft versus host disease (GVHD) was seen in 9(50 %) of the patients and only 2(11 %) presented chronic GVHD. Four patients presented autologous chimerism and consequently secondary engraftment failure. Of the 10 alive patients, 7 maintained stable full donor chimerism and 3 stable mixed chimerism. All of them area in good clinical conditions, absence of recurrent infectious diseases and only one patient still receive monthly intravenous immune-globulin therapy. Six (37,5 %) patients died: 5 of sepsis and 1 of grade-IV acute GVHD. Overall survival (OS) rate was 66,7 % at a median follow up of 14 (1-107)months.
Conclusions: Delays in diagnosis and transfer of PID patients to immunology centers in Brazil can lead to delayed HSCT and consequently a lost in OS. Nevertheless, patients with PID treated with bone marrow transplant in our center had similar rate comparing to reported results from other reference centers and acceptable rate considering the high grade lethality of these diseases, supporting the use of HSCT in patients with IPD.

PO - 094

Brazilian Female Carriers of Chronic Granulomatous Disease

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Introduction: Chronic Granulomatous Disease (CGD) is a rare primary immunodeficiency caused by the abnormal activity of the enzyme complex nicotinamide adenine dinucleotide phosphate oxidase. This deficiency results in the difficulty of generating superoxide anions and destroying catalase positive microorganisms such as *Staphylococcus aureus, Klebsiella sp, Pseudomonas*, among others. X linked The disease is inherited in two forms: autosomal recessive and X linked; the latter being the most common one. X-linked CGD carriers may be asymptomatic or present severe clinical manifestations. We evaluated clinical manifestations reported by female relatives of CGD patients.
Methods: We established a collaborative study among the main reference centers on PID in Brazil. Protocol was submited to respective ethical committee. Carrier condition was confirmed by NBT (nitroblue tetrazolium) or DHR (Dihydrorodamine) tests. The same questionnaire was applied in the different centers.
Results: 18 female CGD carriers (mean age:; min-max) were reported: 11 symptomatics and 7 asymptomatics. Mean age of first symptoms ($n = 11$) was 17.2 years old (9-28 years). The main clinical manifestations reported were furunculosis (6/11); inflammatory intestinal disease (3/11); other infections (7/11).
Conclusion: The concept of Primary Immunodeficiency for CGD patients with complete defect on NADPH oxidase system should be revised. In some situations, oxidase activity is so impaired that clinical symptomatology could lead to severe disability. Therapeutic approach could be necessary in those cases.

PO - 095

Clinical Features of Patients with Chronic Granulomatous (CGD) Disease in Paraguay

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Chronic Granulomatous Disease (CGD) is caused by defect in one of the subunits of nicotinamide phosphate (NADPH) oxidase, resulting in failure of phagocyte to generate superoxide. As a result, CGD patients usually suffer from severely recurrent, often life-threatening bacterial and fungal infections.
Objective: To describe the pattern of bacterial and/or fungal infections that required hospitalization in patients with CGD.
Patients and Methods: Patients with diagnosis of CGD and hospitalized between January 1991-June 2017, were included in the study. Clinical and laboratory data were retrospectively collected from the patient `s medical records, and included age at onset and diagnosis, parental consanguinity, family history, clinical manifestation, frequency of infections, complications of BGC vaccine, days of hospitalizations and outcomes.
Results: A total of 11 patients with CGD (8 male and 3 female) were included. All patients were from 8 unrelated noconsanguineous families. There were two families with more than one member affected (one family had two sisters and the other two cousins and one aunt). Two of 11 patients (18,2 %) had positive family histories with early death histories in other family members within three generations. The mean onset age of symptoms was 14.5 ± 10,3 months and the mean age at diagnosis was de 32.4 ± 25,06 months. All patients received BCG vaccine but none developed complications. Pulmonary infections were the most infections observed in CGD patients (34,3 %, 12/35), and included pneumonia (9/35), lung abscess (1/35), pulmonary tuberculosis (1/35) and bronquiolitis (1/35). Other infections that causes hospitalization were sepsis (6/35, 17 %, with endocarditis in one), adenitis (5/35, 14,3 %), skin and soft tissue infections (4/35, 11,4 %), bacterial meningitis ($n = 1$) and osteomyelitis ($n = 1$). In 18 episodes one microorganism was isolated being *S. aureus* the most frequent ($n = 9$, 50 %), but in 8 cases (44 %) one unusual organisms were isolated [*Aspergillus* ($n = 3$), C*hromobacterium violaceum, Burkholderia cepacia*, *Enterobacter cloacae*, *Serratia marcescens*, *Mycobacterium tuberculosis* (one case each)]. The average hospitalization time was 23, 3 ± 14, 1-day and the cumulative mortality was 27 %(3/11).

Conclusions: In the present serie, CGD was more frequent in males and the age of onset of symptoms was before 2 years of age. The diagnosis of CGD was made relatively fast. The pulmonary infections were the most infections observed and *S. aureus* was most frequent isolated microorganism, but inusual microorganisms were observed in a significant proportion of cases. It is essential to study this disease in patients with life-threatening infectious with prolonged evolution and unusual microorganisms.

PO - 096

Exome Sequencing Reveals Gain-of-Function Mutations in *STAT1* Conferring Predisposition to Chronic Mucocutaneous Candidiasis in Six Colombian Patients

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Introduction: The transcription factor STAT1 plays a critical role in the immune response against mycobacterial, viral and fungal infections. Different mutations in *STAT1* result in diverse clinical phenotypes: AR complete/partial biallelic mutations are associated with mycobacterial and viral infections while AD loss-of-function (LOF) mutations with mycobacterial disease only; in addition, AD gain-of-function (GOF) mutations are associated with autoimmunity and fungal infections. We report GOF-STAT1 mutations in 6 individuals from a large cohort of Colombians affected with mycobacterial, fungal and bacterial infectious diseases.
Methods: We performed whole exome sequencing (WES) in 4 sporadic cases (P1, P2, P3 and P4) and the proband of one family case (P5) and mutations were confirmed by Sanger sequencing in all patients. Flow cytometry was used to immunophenotype peripheral blood lymphocyte (PBLs) subsets and lymphoproliferation to phytohemagglutinin (PHA) and anti-CD3 + CD28. STAT1 phosphorylation after stimulation with IFN-gamma in patients´ PBMC was evaluated by flow cytometry and with an *in vitro* Dual-Glo Luciferase Assay.
Results: Infections in the patients included chronic mucocutaneous candidiasis (CMC) and pulmonary histoplasmosis in P1, CMC and pulmonary TB in P2, and CMC in P3, P4, P5 and P6. We found 4 novel (Q20R, E235G, L354R, C324Y) heterozygous missense mutations in *STAT1* in 4 sporadic cases (P1, P3, P2 and P4, respectively) and the previously reported P329L mutation in P5 and her father (P6). All novel mutations are predicted to be deleterious by SIFT and Polyphen2. Patients´ CD14+ monocytes and the GAS reporter assay showed higher phosphorylation of STAT1 in response to IFN-gamma stimulation, demonstrating that all mutant alleles were GOF. P3, P4 and P5 showed decrease CD27+ memory B cells, CD27 + IgD+ marginal zone-like B cells and CD27 + IgD- class-switched memory. In most patients, proliferation to PHA was normal while proliferation to anti-CD3 + anti-CD28 was decreased.
Conclusion: We report the first cases of GOF-STAT1 mutations in Colombia. STAT1 deficiency in our patients lead to a spectrum of CMC, histoplasmosis and TB, therefore STAT1-GOF mutations should be investigated in patients with these infectious phenotypes. In addition, WES has become an important tool in the identification of genetic defects in patients with PID.
Keywords: Chronic mucocutaneous candidiasis, tuberculosis, STAT1 gain-of-function, whole exome sequencing
Financial support: COLCIENCIAS #111556934990, ECOS-NORD #619-2013

PO - 097

Paracoccidioidomycosis and IL-12 Receptor Deficiency – a Case Report

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Introduction: The IL-12 receptor deficiency is a primary immunodeficiency (PID), in which the IL-12Rβ1 expression fails. A response to INF-γ occurs as usual, however, the production of this cytokine dependent on IL-12 and IL- 23 is abnormal. It is a disease characterized by early onset of infections, classically caused by Mycobacteria and *Salmonella sp*. We present a possible case of the disease in a pediatric patient with systemic paracococcidioidomycosis as her only clinical presentation. It is a mycosis caused by *Paracoccidioides brasilienses*, endemic in Brazil.
Case presentation: A previously healthy female patient, 2 years and 10 months old, started generalized adenomegaly (retroauricular, inguinal, popliteal, infraclavicular, cervical), developing fever, anorexia and bone pain. In an inguinal lymph node biopsy, paracoccidioidomycosis was diagnosed, with systemic involvement, including disseminated lytic bone lesions. The condition improved with the use of antifungals. Patient was referred to immunology for investigation, with normal initial results. The *In vitro* activity of the INF- γ / IL-12 axis, performed twice in the Laboratory of Human Immunology - ICB IV - USP (Prof Antonio Condino Neto), showed a lack of response to IL-12, suggesting a receptor deficiency. Patient awaits genetic sequencing results.
Discussion: Although poorly described in the literature, the association between the IL-12 receptor defect (IL-12Rβ1) and paracoccidioidomycosis was found in this patient, with no other associated infections. It is known that the response of the Th1 adaptive immune system to the fungus via INF-γ and IL-12 is extremely important for disease control. Therefore, the inability to activate this axis prevents the adequate response to the pathogen. The present case alerts us to the fact that it is necessary in our country to research this and other PIDs not only in the presence of mycobacterium and Salmonella sp infections, as well as in cases of paracoccidioidomycosis and other invasive fungal infections.

PO - 098

Actinomycete Infection and Partial Dominant Defect of IFNγ Receptor – a Case Report

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Introduction: Defects of the IFNγ receptor are associated with persistent or recurrent mycobacterial infections. IFNγ is important for the death of mycobacteria and other intracellular bacteria. The objective of this study was to report the case of a patient with IFNγ receptor defect highlighting the identification of unusual infectious agents.
Case Report: GLS, 11 years old, BCG reaction at 4 months of age, ulcerated skin lesions and atypical mycobacterial osteomyelitis at 4 years. After the diagnosis of partial dominant deficiency of IFNγR1 (heterozygous mutation 818del4 in exon 6 of the IFNγR1 gene), he has been maintained in chemoprophylaxis with ethambutol and clarithromycin since 2002, without relevant infections until July / 2009, when weight loss started, as well as hepatomegaly and mediastinal enlargement. Chest CT revealed mediastinal, paratracheal and carinal adenomegalies. After failure to obtain a biopsy of a mediastinal lymph node, the RIP scheme was introduced empirically in September 2009, with prophylactic clarithromycin and ethambutol being maintained. It evolved with clinical and radiological improvement until the fifth month of treatment, when there was recurrence of mediastinal adenopathy and the appearance of supraclavicular lymph node enlargement. Then, the biopsy revealed no infectious agents in special stains. In the microbiological investigation, Actinomycete was isolated. Treatment with SMZ-TMP was initiated and, after 5 weeks of treatment, there was progressive reduction of peripheral lymphadenopathy and radiologic normalization of the mediastinum. In the outpatient evaluation, in March / 2011, patient maintained supraclavicular lymphadenopathy despite antibiotic prophylaxis. Microbiological characterization of Actinomycete evidenced *Nocardia sp*. The association of doxycycline to the antibiotic scheme was oriented by the infectology expertise, and the boy evolved with clinical improvement. He is still in follow-up at the service, and maintains chemoprophylaxis, without new infections.
Discussion: Infections with uncommon infectious agents present in our country should be thoroughly investigated in patients with defects of the IFNγ-IL12 / 23 axis.

PO - 099

Novel Mutations in *NCF4* Gene Confer Non-classic Chronic Granulomatous Disease with Disseminated Histoplasmosis in a Colombian Child

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Introduction: Chronic Granulomatous disease (CGD) is a primary immunodeficiency (PID) characterized by susceptibility to early-onset life-threatening bacterial and fungal infections as well as dysregulated chronic inflammation. CGD results from mutations in the phagocyte NADPH oxidase, a multimeric complex that consists of two membrane-bound components (gp91^{phox} and p22^{phox}) and 3 cytoplasmic subunits (p40^{phox,} p47^{phox} y p67^{phox}) that function to induce reactive O2 species (ROS) in phagocytic cells to stimulate microbial killing. To date, only a single patient with granulomatous colitis and compound heterozygous mutations in p40^{phox} encoded by *NCF4* has been reported as a genetic subgroup of CGD.
Method: We reviewed medical records and performed whole exome-sequencing (WES) on peripheral blood lymphocytes (PBLs) from the patient. Phagocyte NADPH oxidase function was evaluated by the dihydrorhodamine (DHR) oxidation assay and Amplex Red and Luminol and protein expression by FACS and immunoblotting.
Results: A 7 years-old boy born from apparently non-consanguineous parents was diagnosed at the age of 2 years with systemic histoplasmosis. WES was performed in genomic DNA from PBLs and a missense homozygous variation was found in *NCF4* within the phox homology (PX) domain, predicted to be damaging by Polyphen and SIFT2 and with a CADD score of 35. RT-PCR and immunoblotting demonstrated decreased p40^{phox} protein expression respectively in neutrophils and EBV-transformed B cells. In addition, intracellular (IC) ROS production was significantly impaired after physiological stimulation with fMLP, *H. capsulatum* and *C. albicans* on neutrophils and EBV-B, but not with Phorbol 12-myristate 13-acetate.
Conclusion: We report a novel homozygous mutation in *NCF4* selectively impairing intracellular ROS production in a Colombian child. Remarkably, systemic histoplasmosis has not been previously reported in association with classical CGD, therefore our results expand the spectrum of genetic and infectious diseases underlying CGD in humans.
Keywords: NADPH, whole exome sequencing, NCF4, chronic granulomatous diseases (CGD)

PO - 100

Hemophagocytic Syndrome in Children with Mycobacteria Infection Associated with Phagocytosis Defect. Case Presentation

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Introduction: Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening disease characterized by persistent and excessive activation of the immune system, predominantly T lymphocytes and macrophages with excessive production of pro-inflammatory cytokines. It presents with fever, splenomegaly, cytopenias, hemophagocytosis, and defects in cytotoxicity can be demonstrated. HLH can be primary or secondary to infections, malignancy and has been associated with primary immunodeficiencies (PID) as a main or aggregate manifestation. Increased susceptibility to infection by mycobacteria in PIDs has been reported, mainly in combined immunodeficiencies, phagocytosis defects and MSMD. We present the case of a patient with persistent mycobacterial infection, who also developed HLH, showing the importance of the immunodeficiency approach in patients with this association.

Case: Sixteen years old female. Started at 5 years old with to cervical lymphadenopathy, weight loss and fever. Lymph node biopsy showed chronic granulomatous lymphadenitis, positive for mycobacterial infection. Received antifimic treatment for 6 months with improvement. At 10 years old had a new episode of cervical lymphadenopathy with chronic granulomatous lymphadenitis and caseous necrosis in the histopathological report. Antifimic treatment was restarted. Subpopulations of lymphocytes had CD4 + and CD8 + lymphopenia with normal immunoglobulins and complement, HIV negative. Patient returned to the hospital at 16 years old for having a fever of one month of evolution, diaphoresis, weight loss, increase of abdominal perimeter, drowsiness, vomiting, and respiratory distress. Septic shock was diagnosed, requiring management in PICU with mechanical ventilation and vasopressor. During hospitalization with hepato-splenomegaly, cytopenias (anemia and thrombocytopenia), hypertriglyceridemia, elevated ferritin, and bone marrow smear positive for hemophagocytosis, confirming hemophagocytic syndrome initiating treatment (HLH 04 and intravenous gammaglobulin 2grkg). Within the approach with tomographic evidence of cervical, thoracic, abdominal granulomas and PCR (GenXpert) positive for M. tuberculosis. Antifimic treatment was restarted. Currently stable.
Discussion: An imbalance between viral control and immune activation is thought to be an important determinant of the HLH syndrome associated with viral infections (such as EBV) and in a proportion of patients with FHL. Few cases have been reported on hemophagocytic syndrome associated with mycobacteria infection, being mostly reports of HIV positive patients, however it is important to consider in HIV negative patients an underlying primary immunodeficiency, being patients with CID, phagocytic defects and MSMD who most frequently associate mycobacteria as a trigger agent of hemophagocytic síndrome.

PO - 101

Common Variable Immunodeficiency with Granulomatous-Lymphocytic Interstitial Lung Disease

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Introduction: Nearly 50 % of CVID patients have additional noninfectious complications, interstitial lung disease affects between 10 and 20 % of patients, and has showed the strongest association with poo survival.
Clinical abstract: CMG is a 46-year-old female, resident of Mexico City, who is married, works as a financial advisor.
Medical history: Hospitalizations: Multiple admissions with pneumonia diagnosis between 1998 and 2003 (approximately 6 times per year). January 2017: bronchiectasis + community-acquired pneumonia infection. Diseases: Common variable immunodeficiency diagnosed in November 2008, currently on treatment with immunoglobulin at 400-800 mg/kg/dose every 21 days, prophylaxis with clarithromycin 250 mg every 12 h, budesonide/formoterol 160/4.5, 1 inhalation every 12 h and budesonide 100 mcg, 1 inhalation every 12 h.
Present illness: Current condition started in May 2016 with dyspneizing, non-cyanosis-producing coughing bouts, functional class progressive decrease and dyspnea on moderate exertion, with supplementary oxygen being initiated on July 2016 exclusively at nighttime. In January 2017, there is progression to dyspnea with mild exertion and the patient requires continuous supplementary oxygen, which limits her daily activities.
Physical examination: Chest was symmetric, with adequate incoming and outgoing airflow, pulmonary fields with disseminated, crepitant bilateral rhonchus rales on both hemithoraces, with predominance on both pulmonary bases; there were no data consistent with respiratory distress. On palpation, the abdomen was soft and depressible, with perceptible splenomegaly.
Laboratory tests: CBC: WBC: 2000/μL, neutrophils: 1500/μL, lymphocytes: 300/μL, Hb: 10.4 g/dL, Hct: 34.6 %, platelets: 74000/μL
Spirometry: Suggestive of restrictive pattern
HRCT Jan 19, 2017: Marked, generalized pleural thickening. Presence of diffusely-distributed ground-glass-pattern images, with generalized interstitial and septal thickening, and multiple fibrosis markings that cause cylindrical bronchiectases by traction and focal subsegmental atelectases.
Diagnosis: Granulomatous-lymphocytic interstitial lung disease
Discussion: Our patient has a clinic presentation like interstitial lung disease, that is nearly always accompanied by splenomegaly, she has shortness of breath and her HRCT scan of the lungs has ground-glass pattern images as that kind of patients.

PO - 102

Primary Immunodeficiencies: Experience in Three Pediatric Hospitals from Argentinian Litoral Region over a 17 Year Period (2000-2017)

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Aim: Primary immunodeficiencies (PIDs) are a large group of diseases characterized by susceptibility not only to recurrent infections but also autoimmune, autoinflammatory and malignant diseases. The aim of this study was to describe and analyze the distribution, clinical features and eventual outcome of PIDs among three referral hospitals.
Methods: Retrospective data collection study by review medical charts of PID patients (pt) followed at three third level Pediatric Hospitals from Argentinian Litoral Region over a 17 year period (2000-2017).
Some patients were diagnosed in collaboration with Garrahan Hospital, Buenos Aires, whose laboratories conducted specific flow cytometry, functional tests and molecular biology studies. The patients were classified according to The International Union of Immunological Societies (IUIS) Expert Committee on Primary Immunodeficiency classification 2015.
Results: A total of 526 pt were diagnosed. Predominantly antibody deficiencies were the most common (84.22 %) followed by Combined immunodeficiencies with associated or syndromic features (7.41 %), Diseases of immune dysregulation (2.66 %), Immunodeficiencies affecting cellular and humoral immunity (1.52 %), Complement deficiencies (1.14 %), Defects in Intrinsic and Innate Immunity (0.95 %), Autoinflammatory disorders (0.95 %) and Congenital defects of phagocyte number, function, or both (1.14 %). Patients' ages ranged from less than 2 months to 55 years old. 92.58 % were diagnosed before age 15. The most common antibody deficiencies was selective IgA deficiency (83.29 %) followed by Common Variable Immunodeficiency (IDCV) (10.38 %). All pt with IDCV and X-linked agammaglobulinemia are being treated with supplemental gammaglobulin with improvement of their infectious events. 8 pt have undergone Hematopoietic Stem Cell Transplantation (HSCT): X-SICD (1 pt), Hiper IgM (1 pt), XLP1 (1 pt), WAS (1 pt), Griscelli syndrome (1 pt), Chediak-Higashi (1 pt), IPEX (1 pt), IL7a deficiency (1 pt). 1 pt is waiting for the HSCT (XLP1).
Molecular confirmation of the PID was performed in 62 pt. 20 pt (3.80 %) died due to PID or post HSCT complications.
Conclusions: As ESID and LASID registers there was a high proportion of antibodies deficiencies. This initiative will be a step toward a better understanding of PIDs epidemiology in this area. This study is a usefull data base to include in the LASID register.

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Immunoglobuling Risk Management Plan: Workshop on Primary Immunodeficiency for Health Professionals and Patients

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Introduction: The prevention of risks in the manipulation and administration of drugs is fundamental to achieve therapeutic aims with fewer occurrences of side effects. The Argentinean health authority established Risk Management Plan (RMP) as mandatory pharmacovigilance action for the pharmaceutical industry (Disp 5358/12). LH-UNC produces intravenous immunoglobulin G (IVIG) and presented the registry of subcutaneous immunoglobulin G (SCIG) Both are included in the RMP. In collaboration with the HNST and the AAPIDP an integrated training educational action was performed.
Objective: to describe and evaluate a workshop carried out under the RMP of IVIG and SCIG UNC.
Results: In April 2017, the LH-UNC held a theoretical-practical conference on primary immunodeficiency (PID) and its treatments for health team (1st meeting) and family/patients (2nd meeting). The activities were carried out by professionals of health institutions from Córdoba, Buenos Aires and the AAPIDP. By means of a self-designed survey were evaluated:
a) duration: adequate (A), long (L), short (S), No Answer (NA)
b) clarity: very good (VG), good (G), regular (R)
Topic evaluated: 1) workshop of manipulation, conservation, administration of IVIG; 2) Workshop on manipulation, conservation, administration of SCIG; 3) Catheter care; 4) Legal management; 5) Airway care; 6) Skin care; 7) Vaccines; 8) Oral hygiene
1st meeting: attended by 88 professionals. The evaluation was:
1. a) A 91 %, L 2 %, S 2 %, NA 5 %; b) VG 79 %, B 18 %, NA 3 %
2. a) A 92 %, L 2 %, S 2 %, NA 4 %; b) VG 79 %, B 19 %, NA 2 %
3. a) A 78 %, L 4 %, S 4 %, NA 14 %; b) VG 69 %, B 21 %, R 1 %, NA 9 % 2nd meeting: attended by 50 patients/family. The evaluation was:
2. a) A 81 %, L 6 %, NC 13 %; b) MB 93.75 %, B 6 %
4. a) A 81 %, NA 19 %; b) VG 94 %, R 6 %
5. a) A 69 %, S 13 %, NA 19 %; b) VG 94 %, G 6 %
6. a) A 81 %, NA 19 %; b) VG 94 %, NA 6 %
7. a) A 88 %, S 6 %, NA 6 %; b) VG 94 %, NA 6 %
8. a) A 75 %, L 6 %, NA 19 %; b) VG 88 %, G 6 %, R 6 %
In general, they attendant more interest in the activities related to the correct administration of both immunoglobulin.
Conclusion: The experience was positive and enriching; Duration and content were considered relevant. The interaction between professionals, patients, families and industry integrated aspects and realities to deepen critical points in the treatment of PID. The activity allowed the formation of a local group of patients with PID. This would also contribute to improve the pharmacotherapy adherence and safe and effective use of drugs through acquired knowledge, as required by the RMP.

PO - 104

APDS (Activated Phosphoinositide 3-Kinase Delta Syndrome) Resulting from Gain of Function of PIK3CD Mutation

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Case presentation: EAP, male, born 06/27/1984, caucasian, from non - consanguineous parents. Referred to Immunology Department at age 24 due to chronic diarrhea since 1 year of life. Previous medical history included hypothyroidism diagnosed at 9 months, two episodes of pneumonia in early adulthood. Diagnosed with nephrotic syndrome at age 7, submitted to arenal biopsy thats how edimmuno complex deposition membranoproliferative glomerulonephritis. Initially, he presented hypogammaglobulinemia (IgG = 260 mg/dL, IgA = 78 mg/dL, IgM = 37 mg/dL) and hypoalbuminemia (2.4 g/dL), and T and B lymphocytes within the normal range. Inflammatory bowel disease was investigated with enteroscopy that revealed intense lymphangiectasia and chronic erosive inflammation with lymphoplasmacytic infiltrate. A PIK3CD gain of function mutation, located at E1010E / A-c.3029A & gt; B.C was found. Currently he is on monthly IVIG replacement. The mTor inhibitor, Sirolimus was initiated and tha can inhibit signal transduction and decrease proliferation of self-reactive lymphocytes.
Discussion: APDS is a recently described combined immunodeficiency resulting from gain of function mutations in PIK3CD the gene encoding the catalytic subunit of phosphoinositide 3-kinase delta. It is characterized by variable linfopenia of T and B cells, hypogammaglobulinemia with normal or elevated IgM levels, susceptibility to viral infections and autoimmunity. This is an autosomal syndrome caused by mutation of a gene that encodes a protein expressed especially in leukocytes. The case denotes the variability of the clinical phenotypes associated with APDS and PIK3CD gene mutation. From recurrent sinopulmonary infections and recurrent viral infections to autoimmunity which makes early diagnosis of this immunodeficiency hard.

PO - 105

Effect of Interferon-Gamma on Dendritic Cells of Patients with CD40L Defects

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Introduction: Hyper-IgM Syndrome is a primary immunodeficiency caused by mutations leading to defects in immunoglobulin heavy chain isotope exchange and somatic hypermutation resulting in normal or elevated serum IgM levels associated with low serum levels of IgG, IgA, and IgE. The first type of hyper-IgM described was the X-HIGM syndrome linked to the X chromosome, which is due to mutations in the CD40LG gene. Decreased expression of CD40L by T lymphocytes affects monocytes and dendritic cells, decreasing IL-12 secretion by monocytes. This reduced secretion results in decreased IFN-γ production by T lymphocytes, contributing to the increased susceptibility to opportunistic infections observed in these patients. The CD40L protein, encoded by the CD40LG gene, is expressed on the surface of T lymphocytes and interacts with its CD40 receptor, expressed on antigen presenting cells such as B lymphocytes and dendritic cells. Dendritic cells are a key element of the immune system by the connection that they establish between innate and adaptive immunity and the unique ability to modulate the adaptive response. In this connection the CD40L-CD40 interaction plays an important role in antigenic response by acting on dendritic cells, such as

amplifying the antigen presentation and the greater activation, proliferation and differentiation of T lymphocytes.
Objectives: The objective of this work was to evaluate the effect *in vitro* analysis of interferon-gamma in dendritic cells from patients with mutations in CD40LG.
Results: Treatment with IFN-γ induced an increase in CD86 molecule expression in healthy subjects, although this increase was not observed in X-HIGM patients. The production of reactive oxygen species and IL-12p70 were shown to be increased after treatment with IFN-γ in both healthy subjects and patients
Conclusion: The IFN-γ demonstrated ability to potentiate dendritic cell response in both healthy and X-HIGM patients. The results obtained may support possible future clinical trials aimed at the development of new therapeutic options in the treatment of patients with opportunistic infections

PO - 106

Severe Combined Immunodeficiency. A Decade´S Experience at National Institute of Pediatrics, Mexico

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Introduction: Severe combined immunodeficiency (SCID) is considered a primary immunodeficiency disease (PID). It belongs to a group of rare and monogenic diseases and it has been characterized as a heterogeneous, life -threatening syndrome. The prevalence of SCID worldwide is estimated to be 1 in 50,000 to 100,000 live births. SCID disorders are characterized by the lack of protective T-, B-, and sometimes NK-cell responses against pathogens. SCID patients generally present severe and repeated episodes of infections caused mainly by opportunistic pathogens. Amongst the main symptoms we find persistent diarrhea and failure to thrive between the first and second year of age. Delays in making a diagnosis and the start of treatment often result in death at an early age and higher hospitalization costs as prolonged hospital-care stay, intensive care units' and management of comorbidities and complications must be covered. For those reasons this disorder represents a real pediatric emergency. The National Institute of Pediatrics is a reference center for PIDs in Mexico.
Objectives: To report the age at the time of diagnosis. To determine which is the principal immunologic phenotype. To describe the clinical manifestations and to find out what are the most common opportunistic pathogens in this group of patients. To determine what are the laboratory parameters found at the time of diagnosis, the treatment given to the patients and report what was the prophylaxis scheme received by infants who were diagnosed with SCID.
Results: This was a retrospective study conducted at the National Institute of Pediatrics; the period covered was from 2007 to 2017. Patients from the clinic and hospitalization areas within the National Institute of Pediatrics with SCID diagnosis were included in the study. A total of 60 patients with SCID diagnosis were included in this study from which the median age at onset of the infections was 60 days of age (range 17 days–5 months). Mean age at the time of diagnosis was at the 5th month of age, with an average 3 months of diagnostic delay (up to 7 months) since the onset of first infections. Seventy-seven percent of the patients were male. A positive family history of early deaths was found in 63 % of the families. he immunologic phenotype present in our population was T- B-NK+ in the 50 % of the cases, T-B + NK- in the 33 % of the cases T-B + NK+ in the 9 % and T-B-NK- in the 8 % of the cases. Lymphocytopenia (<3000 cells/mL) was present in 82.5 % of patients. Eighty-five percent of the patients with a typical presentation of SCID had CD3+ T cell counts of <500 cells/mL. Infections with opportunistic agents such as Bacillus Calmette-Guérin (BCG), Pneumocystis jiroveci (PJ), Cytomegalovirus (CMV) or Candida species were present in 90 % patients at the time of diagnosis. The most common clinical manifestations of all patients were pneumonia (72 %), recurrent oral candidiasis (27 %), chronic diarrhea (70 %), failure to thrive (55 %). Anti-tuberculosis, -bacterial, -viral and -fungal prophylaxis were used in 30 %, 72 %, 10 %, and 63 % of the patients, respectively. And IVIG was administered to all the patients. Hematopoietic bone marrow stem cell transplant was performed in 63 % of the patients.
Conclusions: SCID patients present severe infections within the first 6 months of age. The median age at onset of infections in our patients was 2 months of age, with a delay in the diagnosis of 3 months. The infections found in our cohort correlate with the findings reported by other studies in the literature, with pneumonia and chronic diarrhea being the most frequent conditions in this group of patients. Lymphopenia is one of the most relevant findings in patients with SCID and therefore screening in this group of patients should take place. Doing this kind of studies are important to know and recognize the principal clinical manifestations present in the Mexican population with SCID diagnosis due to realize an early diagnosis and improve the prognosis with an early treatment.

PO - 107

Clinical and immunological features of Patients with Wiskott-Aldrich Syndrome in Mexican Kids, Case Series Report

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Introduction: Wiskott-Aldrich syndrome (WAS) is an X-linked Primary Immunodeficiency, characterized by micro thrombocytopenia, eczema, recurrent infections, malignity and autoimmunity.
Case series presentation: We included 23 WAS patients referred to the Immunodeficiency Research Unit (IRU) of INP for diagnosis from 2004-2017, they were from 22 families. We reported the median (minimums and maximum). Age at the beginning was two months (0-30), Age at diagnosis was 14 (1-69). Maternal history of male death in infancy was presented in 11/23 patients. 2/23 presented Inbreeding. At diagnosis 86 % had recurrent infections, 95 % eczema and 100 % bleeding. Autoimmunity was present in 52 %: AHA 30 %, BID 21 %, vasculitis 17 %, arthritis 8 %, interstitial pneumonitis 8 %, APS 4 %, glomerulonephritis 4 %. Two patients developed cancer: lymphoproliferative syndrome associated with EBV and lung cancer. Thirty percent had allergy: 4/23 CMPA, 3/4 had another food allergies, 2/23 drug allergy, 2/23

urticaria, 1/23 prurigo by insects. Seven patients died: infections 3/7, CNS bleeding 2/7 and neoplasia 2/7. Infections were: Acute gastroenteritis 71 %, pneumonia 68 %, sepsis 57 %, AOM 42 %, cellulitis 34 %, UTI 17 %, chickenpox 13 %, conjunctivitis 13 %, abscesses 13 %, conjunctivitis 13 %, sinusitis 10 %; Other infections were balanitis, periorbital cellulitis, catheter-associated infection, otitis externa, CMV retinopathy, neutropenic colitis, contagiosum molluscum, oral candidiasis, fungal esophagitis, impetigo, ocular and oral herpes. Twenty-sex percent presented chronic diarrhea. Isolated agents were: CMV 8/23, *E. coli* 7/23, *E. histolytica* 5/23, *Candida spp* 4/23, *Salmonella spp* 4/23, *S. pneumoniae* 4/23, *HIB* 3/23, *G. lamblia* 3/23, *Enterovirus* 2/23. Immunoglobulins (mg/dL) were: IgG 1067 (168-3710), IgM 83 (4-555), IgA 131 (7-482). 9/23 had IgE determination, of which 8 were elevated. Lymphocytes (cells/microliter) were: CD3+ 1324 (34-3368), CD4+ 696 (12-2891), CD8+ 426 (20-1953), CD19+ 243 (0-1180), CD16/56+ 631 (89-1520). Four patients had lymphopenia, WASp expression in CD3+ cells was determined in 19 patients by flow cytometry, it was absent 14/19, decreased 3/19 and bimodal pattern 2/19. At diagnosis all patients began prophylaxis (cotrimoxazole, itraconazole) and GGIV replacement, 3 were splenectomized, 47 % received rituximab, 7 patients were transplanted, 3 survived. Median age at transplantation was 23 months (1-95).

Discussion: The WAS suspicion has increased because of awareness programs established by FUMENI and the IRU of INP in 2009, remarkable 16 patients have been diagnosed in the last 3 years. However delay in diagnosis continues, because of patients are diagnosed and treated as TPA. Any male patient with persistent TPA should be considered to rule out WAS. The expression of WASp by flow cytometry is a rapid and accessible diagnostic method available in the IRU of the INP.

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Autoimmunity Associated with Good Syndrome: Case Series of a Forgotten Immunodeficiency

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Background: Good's syndrome is a rare cause of humoral and cellular immunodeficiency associated with thymoma, with few cases registered in the literature associated with different manifestations of autoimmunity up to 58.6 %, being the most common pure red cell aplasia in 34.8 % and myasthenia gravis in 15 %.
Objetive: Describe a series of 4 cases Good's Syndrome associated with autoinmmunity.
Methods: Case 1 describes 78-year-old female with diagnosis of type 2 diabetes mellitus and vitiligo; After diagnosis of Good Syndrome in 2013 started with generalized dermatosis. Case 2 describes a 45-year-old male with a diagnosis of Good's syndrome in 2013, who later had xerophthalmia and xerostomia. Case 3 describes 55-year-old female with diagnosis of thymoma of lymphocytic predominance in 2002 after surgical resection in 2003 beginning with anemic syndrome requiring immunosuppressive therapy with a history of recurrent respiratory infections and hospitalizations due to pneumonic plaques associated with mucocutaneous candidiasis and bronchiectasis Being determined in hospitalization of the 2016 hypogammaglobulinemia, integrating diagnosis of Good's syndrome, finalized by pneumonia at 6 months of diagnosis. Case 4 describes male of 56 years old with thymoma antecedent in 2014 and respiratory infections of repetition, with laboratory finding of hypogammaglobulinemia in determination of immunoglobulins as part of diagnostic protocol.
Results: Case 1 was diagnosed with disseminated lichen planus following a skin biopsy. Case 2 positive sialometry and minor salivary gland biopsy were performed in 2016, diagnosing Sjogren's syndrome. Case 3 corroborated pure red cell aplasia after hematic biometry and bone marrow biopsy. Case 4 was a diagnosis of Good syndrome, which until now has not found evidence suggestive of autoimmunity manifestations.
Conclusions: Autoimmunity manifestations usually occur in 56-58 % of patients with Good syndrome, and it is present in 75 % of our series of cases, and it's associated with a worse prognosis of the disease.

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Disseminated BCG as the First Clinical Manifestation in Two Patient with NEMO Deficiency

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Introduction: Patients with NEMO (NF-kB essential modulator) defects have a broad susceptibility to infections including pyogenic bacteria, environmental mycobacteria, and to a lesser extent parasites, viruses and fungi. Clinical manifestations are wide and can overlap with other causes of combined immunodeficiency (CID), particularly when disseminated BCG infection occurs at the onset. This represents a challenge for the definitive diagnosis.
Objective: We present two male patients (Pt) with two different mutations in the *NEMO* gene with disseminated *Mycobacterium bovis* infection at the onset.
Results: Both patients presented at 2 months and 4 months of age respectively, with a history of fever and malaise. Findings on physical examination included hepato-splenomegaly and an erythematous rash. They had received BCG vaccination at birth and had developed a subcutaneous nodule at the site of inoculation. Pt1 presented with severe ascites associated with hypoalbuminemia (1.3 g/dL) and low serum IgG levels (137 mg/dL). Pt2 presented with a decreased absolute count of CD4+ T cells (564/mm^3). Both Pts had a normal relative value of naïve CD4+ T cells (86 %) and a normal lymphocyte proliferation assay. Serum levels of IgM were normal (Pt1: 117 and Pt 2: 246 mg/dl) and IgA was normal in Pt1 (50 mg/dL) and high in Pt2 (835 mg/dl). Excluding combined immunodeficiency. Both patients underwent blood cultures, bronchoalveolar lavage (BAL) and skin biopsy. *Mycobacterium bovis* was found on blood culture of Pt1 as well as on BAL after death. Similarly, *Mycobacterium bovis* was found on BAL, skin biopsy and hepatic puncture of Pt2. Mendelian susceptibility to mycobacterial disease was suspected but the expression of IL-12 and IFN- receptors were normal. A decreased expression of the NEMO protein was found, which led to functional assays, which also showed abnormal results. Molecular analysis detected mutations in the *NEMO* gene T1488C in Pt1 (detected post mortem) and A288P in Pt2. Both patients died of disseminated infection at 3 and 10 months of age respectively.
Conclusions: We present two patients with severe disseminated infection caused by *Mycobacterium bovis* as their first manifestation. However, besides the knowledge that NEMO deficiency may cause mycobacterial infection the clinical manifestation may overlap both diseases and the delay in the culture may complicated the initial suspicion of NEMO deficiency.

PO - 110

Severe Combined Immunodeficiency. About a Case

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Introduction: Severe Combined Immunodeficiency (IDCS) is a primary immunodeficiency with a decreased immune system and is caused by functional or structural abnormalities of genetic origin[1], has T-cell lymphopenia, with or without B-cell deficiency, NK cells, Phagocytic and/or complement, patients present infections by all kinds of microorganisms, a greater predisposition to tumors[2,3]. The incidence is 1/100,000 live births. The diagnosis of suspicion is clinical, the definitive diagnosis is identifying the mutation in the gene that codes for the affected protein. It is important to make an early diagnosis to avoid complications and sequelae by infections, definitive treatment through bone marrow transplantation[4]
Clinical case: Male of 2 years, consanguineous parents (cousins), mother with blindness secondary to brain tumor, newborn by cesarean section at 38 weeks, weight 3.400, up to 6 months, poor progress of weight, incomplete vaccines. From 6 months of life recurrent hospitalizations with multiple antibiotic regimens due to Gastroenteritis, Chronic Malnutrition, Moniliasis, Pneumonia, Suppurative Otitis, at 1 year 4 months presence of tumor in right eye. Complementary studies are performed: cellular compromise (TCD4 lymphopenia) and humoral (hypogammaglobulinemia), low uric acid. PAMO and tumor biopsy: Classic Hodgkin's Lymphoma, mixed cellularity variant. He receives chemotherapy with remission of the tumor, gammaglobulin every 3 weeks, prophylaxis with cotrimoxazole and fluconazole.
Discussion: It is important that we suspect and arrive at the definitive diagnosis and start early treatment; to prevent infections provide a better quality of life.
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PO - 111

Successful Management of Hydroxychloroquine in Lymphoproliferative Syndrome

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Autoimmune lymphoproliferative syndrome (ALPS), is described as a failure of the apoptotic mechanisms to mantain lymphocyte homeostasis, which presents as an accumulation of these cells in lymphoid tissue, hepatoesplenomegaly and recurring multilineage cytopenias. (1) This cytopenias occur since childhood due to autoimmune peripheral destruction and/or splenic sequestration of blood cells. Patients with ALPS have an increased risk of B-cell lymphoma. (2)
We describe 1 case of autoinmune lymphoproliferative syndrome, diagnosed in our hospital, in whom a heterozygous variation of FAS gene in c.683-704delinsCT was found, resulting in a deletion of 22 pairs of bases and an inserction of 2 pairs of bases which compromises the reading frame of the protein. The mutation has not been reported en NHBLI database.
We reviewed the literature regarding this syndrome and how it is treated.
The 1-day old patient presented within the 2 hours of being borned, with generalized petechiae, equimosis, splenomegaly and trombocytopenia. He was sent to our hospital for further studies. Infectious diseases such as Epstein Barr virus, parvovirus B19, cytomegalovirus, Herpes, HIV, Toxoplasmosis, were ruled out. Neonatal aloimmune trombocitopenia was considered initially, because mother had mild trombocitopenia as well. Immunoglobulin G and esteroids were started with apropiate initial response. He recieved eritrocyte and platelets transfussions. He was discharged from the hospital, never the less, he returned at day 4 with leucopenia, severe trombocitopenia and hepatosplenomegaly. He required a new cycle of eritrocyte and platelets transfusions. Bone marrow biopsy was done which reported abscense of abnormal T or B cells. Anas, C3 and C4, were done also as part of autoimmune study reporting normal in the patient and his mother. Vitamin B12 levels were above normal range. Systemic esteroid was indicated as a long term therapy for platelet stability. He recieved in total 4 cycles of inmunoglobulin. No celular or humoral immunodeficiency was documented. The patient's father had personal history of lymphoid mass and splenomegaly at age 9, and our patient had a 7 year old sister with splenomegaly since she was 6 months old, with later diagnose of autoimmune lymphoproliferative syndrome at age 1. Her last documented episode of cytopenia was when she was 6 years old, with no current treatment at the time our patient was borned. With these family's background, genetic test for ALPS was performed, founding a heterozygous variation of FAS gene in c.683-704delinsCT resulting in a deletion of 22 pairs of bases and an inserction of 2 pairs of bases which compromises the reading frame of the protein.

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Ataxia-Telangiectasia in Rio Grande do Norte: Immunological and Clinical Features of 5 Patients

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Introduction: Ataxia-telangiectasia (AT), an autosomal recessive genetic disorder, it's a syndrome characterized by progressive cerebellar ataxia, oculocutaneous telangiectasias, immunodeficiency and cancer susceptibility.
Case report: Five case reports (4 males and 1 female) are presented based on clinical and laboratory findings. Three of them have history of consanguinity. The age of diagnosis varied between 3 and 12 years. Three out of 5 patients presented ataxia as initial clinical condition at ages of 1, 2 and 6 years, and the other two presented pneumonia (PNM) at ages of 1 and 8 years. The most frequent clinical presentations were ataxia (100 %), cutaneous and/or ocular telangiectasias (100 %), dysarthria (80 %), ocular apraxia/dyspraxia (80 %). It was observed Cafe au Lait spots in two of them. Eighty-percent had previous history of infections, mainly PNM. Two patients started using wheelchair after 15 years of age. All they, except one, exhibited high levels of alpha-fetoprotein. There was a

variation in IgA concentrations: two patients presented normal values, two presented low and one presented elevated. In a singular case, number of B, T cells and subpopulations decreased. All patients received basic vaccination and prophylactic measures. One patient died at age of 18y due to respiratory insufficiency.
Conclusion: AT is a disorder associated with variable clinical and laboratory presentations. It should be suspected in children with early onset of neurological impairments, telangiectasia and recurrent episodes of infections. Early diagnosis is essential for management of clinical conditions, adoption of prophylactic measures, and genetic counseling of parents.

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Series of Scid Cases in Tertiary Pediatric Hospital

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Introduction: Severe Combined Immunodeficiency (SCID) are considered the most serious primary immunodeficiencies. In this report we will describe six cases of immunodeficiencies emphasizing symptoms, diagnosis and outcome.
Cases: Six patients, whose clinical, personal and family history and laboratory tests were compatible with severe combined immunodeficiency (SCID), were evaluated. The age at onset of symptoms varied between 1 month and 5 months of life and the diagnosis was between 1 and 7 months. Five patients were male and one female. All patients underwent a clinical and laboratorial screening protocol for primary immunodeficiency. They performed lymphocyte counts, Immunoglobulin dosages, immunophenotyping, serologies and investigation of opportunistic microorganisms. They have received immunizations, according to the current Brazilian calendar, until the moment of diagnosis, including BCG and rotavirus vaccine. And all the patients presented symptoms or complications related to them (diseases of the respiratory tract and gastrointestinal tract). Treatment included human immunoglobulin, antibiotic prophylaxis, antiretroviral, immunization with palivizumab and wide coverage for disseminated tuberculosis, with the exception of one of them. Four patients underwent genetic analysis, one with expression of CD45 and IL7ra (CD127) mutation, two of them with mutation not yet described in literature (de novo mutation). Hematopoietic cell transplantation (HCT) was indicated to all cases, but 2 them died before HCT. One patient received a successful haploidentic cell transplant, and now is cured and 3 are on post-HCT treatment.
Discussion: In these cases, we conclude that early diagnosis of SCID through the newborn screening with TRECs technique, is essential for early treatment with hematopoietic cell transplantation, that contribute for better prognosis and disease progression, enabling cure. It would also allow greater safety in the indication of the vaccines of living microorganisms, avoiding adverse effects and infection by these vaccines, as we have observed in all cases of our series. SCID is fatal, usually within the first year of life, unless the underlying defect is corrected.

PO - 114

Combined Immunodeficiency Syndrome in Adult Patient: New Phenotype

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Introduction: CD19 deficiency is a rare immunodeficiency with reduction of antibodies and B lymphocytes, but it may be accompanied by manifestations by atypical germs and be associated with another primary immunodeficiency even in adults.
Case Presentation: Male patient, 20 years old, previous history of recurrent urinary infections, respiratory infections and dermatitis since childhood. He started with diarrhea and evolved with arthralgias on elbows, knees and hands symmetrical, associated with morning stiffness longer than 2 h. He received treatment with prednisone 40 mg 1xd for 3 months with clinical improvement. Subsequently, he presented with herpes facial zoster with cellulites. He started with productive cough, dyspnea, fever, and fatigue. Chest CT revealed: tree opacities in budding in the middle lobe and right base, diffuse bronchiectasis in the middle lobe and lingula. Tests showed bronchoalveolar lavage with positive AFB and culture with Mycobacterium abscessus abscessus. He received treatment with amikacin, imipenem and clarithromycin for 60 days. Laboratory tests showed the following results: Hb 14.5 g / dL, VCM 83.1 micra, 169,000 platelets, 7010 leukocytes, 78 % segmented (5468 / mm3), 2 % lymphocytes (140 / mm3) Mm 3), 3 % eosinophils (210 / mm 3) 0 % basophils. Anti-HIV NR, anti-HTLV 1 and 2 NR, C3 100 mg / dl, C4 25 mg / dl, IGE 0.24 IU / ml, total protein 6 g / dl, albumin 4.83 g / dl, gamma globulin 0.40 g / dl (VR: 0.67-1.47 g / dl), IGA 57.4 mg / dl, IGF 345.5 mg / dl, IGM 41.4 mg / dl, 0.4 % CD19 (0.56 / 42 % (0.59 / mm3), CD3 66.2 % (92.7 / mm3), CD4 34.3 % (48 / mm3) HLA B27 positive, FAN NR, Rheumatoid factor NR, anti-A 1 / 64, anti-B NR, anti-rubella IGM NR, anti-rubella IGG Reagent. Lymphocyte immunophenotyping was carried out months after: total leukocytes 5800, 23.6 % lymphocytes (1369 / mm3), CD19 1.1 % (15 / mm3), CD20 1.2 % (16 / mm3), CD3 83.6 % (1145 / mm 3), CD4 48.7 % (667 / mm 3), CD8 35.7 % (489 / mm 3), NK 10.4 % (142 / mm 3). The patient received human immunoglobulin. Evaluation of IL12 / IFNγ Axis activity: LM + IL12 669.9 (control 7209.1 pg / ml), LM + IFNγ 10009.5 (control 1738 pg / ml), PPD + IL12 62.1 (control 6583 pg / ml), PPD + IFNγ 415.6 (control 354.6 pg / ml). He than started prophylaxis with itraconazole and maintained azithromycin for 1 year.
Discussion: The patient presented hypogammaglobulinemia associated with reduction of CD19 which did not justify the infection with Mycobacterium abscessus, so it was followed the investigation that evidenced IL12 Receptor Deficiency. Therefore, in the presence of atypical germs, it is important to further investigate other associated immunodefficiencies and thus to find Combined Immunodeficiency Syndrome even in adults.

PO - 115

Case Report of Wiskott Aldrich Syndrome with Thrombocytopenia and Variable Platelets Volume. New Mutations?

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Introduction: WAS is a rare X-linked immunodeficiency. The classic form is characterized by combined immunodeficiency, microplatelet thrombocytopenia, eczema, autoimmunity and neoplasia. We described 3 WAS cases with thrombocytopenia and platelets of variable volume.
Case report: Between 2014 and 2017, we followed 3 boys with eczema, recurrent infections and thrombocytopenia with platelets of variable volume. We confirmed the WAS by absence of marked WASP in lymphocytes and genetic mutations. **Patient 1**: 2 years old, had intermittent fever, thrombocytopenia and autoimmune hemolytic anemia. Exams: MPV: 3.54-14.8 fL, CD4 and CD8 < p10, reduced lymphocytic T proliferation, high levels of IgA and IgE, intermittent eosinophilia and neutropenia. Prophylaxis: trimethoprim sulfamethoxazole (TMT/SMT) and IVIG.

Follow up: sepsis by *Klebsiella pneumoniae* and *Enterobacter cloacae*, oral and esophageal moniliasis, recurrent herpetic stomatitis, esophageal stenosis secondary to EBV ulcers. Prophylaxis added: fluconazole and acyclovir.
Mutation: **Exon 02-g**.8422_8429delCCTTAGG/**p**.Gly125Ter. HSCT in 09/16/2016, 3 years old, good outcome. **Patient 2**: 3 months old, hospitalized with myocarditis, hypertension and hepatitis. Isolated CMV (PCR 14000 copies). Previous history: pulmonary sepsis by *S. aureus.* Recurrent herpetic stomatitis ocurred on follow-up. Prophylaxis: TMT/SMT, IVIG and acyclovir. Exams: MPV: 7.8-10.8 fL, CD4 < p10, normal lymphocyte T proliferation, high levels of IgA and IgE, intermittent eosinophilia.
Mutation: **Exon 07-c**.706C > T/**p.**Arg211X. HSCT was indicated. **Patient 3**: 7 months old, with enterorrhagia and recurrent cutaneous vesicles since 3 months old. Exams: MPV: 4.3-7.9 fL, CD4 < p10, CD8 > p90 and CD19 p10, IgE 2500, persistent leukocytosis and eosinophilia. Follow-up: ocular herpes, intermittent diarrhea, gastroenteritis by CMV (PCR 10000 copies) and sepsis by *S. aureus* and *K. pneumoniae***.** Prophylaxis: acyclovir and IVIG.
Mutation: **Exon 02-c**.313delC/**p**.Gln80Lys. HSCT was indicated.
Discussion**:** WASP is a regulatory key for signaling and reorganization of the cytoskeleton in hematopoietic cells. Phenotypes associated to WASP mutations range from X-linked thrombocytopenia to neutropenia and platelets with reduced, normal or large volume. The absence of microplatelets associated to the clinical condition and genetic analysis compatible with WAS shows that immune mechanisms are poorly understood and that studies with a greater number of patients are necessary.

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Novel Mutation Causing Activated PIK3KINASE Delta Syndrome (APDS) in a Brazilian Family

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Objective: To describe the clinical and immunological features, gene mutations and treatment of Brazilian family patients with activated phosphoinositide 3-kinase δ syndrome (APDS).
Method: We performed the genetic investigation on a family with 7 components presenting a presumed primary immunodeficiency disease due recurrent infections. Data from clinical features and laboratorial work-up were obtained on their medical files.
Result: The mean age of onset disease was 1 year old while the median age of diagnosis was 15 year old; four (57 %) patients were female. All patients present remarkable history of respiratory infections, including pneumonias (100 %), sinusitis (100 %) and bronchiectasis (85 %). They also present hepatosplenomegaly (100 %), lymphadenopathy (100 %), diarrhea (28 %), warts (85 %), and B cell lymphoma in one patient (14 %). Immune work-up showed elevated IgG (57 %), elevated IgM (28 %), low CD4 numbers (28 %), low CD19 levels (28 %) and poor response to polysaccharidepneumococcus vaccine in 6 patients (85 %). Six patients are on immunoglobulin replacement therapy with decrease on the number and severity of infections. After 5 years follow up, all 7 patients are alive; we indicated oral rapamycin for two patients in order to decrease the non-neoplastic lymphoproliferation. The pedigree was suggestive of an autosomal dominant pattern and genetic investigation showed a novel 9 base pairs heterozygous insertion in the exon 13 of *PIK3CD* gene leading to p.529insHEK located on the helical domain, associated with APDS.
Conclusion: APDS is a combined immune deficiency with a large spectrum of clinical and laboratorial findings. The variable allelic penetrance on heterozygous gain of function mutations is considered the source for different severity grades observed in patients with APDS. The immunoglobulin replacement is essential to improve quality of life and reduce pulmonary damage, even patients with normal IgG levels due the poor quality of their specific antibodies. As a novel mutation, the long term follow up of this family can improve the knowledge around APDS.

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Clinical and Laboratorial Features of Patients with 22Q11.2 Deletion Syndrome

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Introduction: 22q11.2 deletion syndrome is the most common chromosomal microdeletion disorder, estimated to result mainly from non-homologous meiotic recombination events (93 %) and can also appears in an autosomal dominant manner (7 %), occurring in approximately 1 in every 1,000 fetuses. The genetic tests currently used for diagnosis are FISH (fluoruescence in situ hybridization), MLPA (multiplex ligation-dependent probe amplification) or chromossomal microarray. Multiple findings can be found in these patients. Therefore, some phenotypes were already described such as DiGeorge syndrome, velocardiofacial syndrome, conotruncal anomalies face syndrome, Sedlackova syndrome, among others. In 1960s, when the illness was first reported and named DiGeorge syndrome, a clinical triad composed by immunodeficiency, hypoparathyroidism and congenital heart disease was described. Nowadays, DiGeorge syndrome is known to have a heterogeneous presentation that includes facial dismorphisms, palatal, gastrointestinal and renal abnormalities, autoimmune disease, variable cognitive delays, behavioral abnormalities and psychiatric illness.
Objectives: To evaluate the clinical and laboratorial features, as well as the outcome of 28 patients with DiGeorge syndrome.
Results: Twenty eight patients were evaluated. Eleven patients (39 %) have died between 4 and 7 months of life due to cardiac complications secondary to infections and cardiogenic shock. Three patients lost clinical follow-up. Twenty seven patients (96 %) presented some cardiac defect; 22 patients (78 %) presented thymus abnormalities (19 aplasia and 3 hypoplasia); 22 patients (78 %) presented immunodeficiency; 20 patients (71 %) presented dismorphisms and, 20 patients (71 %) presented hypocalcaemia. Genetic diagnosis was confirmed in 8 patients (7 patients by FISH and 1 patient by MLPA).
Conclusion: The main cause of death is cardiac defects and secundary complications. Neonatologists must be alert to these conditions, especially if associated with others typical features. Immunodeficiency can be present in most of cases and should be investigated especially in patients with thymus abnormalities. The lack of recognition, unfamiliarity with genetic tests and the wide variability of the clinical presentation lead to diagnosis delay. Early diagnosis, preferably prenatal or neonatal, could improve outcomes and reduce mortality.

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Omenn Syndrome: Description of a Clinical Case

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Introduction: Omenn Syndrome is a phenotype of Severe Combined Immunodeficiency (SCID) with onset shortly after birth. It presents with

generalized exudative erythroderma, hepatosplenomegaly, lymphadenopathy, recurrent infections, diarrhea, failure to thrive, eosinophilia and high IgE serum levels. It may be present in any type of SCID, being most frequent on patients with mutations in genes RAG 1 and RAG 2.
Description of the case: JKGB, female, born in 4/4/16, first daughter of nonconsanguineous parents. At 15 days of life, she presented with fever, skin peeling and edema. Sulfametaxazole and trimethoprim were prescribed without improvement. Purulent skin exudation, diarrhea and irritability were additional manifestations. Physical examination with 46 days of life revealed generalized erythroderma and skin peeling, anasarca, rarefaction of eyebrows and eyelashes, hepatosplenomegaly and multiple adenopathies. Laboratory tests showed anemia, lymphocytosis (27000 cells/mm^3), eosinophilia (>5000 cells/mm^3), IgE >5000 mg/dL, hypoalbuminemia and absence of thymic shadow in chest X-ray. Despite the presence of lymphocytosis in peripheral blood, lymphocyte immunophenotyping evidenced the absence of naive T and B cells, with the presence of NK cells. TREC (T Cell Receptor Excision Circles Analysis) was performed with a value of 2/μL (normal- >25 μL). Donor research has begun for hematopoietic stem cell transplant. The recommended treatment was human immunoglobulin infusion, cyclosporine, corticosteroids, as well as prophylaxis with fluconazole, isoniazid and sulfametaxazole and trimethoprim. At seven months, patient started with septic shock, acute respiratory failure and death.
Conclusion: This case demonstrates the importance of early diagnosis of SCID with immediate institution of treatment. The delay in the diagnosis or in the accomplishment of the hematopoietic stem cell transplant can compromise the prognosis, due to progressive clinical deterioration of the patient.

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Case Report: Delayed Diagnosis of SCID patient due to Unnoticed Warning Signs of the Disease

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Introduction: Severe combined immunodeficiency (SCID) is a group of genetic disorders characterized by T lymphocyte defect due to arrest of T-cell differentiation, which can be associated or not with disturb of differentiation of B lymphocytes and natural killer (NK). The lack of lymphocytes results in early onset of severe and recurrent infections. Without proper diagnosis and treatment, patients might die by the age of one year. Candidiasis, persistent diarrhea, growth impairment and interstitial pneumonitis are the most frequent manifestations. In countries where BCG vaccine is mandatory, adverse reactions to BCG can be the earliest warning sign suggesting a primary immunodeficiency, such as SCID. Newborn Screening is able to identify SCID patients through TREC and KREC quantification by Real Time PCR.
Case report: Male, full-term, Brazilian, born to nonconsanguineous parents. He received BCG, in his first week of life. At 1 month, he started receiving cow milk formula and presented melena. At two months he had an episode of diarrhea, fever, eczema, and cough. His blood count showed 17.610 /mm3 leukocytes with 10 % lymphocytes and he was hospitalized for 7 days to receive intravenous antibiotics. Despite the use of different milk formulas he continued to present diarrhea. When he was four months old, he presented fever, diarrhea and cough, with normal chest x-Ray. The diagnosis was rotavirus infection. Fifteen days later, he was admitted to the ICU with pneumonia. BCG vaccine was not healed after four months, showing suppuration and axillar lymphadenopathy. White blood cell count showed reduced number of lymphocytes. By suspecting of SCID flow cytometric was performed and revealed the baby to be a $T^-B^-NK^-$ SCID. Intravenous immunoglobulin and daily antibiotic and antifungal drugs were used until he could be submitted to hematopoietic stem cell transplantation (HSCT).
Discussion: By reviewing the patient's history we observe lymphopenia since his first hospitalization, at 2 months. Even if excluding cow milk protein did not resolve gastrointestinal symptoms the child was treated as having allergy up to four months. Right axillary lymphadenopathy and persistent ulcer at the site of BCG vaccine did not raise aware to immunodeficiency. Newborn screening for SCID is essential to enable early diagnosis, since it does not rely on recognition of clinical and laboratorial signs.

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Routine Lab Tests Surveillance: a Success History of Pid Identification

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Introduction: DiGeorge Syndrome (DGS) occurs due to a deletion on chromosome 22 (22q11 del). Clinical manifestation is highly heterogenous. Absence or hypoplasia of the thymus is common and results in immunodeficiency due to T lymphopenia. Heart abnormalities are also related to DGS, mainly cono truncal deformities, however some studies link congenital heart diseases to DGS as well. Parathyroid dysfunction may cause hypocalcemia and seizures. A systematic active search for primary immunodeficiencies in our hospital, based on surveillance of laboratorial tests, was responsible for the identification of a baby with lymphopenia.
Case Report: The patient, a 4 month old girl, was admitted to the intensive care unit due to a cardiac arrest after seizures. She was born to nonconsanguineous parents and had no family history of neurological or cardiac disorders. There were no reports of previous infections in the hospital chart. After the identification of lymphopenia we started immunological evaluation. By the time of interview with her parents we found out that the baby was receiving isoniazid to treat a local BCG adverse reaction. Low calcium levels were identified among the exams done during ICU admission. TREC and KREC were performed showing 0 to TREC and 144 to KREC. Flow cytometry was consistent with TREC and KREC assay, revealing absence of CD3, CD4 and CD8, CD19 1.247 cells/ul and NK 381. She developed enlargement of right axillary lymph node and presented no healed BCG scar. Echocardiogram showed valvar pulmonary stenosis and short pericardial leakage, with patent oval foramen. Fluorescent in situ hybridization (FISH) showed a 22q deletion. Since the identification of immunodeficiency the child receives treatment for BCGitis, daily prophylactic antibiotic and antifungal and immunoglobulin replacement each 21 days.
Discussion: A systematic surveillance of laboratorial tests generally performed in our hospital allowed the identification of a primary immunodeficient patient before infectious complications, other than BCG adverse reactions, were installed. While newborn screening for primary immunodeficiency is not mandatory in our country this can be a strategy to help improving primary immunodeficiencies presenting with cytopenias.

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Novel JAK3 Mutation in a Brazilian SCID Patient Disrupts Splicing Causing Exon 17 Skipping

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Introduction: Severe Combined Immunodeficiency (SCID) is the most severe form of primary immunodeficiency, typically characterized by absence of T cells, causing a profound impairment of cellular and humoral immunity. Defects in *JAK3* are known to cause an autosomal recessive form of SCID with absent or markedly diminished numbers of T and NK cells and normal numbers of B cells (T-B + NK-SCID). Clinical presentation includes early onset recurrent infections by opportunistic pathogens, diarrhea, failure to thrive and severe reactions to live vaccines, leading to progressive morbidity and mortality unless hematopoietic stem cell transplantation (HSCT) is performed. Here we describe a female SCID patient with a novel splice site mutation in *JAK3* diagnosed early in life before the presence of recurrent infections due to family history.
Case presentation: A.R.R., Brazilian, female, 2 months old, presented a facial rash and was referred for immunological evaluation due to a deceased brother suspected of SCID. The patient presented undetectable TRECs (T-cell receptor excision circles) and normal KRECs (kappa-deleting recombination excision circles), and lymphocyte subset counts defined a T-B + NK- SCID ($CD3^+CD4^+$: 61 cells/m^3; $CD3^+CD8^+$: 162 cells/mm^3; $CD19^+$: 1145 cells/mm^3; $CD3^-CD16^+CD56^+$: 39 cells/mm^3). The *JAK3* gene sequence was investigated by *Sanger* sequencing and exhibited a homozygous single nucleotide variant (c.2350G > A) located at end of exon 17 that predicted a disruption of the donor splice site. The cDNA sequencing was performed and found to have an absence of exon 17, which confirmed the predicted effect on the mRNA sequence. This alteration creates an in frame reading leading to a premature stop codon 60 amino acids downstream of the mutation and predicts a truncated nonfunctional protein. The patient was submitted to HSCT with minor complications and after 2 years, she continues well under bone marrow transplantation follow-up.
Discussion: The present case illustrates the importance of early diagnosis and active treatment for SCID patients which correlates with better outcomes. The newborn screening for SCID is a reliable, cost-effective and feasible method to reach this goal and has been used in several countries. This case also presented a novel splice mutation on the *JAK3* gene and the methodologies used to approach the causal association between genotype and phenotype, essential to access the mutation pathogenicity and provide information for genetic counseling.

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Phenotypic Expression in Omenn Syndrome with Homozygous RAG2 Mutation in a Mexican Patient

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Introduction: Omenn Syndrome (OS) is a primary immunodefiency caused by hypormophyc RAG mutations. The clinical and immunologic manifestations are: early-onset erythroderma, lymphandenopathy, hepatoesplenomegaly, eosinophilia and severe hypogammaglobulinemia with increased IgE levels and presence of autologous, oligloclonal activated T cells with absents B cells. Interestingly, the patients with RAG 1/ RAG2 mutation have a wide variability of clinical phenotype, from a Severe Combined Immunodeficiency (SCID) to the atypical OS.
Our work is focused on the identification of genetic mutations in a patient with clinical manifestations of atypical OS.
Clinical presentation: 8 months old girl with healthy consanguineous parents (cousins in first degree), at birth she was vaccinated with BCG and B hepatitis. Her 3 siblings died: a sister at 2 months old, secondary to pentavalent vaccine, brother at 3 month old because pneumonia and brother with SCID at 12 months old, after hematopoietic stem cell transplantation (HSCT). At 1 month and 27 days old she presented bilateral otic effusion, eczema, alopecia, generalized dermatitis, both last lessons of 5 days of evolution. Otitis improved but at 3 months old she presented protacted diarrhea and one month later, pneumonia. Generalized dermatitis and alopecia worsened and treatment with immunosupressors was started. Laboratory test: Leucopenia, lymphopenia, eosinophilia, positive PCR CMV, IgG: 223 mg/dl, IgA: 1 mg/dl, IgM: 1 mg/dl, IgE: 0.08 UI/ml. Lymphocytes: 1097 cel/ul, CD3+: 577 cel/ul, CD4+: 534 cel/ul, CD8+: 26 cel/ul, CD19+: 3 cel/ul, CD20+: 1 cel/ul, CD16 + 56 + 57+: 515 cel/ul, antiCD3 and PHA lymphocytic proliferation was positive, CD45 + RO+: 5264 cel/ul, CD45+ RA+: 1 cel/uL. Exome sequencing shows homozygous mutation on RAG2 c.104G > T, p. G35V. The mutation was verified by Sanger sequencing in the patient and as in the parents. Treatment was started with GGIV, cotrimoxazole, fluconazole, antifimics, antibiotics and antivirals and on May, 31 2017, HSCT was performed.
Discussion: The clinical and immunologic manifestations are compatible with atypical OS. The immunophenotype was T + B-NK+ the lymphocyte proliferation was normal and we found mainly CD45 + RO+ T cells wich shows that these cells are from the mother. Genetic studies based on a new generation sequencing reported mutation on RAG 2 c.104G > T, p.G35v. This mutation has been reported in other three patients around the world, but in our knowledge its the first mutation in México and the first for an atypical OS.

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Two Novel Mutations in *ZAP70* Gene that Result in Human Immunodeficiency

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The essential role of ZAP-70 in TCR signal transduction has been demonstrated by defects in the development and activation of T lymphocytes as a result of ZAP-70 deficiency. Most ZAP-70-deficient patients suffer from a form of severe combined immunodeficiency characterized by a selective lack of peripheral CD8+ T cells and the presence of peripheral CD4+ T cells that remain unresponsive to TCR-mediated stimuli *in vitro*. Moreover, the majority of the patients have normal B cell numbers, although some differences in B cell function have been noted. Accordingly, various ZAP-70 mutations have been described, resulting in distinct forms of human T cell-immunodeficiency. In most cases, the mutations are located within the kinase domain and result in the absence of ZAP-70 protein. Here we describe two novel mutations in the ZAP-70 protein of a one-year-old patient with clinical manifestations that are consistent with those reported for most patients with ZAP-70 deficiency (recurrent

infections, chronic diarrhea, failure to thrive, and low numbers of circulating $CD8^+$ T cells). Protein 3D modeling predicted that the resulting amino acid substitutions (G13R and R400W) were probably deleterious for function. Bioinformatic analyses also revealed that G13 and R400 of ZAP-70 are almost perfectly conserved among vertebrates and no SNPs have been reported at these positions. We further describe that these mutations result in important reduction of ZAP-70 protein expression and inability to mediate TCR-dependent signals. Importantly, we have characterized the second mutation reported for the first SH2 domain of ZAP-70.

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Severe Combined Immunodeficiency - Case Report

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Introduction: Severe combined immunodeficiency (SCID) is a primary immunodeficiency with several genetic causes that lead to severe deficiency of T and B lymphocyte function with low antibody production. In some types of diabetes, there is also disfunction of Natural Killers - NK cells. This case report describes a child with severe combined immunodeficiency with absence of T and B lymphocytes (SCID T-B-NK +).
Case presentation: Infant, 3 months old, male, presented sepsis with a pulmonary focus. BCG vaccine scar with phlogistic signs and ipsilateral axillary lymph node enlargement. Born of cesarean delivery, term, birth weight 3560 g. The BCG and Hepatitis B vaccines were administered at the Hospital, and also vaccinated with VIP, PENTA, Rotavirus and Pneumococcal. Consanguineous parents - first cousins. The patient has a 9-year-old sister and his brother died at 7 months old for sepsis and BCGitis. Hemoglobin: 8.83 g / dl; Hematocrit: 25.90 %; Platelets: 374 mm^3; Leukocytes: 1.940 mm^3; Segmented: 368 mm^3; Rods: 77.6 mm^3, Metamielocytes: 97 mm^3, Myelocytes: 33 mm^3, Lymphocytes: 291 mm^3, Monocytes: 795 mm^3. Immunoglobulins: IgA: 4 mg / dl; IgG: 84 mg / dl; IgM: 5 mg / dl. TRECs and undetectable KRECs. Immunophenotyping by flow cytometry Lymphocytes: Total 690 mm^3, CD3 - 3 % (20.8 mm^3), CD4 - 1.9 % (12.4 mm^3), CD8 - 0.21 % (1.4 mm^3), CD45RA + CCR7 + - 18.2 % (0.3 mm^3), CD 19 - 0.72 % (5 mm^3) and NK - 91 % (627.9 mm^3). HLA 100 % compatible with a transplantation of bone marrow transplantation, nowadays the patient is in post-transplant follow-up.
Discussion: Studies estimate that 6 million people are living a type of immunodeficiency all over the world. Primary immunodeficiencies more than 250 different entities, among which SCID is included, constituting a severe form of immunodeficiency, which requires attention. Some countries already have TREC dosages included in the neonatal screening program. In Brazil, this screening is not yet available in the Public Health Care, however, children with recurrent sepsis infection or family history of early death should be investigated for immunodeficiency.
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Particularities of Newborn Screening in Preterm Babies: a Case Report

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Introduction: Severe Combined Immunodeficiency (SCID) is a group of disorders that are characterized by the absence of T lymphocyte. Furthermore, issues in B lymphocytes and natural killer (NK) cells development could also be present (T-B + NK+, T-B + NK-, T-B-NK+, and T-B-NK-). Although newborns with SCID appear healthy at birth, they are more susceptible to severe infection, which initiates in the first months of life. Moreover, without a treatment SCID patient may die by two years old. For these reasons, early diagnosis is crucial for patient prognosis and newborn screening by TREC and KREC quantification is the indicated approach.
Case Report: A girl that was born at 28 weeks of gestation due to maternal hypertension and fetal bradycardia. The parents are non consanguineous. She was taken to intensive care unit soon after birth and developed two pneumonias in her first month of life, a fungal sepsis, and acute renal injury. After that, she was referred to our hospital. At this time she presented a splenic abscesses, jugular thrombosis and anasarca. We observed low levels of lymphocytes in blood cell count and performed TREC and KREC quantification by qPCR, which showed a T-cell lymphopenia (TREC: 0 copies/μl and KREC: 364 copies/μl). The result was consistent with flow cytometric analysis showing low T and normal B cell numbers. Considering her medical history and lab tests she was diagnosed with SCID. However, we performed DNA sequence of SCID related genes for this baby and found no pathogenic mutations. The baby died from pulmonary complications after a few weeks.
Discussion: Several studies described that preterm newborns have a more immature immune system when compared with term newborns. Consequently, they are more susceptible to infections and sepsis. Furthermore, some newborn screening programs demonstrate that preterm infants have a high rate of false positive results when the exam is done before the equivalent age of 37 weeks gestation. For our patient, the TREC and KREC assay was performed earlier than that, and we did not have time to repeat the test. Immunophenotyping have some particularity in preterm as well, because of lack of age-matched reference values, prenatal corticosteroid administration and the chance of maternal or post-transfusion engraftment. A broader and more careful analysis of SCID neonatal screening are necessary to establish values and warning signs for preterm babies.

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Hemophagocytic Lymphohistiocytosis Associated with Severe Combined Immunodeficiency in Adolescents: Clinical and Laboratory Evolution

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Introduction: (HL) is characterized by high fever, hepatosplenomegaly and neurological signs associated with pancytopenia, hepatitis, hypertriglyceridemia, hypofibrinogenemia, hyponatremia and increased ferritin.
Case Report: LMF, male, 18 years old, diagnosis with HL sindrome and Severe Combined Immunodeficiency 2 years ago. Pacient without

underlying pathology, was admitted to the pediatrics sector with diffuse skin lesions (ulcers and crusts), weight loss (6 kg in 1 month), fever, started 7 days before admission. Exams: leucopenia, gA = 0/IgM = 55/IgG = 510/IgE = 180/C3 = 57/C4 = 11/DHL = 399; Ferritin = 14575 and biopsy of skin lesions with necrosis and bacterial colonization. Even with antibiotic therapy, he maintained a high fever daily, poor perfusion and hypotension. On the 17th day of hospitalization, presented generalized tonic-clonic seizure, cyanosis in the extremities, and was transferred to the ICU, where he stayed for 11 days. Myelogram on day 17 of hospitalization: pancytopenia and rare histiocytes in hemophagocytes. Immunophenotyping: low values of B lymphocytes, T lymphocytes and Natural killer cells. No related causes were found like specific malignancies, autoimmune or infectious diseases. No family history suggestive of LH. The patient receave treatment with Etoposide for 10 months and intravenous immunoglobulin replacement, with clinical and laboratory improvement. After one month of treatment, after a new myelogram, he did not present cells in hemophagocytosis. Immunophenotyping, after 9 months, showed improvement of B lymphocytes, T lymphocytes and NK. IgA < 41;IgG = 691;IgM = 33;C4 = 40;DHL = 142. Currently using cyclosporine and human immunoglobulin, chemoprophylaxis with acyclovir, bactrim® and fluconazole. Due to the clinical and laboratory improvement, there was no indication of transplantation.
Discussion: HL is a rare, serious disease and may be confused with sepsis. Its highest prevalence is in childhood. There are two forms: genetics, related to underlying defects such as Chediak-Higashi Syndrome, and acquired immunodeficiencies, which may also be associated with genetic mutations, viral, autoimmune or neoplasia. We report a case in adolescent, probably secundary to infection and up to the moment with a satisfactory evolution.

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Griscelli Syndrome Type-2 with Hemofagocytosis: a Case Report in the Hospital Escuela Universitario

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Introduction: In 1978 Griscelli and Prunieras described the first case of Griscelli Syndrome (GS) associated with partial albinism and immunodeficiency, describing that it is an autosomal recessive disorder, reported in at least one hundred cases in patients with origin from the Middle East or Mediterranean and born in family consanguineous[1]. At present, this is classified into three types based on their clinical manifestations and molecular diagnosis, which are detailed below: GS-1 with a mutation in the gene that codes myosin Va (*MYO5A*) located on chromosome 15q21, in charge of regulation and transport of melanin to organelles of melanocytes and neurons. When presenting the mutation, phenotypically shows partial albinism and neurological disorders by pathological deposition of melanin in the central nervous system that occur at birth[2]. GS-2 has a mutation in the *RAB27A* gene, also located on chromosome 15q21, which is involved in the secretory pathway with intracellular regulation, being essential for the release of cytotoxic granules of T lymphocytes, NK and cell destruction, leading to an uncontrolled cytotoxic activity of lymphocytes and macrophages leading to a Hemophagocytic Lymphohistiocytosis (HLH) characterized by a proliferation of normal morphology histiocytes with intense phagocytic activity of hematopoietic cells along with fever, cytopenia, anemia, jaundice by hepatosplenomegaly. Histopathological findings include: an accumulation of lymphocytes and macrophages in tissues such as spleen, lymph nodes, bone marrow, liver and cerebrospinal fluid along with partial albinism and blond-platinum hair[3]. Between 80% and 90% of the cases present elevated triglycerides, but the more specific ones increase their values in ferritin and the cytokines TNF and INF-γ. Mortality related to the syndrome is high, initiating treatment early with immunochemotherapy and bone marrow transplantation. In the case of GS-3 it is a benign form with partial albinism without neurological or immune affectation[4]. In this paper, we describe the first case of GS-2 diagnosed in Honduras clinically and confirmed with molecular tests.
Case presentation: Female patient from the Pajarillo Village in Cantarranas, Department of Francisco Morazán, 2 years old, weighing 10.4 kg, size 86.5 cm, has pale skin, with blond-platinum hair (Figure 1.A) and no hypopigmentation in the iris. He attends the Cantarranas Health Center because he shows a generalized clonic tonic convulsion with oculogyrics. Due to the severity of the clinical manifestations, it is referred to the Hospital Escuela Universitario (HEU) in Tegucigalpa, showing in the initial evaluation: otorrhea of the right ear; fever of 38.5 °C for two continuous weeks; Jaundice; Hepatosplenomegaly with collateral circulation; edema in lower limbs; Hemiparesis Brachiocrural right; Diarrheal episodes. Laboratory tests are requested, revealing the following: Hemogram showing pancytopenia, prolonged coagulation times, bacteriological cultures without growth of microorganisms, decreased albumin, hypertriglyceridemia, hypercholesterolemia, liver function tests altered with these results, arouses the suspicion of a Myeloproliferative Syndrome. Bone marrow aspirate is performed, reporting moderate phagocytosis of red series and flow cytometry showing decreased counts of: CD3, CD4, CD19, CD56. During the first days in the hospital the patient is still febrile, with a general state of decay. Hair samples showing accumulations of melanosomes were observed under the microscope (Figure 1.B). In addition, a Brain Computed Axial Tomography (CAT) was performed showing a hypodense region in the left temporoparietal zone (Figure 1.C). For the above described, GS2 was diagnosed clinically, starting the treatment when applying: triple Dexamethasone, Etoposide VP-16, Cyclosporin along with antibiotic coverage to avoid bacterial infections[5,6]. Thus, the search for the gene mutations is performed by means of next generation sequencing. A homozygous mutation (G>C transversion) was found in the position G 55,516,086 (GRCh37/hg19) of forward strand, which corresponds to an absolutely conserved G in the donor-splice site (467+1 G>C). This mutation would disrupt splice in this site, and if a resultant mRNA is translated, it would generate a protein truncated at amino acid position G156. For two months, she was treated with a favorable response, recovering and granting discharge. The patient keeps control and review, but this was abandoned. After eight months of diagnosis, he returns to the hospital with complications presenting with a brain abscess, leading to a septic shock and then death.
Discussion: A total of 101 cases with clinical and laboratory characteristics of GS2 have been reported in the literature. Among the total number of cases, 54 patients were sequenced to search for the mutation for GS2, according to the *Online Mendelian Inheritance in Man (OMIM)*[7].
Clinically, patients with GS2 may have a presentation to HLH, partial albinism and blond-platinum hair, with susceptibility to recurrent pyogenic infections, recurrent episodes of fever, hepatosplenomegaly, and lymphadenopathy. In most cases with GS2 develops HLH, being known as the "accelerated phase" that manifests from 6 months to 12 months of age. In neurological symptoms, it can be observed in GS2 patients, which are related to the development of HLH[8]. However, since blond-platinum hair coloration may be subtle, it is important to consider the diagnosis in patients without obvious signs, as they are initially diagnosed with HLH, further stressing the importance of considering GS2. As the patient presented partial albinism and blond-platinum hair, also characteristic in Chediack-Higashi Syndrome, but when she observed on the bone marrow aspirate plate, she did not present intracytoplasmic inclusions in the neutrophils[9] but a red series haemophagositosis. In addition, they presented hepatosplenomegaly, marked neutropenia and hypertriglyceridemia, which are included in the diagnostic criteria of the Histiocyte Society for Hemophagocytosis[5]. At the same time, the diagnoses of: Myeloproliferative Syndrome, Gastroenteritis, Hemolytic

Anemia, Hepatitis Infection, Autoimmune Hepatitis, Mononucleosis and Leptospirosis were ruled out.

Also, current HLH therapy is targeted against the T lymphocyte and hyperactivated histiocytes[10], combining pro-apoptotic chemotherapy with immunosuppressants. The use of the HLH-94 protocol of the "Histiocyte Society" as a treatment guide was intended to obtain remission of the inflammation state and to cure definitively with allogeneic transplantation of hematopoietic stem cells. HLH-94 combines Etoposide / Dexametazone Intravenous or oral together with maintenance therapy with cyclosporine. As for the molecular diagnosis in identifying the *RAB27A* gene and family history of consanguinity through records, with several early deaths in the patient's family, it was valuable information to support the decision to perform the treatment and genetic counseling. GS-2 with an early diagnosis is important, since it facilitates the early initiation of an adequate treatment, reducing the risk of developing neurological sequelae. Limitations were present during the study of this case, since we lacked some routine and special laboratory tests to evaluation and control, such as: Ferritin, histocompatibility tests to perform to patients and relatives as possible bone marrow donors.

Acknowledgements: Genomic Medicine of HCFMRP-USP, and FAPESP and CNPq for financial support to EME and Dr. Jorge Carrasco, Microbiology Faculty, UNAH.

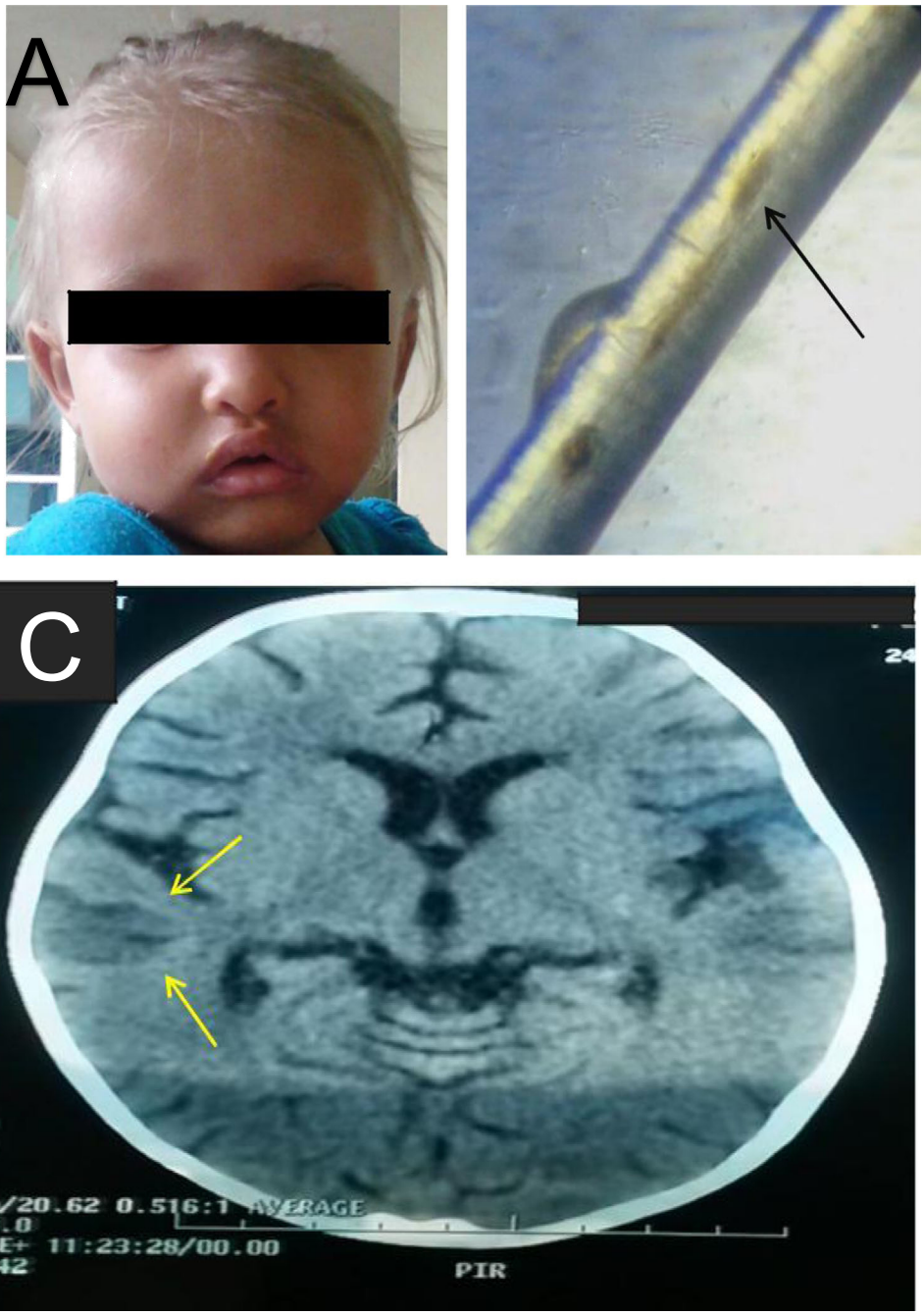

FIG 1. Images of alterations by GS-2. (A) Patient with blond-platinum hair (B). Hair of the patient with irregular pigmentation and accumulations of melanin observed under a microscope at 40 x. (C) Hypodense region in left temporal-parietal area seen from a CAT. Source: Photographs taken by David Peralta and the Department of Radiology HEU. September 2015.

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The First Patient Reported with Genetically Confirmed X-Linked Severe Combined Immunodeficiency in Peru Treated with Gene Therapy

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Introduction: X-linked severe combined immunodeficiency (X-SCID) is a life-threatening condition that impairs cellular and humoral immunity [1]. Mutations in the IL2RG gene lead to absent production of the common gamma chain protein [2, 3], resulting in an absence of T and NK lymphocytes, with a normal B-lymphocyte count [4]. Immunoglobulin production is impaired despite the presence of normal B-cell numbers [5]. Patients present in the newborn period with chronic diarrhea, failure to thrive and severe, recurrent infections. [7-9]. Asymptomatic children with family history of X-SCID should be fully evaluated.

Case presentation: X-SCID was suspected in pregnancy because patient´s mother, a 33-week-pregnant woman, came to her medical check up with a great fear: her 2 previous sons died by severe early-onset infections; one of them had no T lymphocytes. She was concerned that her coming male baby would have the same outcome. Since X-SCID diagnosis rose to 50 %, we decided to manage him as potentially sick: cesarean birth, strict isolation, breastfeeding and vaccines avoidance, immunologic testing to confirm diagnosis and urgent hematopoietic stem cell transplantation (HSCT). At birth, immunophenotype was compatible with X-SCID and genetic tests confirmed the diagnosis. Intravenous immunoglobulin and antibiotic prophylaxis was initiated until referral patient for an available novel treatment: gene therapy.

Discussion: Regarding our case, patient's family history allowed us to suspect X-SCID and to establish an appropriate management since birth. Our patient had a classical immunophenotype. As we expected, a pathogenic mutation was found in the IL2RG gene. Primary treatment for X-SCID is HSCT [10, 11]. It has been established that better outcomes are achieved in patients who receive transplantation in early infancy, below 3.5 months of age [10]. Temporary management includes immunoglobulin administration and antibiotic prophylaxis [12]. The role of gene therapy is being investigated; there is evidence of effectiveness, but potential of oncogenic insertions should be considered [13]. Patient was referred for a gene therapy protocol because there was no sibling donor and lack of experience in haploidentical HSCT in our home institution.

Conclusions: We report the first patient with genetically confirmed X-SCID in Peru. Diagnosis was suspected due to his family history. Early diagnosis allowed an adequate management until his referral to a gene therapy protocol. Family background is a key point, allowing a timely diagnosis and a prompt immune reconstitution.

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Disseminated Mycobacteriosis: a Warning Sign for Primary Immunodeficiency

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Introduction: The Bacille Calmette-Guerin (BCG) vaccine, composed of a live, attenuated Mycobacterium bovis strain, is used to prevent severe forms of tuberculosis, inducing T-helper type 1 (Th1) responses. In Brazil, the BCG vaccine is administered soon after birth. Although considered generally safe, there are several complications, ranging from local reaction to disseminated mycobacteriosis. However, disseminated BCG disease, which is associated with a high mortality rate, is very rare, suggesting an underlying immunodeficiency.
Case presentation: we present a five-months-old-male, referred to the immunology department of the Clinics Hospital of Federal University of Minas Gerais. During hospital admission, was reported a daily fever, since 3 months of age, associated with hyporexia and loss of weight. Parents observed an ulcerated, purulent, progressively increasing lesion at the site of administration of the BCG vaccine, with no signs of expected healing. Search for bacillus acid alcohol positive. Diagnosis of disseminated mycobacteriosis was performed during hospitalization (total time spent in hospital: 35 days). Previous history: newborn term, cesarean, birth weight = 3600 g, Apgar 9/9; made oral home antibiotic therapy (amoxicillin) on two occasions (otitis / persistence of fever); no history of respiratory infection; vaccines updated (at the time). Family History: non-consanguineous parents; has two brothers (male gender, healthy). He presented the following changes in laboratory screening for primary immunodeficiency: absolute lymphopenia associated with eosinophilia, immunophenotyping of lymphocytes (T-B + NK-) and IgA and IgM immunoglobulins decreased. Diagnosis of severe combined immunodeficiency (SCID). Currently, at 10 months of age (birth date: 09/08/2016), with adequate neuropsychomotor development and satisfactory weight gain, using: Human Immunoglobulin IV every 21 days, Tuberculostatics, Fluconazole and SMT + TMP prophylaxis. He's waiting for the transplant, scheduled for August 2017, with a related allogeneic donor.
Discussion: the administration of BCG vaccine soon after birth remains controversial, since it may be difficult to distinguish between those with primary immunodeficiency in a such early age, which would contraindicate the use of the vaccine. Therefore, the diagnosis of SCID is often made after the onset of severe infections and after administration of the BCG vaccine.

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Chronic Diarrhea and Hepatitis by Epstein-Barr Virus: a Case of Combined Immunodeficiency

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Introduction: Combined immunodeficiencies (CID) are rare genetic disease group characterized by T-cell lymphopenia with a lack of cellular and/or humoral immunity[1]. Several types of CID have been defined. Severe combined immunodeficiency (SCID) the most severe and letal form. Mutations in 39 different genes have been found to cause these conditions[2]. Affected children develop severe bacterial and viral infections usually within the first six months of life[3]. Therefore, early diagnosis of CID is crucial in order to reduce the risk of early death and to improve the long-term quality of life[4].
Case presentation: We describe an atypical case of SCID in a nine-year-old girl presenting chronic diarrhea that led to faltering growth and Epstein-Barr virus chronic infection. Evolution: A nine-year old girl who presented chronic diarrhea associated with abdominal distension and failure-to-thrive within the first year of life. She was first evaluated at the Pediatrics Outpatient Clinic and celiac disease was suspected. Gastrointestinal endoscopy was performed and biopsy showed vilosity atrophy, gastritis by H. pylori and duodenal cryptosporidiosis. A gluten-free diet was initiated with maintenance of low ponderal gain. During follow-up, hepatomegaly was notated and hepatic biopsy was performed, which showed chronic hepatitis. Serologies to CMV, toxoplasmosis, hepatitis (A, B and C) and HIV were negatives. EBV serology was positive (IgG > 750 and IgM > 160). Immunological investigation was performed (Table 1). Due to suggestive clinical presentation and diminished cellular immunity, diagnose of combined immunodeficiency was made. Genetic analysis to seven important genes for SCID was done, which showed one homozygotic missense mutation at exon 4 on IL7R gene (c.412G > A). Patient was referred to a Transplantation Center.
Discussion: CID is a genetically heterogeneous group of disorders affecting T cell development that causes symptoms in early infancy, typically pneumonitis, chronic diarrhea and failure to thrive[1]. Usually infants with SCID suffer from fatal opportunistic infections caused by bacteria, viruses, mycobacteria or fungi, however there has been reported a significant number of patients with similar symptoms beyond the age 1 year over the last decade[5]. These atypical features in older patients are characterized as SCID variants, caused by hypomorphic mutations of the same genes that cause classical SCID[2]. Therefore, SCID may not be not clinically apparent at birth and some infections complications may not initially be distinguishable from routine childhood infections, which leads to delayed diagnosis[6]. Mutation on IL7R gene, as found in this patient, predispose to severe viral infections, such as EBV[7]. Early diagnosis is important for diminishing infectious complications and improving overall survival after transplantation.

Table 1 – Laboratory tests

Imunoglobulins			
AGE 3	IgA - 827mg/dl; IgM - 231mg/dl; IgG - 2380mg/dl		
AGE 5	IgA - 1398,1mg/dl; IgM - 158,3mg/dl; IgE - 50,9UI/dl		
AGE 7	IgA - 1591mg/dl; IgM - 156mg/dl; IgG - 1577,0mg/dl IgG1 - 12100mg/l IgG2 - 2810mg/l IgG3 - 667mg/l IgG 4 - 587mg/l		
Subsets of T-cell			
AGE 8	CD4 -780mm³/46,7%	CD8 - 296mm³/ 17,7%	CD19 - 306mm³/ 18%
Complement system			
AGE 6	C3 - 206,1mg/dl	C4 - 31,1mg/dl	CH50 - 202 U CAE
Autoantibodies			
AGE 3	Tissue antitransglutaminase IgA 48,9	Anti-Endomysium IgA 1/10	
AGE 5	Tissue antitransglutaminase IgA 56,4	Anti-Endomysium IgA negative	
AGE 7	FAN 1/160		

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NF-KB2 Mutation in a Girl with Early Onset CVID, Alopecia Totalis and Functional NK Cell Deficiency

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Introduction: Heterozygous c-terminal variants in NFκB2 have been associated to early onset CVID, central adrenal insufficiency and ectodermal dysplasia. Affected natural killer (NK) cell function has only been described for one case in literature. We present a patient with early onset CVID, complete alopecia and severe systemic recurrent CMV infection associated with functional NK cell deficiency.
Case Description: A previously healthy girl with no family history of endocrine or immunologic diseases presented at 2 years of age with hair loss progressing to alopecia totalis; trachyonychia, psoriatic-like dermatitis and atopic dermatitis. Subsequently she developed recurrent bacterial upper and lower respiratory infections. Immunologic evaluation at 6 yrs showed hypogammaglobulinemia (IgG 180, IgA < 4, IgM 4), low B cells with almost only naïve B cells (98 %). Antibody titers to tetanus and pneumococcal vaccines were not protective. T and NK cell numbers were normal, however, T -cell proliferation to PHA was slightly decreased. The diagnosis of CVID was established, and IVIG replacement started. She remained free of infections until 9 years of age when she developed CMV pneumonia that recovered after prolonged ganciclovir treatment. She persisted with recurrent respiratory infections despite IVIG, requiring prophylactic antibiotics. NK cell function was assessed by chromium release assay and demonstrated absent NK cell function. A heterozygous non-sense mutation in NFκB2 gene [c.2608C > T (NM_002502.5, p.Gln870] was identified by Whole exome sequencing (WES). At 12 yrs she was admitted with severe gastroenteritis with generalized intestinal edema, acute renal failure and massive urinary protein loss. Quantitative CMV PCR was positive in blood (>2 x 10^6 copies) and renal biopsy. Renal histology showed tubular atrophy, interstitial inflammation and discrete focal glomerular mesangial proliferation, suggestive of minimal change nephropathy. She required critical level care and was treated with systemic steroids, IVIG, broad-spectrum antibiotics, valgancyclovir and hyperimmune CMV immunoglobulin leading to full clinical recovery. Pituitary function was studied and demonstrated reduced serum cortisol and ACTH levels and thus glucocorticoid replacement was initiated.
Discussion: As previously reported, heterozygous NFκB2 mutations can cause CVID, endocrine dysfunction and ectodermal dysplasia. In our patient, the main clinical manifestation was immunodeficiency and skin alterations. Pituitary hormone deficiency was detected after her mutation was identified. Decreased NK cell function potentially explains her susceptibility to invasive CMV infections. To our knowledge, this is the second report of NFκB2 mutation associated with abnormal NK cell function, suggesting NK cell function should be assessed in patients with mutations in non-canonical NFkB pathway.

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Late Diagnosis in a Patient Hospitalized with Classic Signs of Severe Combined Immunodefiency

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Introduction: Severe combined immunodeficiency (SCID) have an incidence of 1/58,000 live births, these patients present recurrent opportunistic infections in early age. It important clinicinal suspicion in patients with provide timely treatment.
Clinical Presentation: Three month old male with a 19 year old mother, product of second pregnancy, no familial background for immunodeficiency neither consanguinity in parents. Brother died at 10 months of age without an apparent cause. Our patient started with dyspnea, cough, fever and was admitted to emergency room with diagnosis of severe pneumonia. During hospitalization with poor response to antibiotic. At physical exam, he had cutaneous hyperpigmentation, whitish plaque that did not detach upon rasping located on oral mucosa, ulcers in the genital region and finally, he was hypotonic with choreatatosic movements. Immunoglobulins and low subpopulation of lymphocytes were reported with an immunophenotype T-B-NK-, so the first dose of gamma globulin IV 5 grams was administered. Hematopoietic Stem Cell Transplantation (HSCT) of unpaired cord is performed at 6 months of age. Currently in post-transplant management.
Laboratory Results: Hb8.49 g/dl Hto24.2 % Plaq 63 m/ul Leucos 2.46miles/ul Neutrófilos 1.670 Linfocitos 210 Eosinófilos180 Monocitos 380 Basófilos 10. IgG 130 mg/dl IgA 1 mg/dl IgM 3 mg/dl IgE 0.20 UI/ml. Leuc 700 cel/uL Linf 4.40 % Absolute Linf 31 cel/uL LT 7.31 % CD3 2cel/uL CD4 2 cel/uL NK15 cel/ui CD8 1cel/uL CD19 5cel/uL CD 20 5 cel/uL. ACTH 55.2 pg/ml, cortisol 18.11 mcg/dl, 17 hidroxiprogesterona 1.12 ng/ml, Rx: thymic shadow was absent by radiography. Bone marrow: abnormal in M2 with dysplastic changes
Discussion: The phenotype expression of SCIDs can affect multiple organs, in the case to be discussed the hyperpigmentation of skin causes to consider the diagnosis of congenital suprarenal hyperplasia, nevertheless, the patient presents typical clinical symptoms of SCID, because of bicytopenia and severe infections, so the immunophenotype TB-NK- results added to multisystemic damage, makes us suspect Adenosine Deaminase Deficiency (ADA). The survival of these patients relies on early diagnosis and it is essential to provide a specific treatment with HSCT or gene therapy.

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GATA 2 Deficiency, the Importance of Diagnosis

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Introduction: GATA-2 deficiency was recently described in 2011 as common cause of overlapping syndromes; monocytopenia and mycobacterial infections syndrome; dendritic cell, monocyte, B, and natural killer lymphoid deficiency; familial myelodysplastic syndromes/acute myeloid leukemia and Emberger syndrome. It constitutes a challenging group of diseases for the clinician because of the low incidence and for the little knowledge of general practitioners, because of that, and the variations in the clinical phenotype, the time that elapses between the appearance of the first clinical manifestation and the time of confirmed diagnosis is quite long in many cases.
Clinical Presentation: 25-year- old female with no familial background for immunodeficiency neither consanguinity in parents. She started at 11 years old with repeated high respiratory tract infections. Hospitalization for a month for complicated chickenpox. Next year presented cervical lymph node tuberculosis caused by mycobacterium bovis treated with antifimic for 2 years. Three years later presented a right leg cellulitis with intrahospital antimicrobial treatment. Coursed with chronic lymphopenia, neutropenia, treated with filgrastrim, with diagnostic of medullary hypoplasia at 20 years old. Two years later left hemicolectomy secondary to CMV tumor. She underwent 3 occasions with condylomatosis disseminated refractory to treatment in the rectovaginal region. Patient with the suspicion of primary immunodeficiency to GATA 2 deficiency, genetic study with a point muting of the GATA 2 gene in amino acid 74 (Glycine-Ac. Aspartic). The allogeneic hematopoietic stem cell transplantation protocol began being donor the direct Brother.
Laboratory Results: Leucos 2400 cel/ul, Linfos 500 cel/ul Monocitos 10 cel/ul Neutros 1910 cel/ul IgG: 1750 mg/dl, IgA: 130 mg/dl, IgM: 242 mg/dl, IgE:16.5. Linf T- CD3 74 % 518 cel/ul, CD3 + CD4 48.5 % 338 cel/ul CD3 + CD8 25.4 % 177cel/ul CD19/CD20 1,07 % CD 56 23.2 % CD5 76 % CD19 2 % CD20 22 %.
Discussion: Since the infancy our patient began with severe viral and mycobacteria infections, evolving to bone marrow hypocellularity with neutropenia, lymphopenia and tendencies to solid tumors Clinical presentation strongly suggestive of primary immunodeficiency by GATA 2 deficiency. Identification of *GATA2* mutations is critical for the management of these patients, making diagnosis in the young age and before the development of organ damage or malignancy is the ideal moment to hematopoietic stem cell transplantation to prevent the early evolution of the disease.

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Long-Term Efficacy, Adverse Events, and Tolerability of Recombinant Human Hyaluronidase-Facilitated Subcutaneous Infusion of Immunoglobulin G in Patients Aged ≥18 Years with Primary Immunodeficiency Diseases

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Objectives: Recombinant human hyaluronidase (rHuPH20)-facilitated subcutaneous infusion of immunoglobulin G (IgG) (fSCIG; HyQvia) overcomes some of the limitations associated with intravenously and conventional subcutaneously administered immunoglobulin G (IgG) and can be administered at rates, volumes, and frequencies similar to intravenous IgG (IVIG) but with better systemic tolerability. We report the efficacy, safety and tolerability of fSCIG in adult patients aged ≥18 years treated for up to ~3.5 years in the pivotal phase 3 study and its extension.
Design and Methods: Patients aged ≥18 years with PID received IVIG for 3 months, then fSCIG every 3 or 4 weeks for ~18 months, followed by up to an additional 21 months. fSCIG was discontinued after up to ~3.5 years of exposure.
Results: A total of 52/61 patients aged ≥18 years completed the pivotal study; 51 patients participated in the extension study. Maximum fSCIG exposure was ~3.5 years (139 patient-years). Adverse reactions (ARs; defined as causally and/or temporally associated adverse events [AEs] occurring within 72 h) per infusion were 0.19 (local) and 0.18 (systemic) with fSCIG, and 0.31 (systemic) with IVIG. No serious AEs related to fSCIG were reported. Infection rate with fSCIG was 2.98/patient-year. Of 2450 fSCIG infusions, 98 % required no changes in administration parameters. Twelve patients developed binding anti-rHuPH20 antibody titers ≥1:160 on ≥1 occasion with no associated ARs; titers declined to levels observed in the normal population in all patients who continued on treatment with fSCIG. No patient developed neutralizing anti-rHuPH20 antibodies.
Conclusions: In patients aged ≥18 years who were treated with fSCIG for up to ~3.5 years, infection rates were low, infusions were well-tolerated, with low rates of local ARs and, despite infusion volumes and rates similar to IVIG, systemic AE rates were lower with fSCIG than with IVIG.

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Long-Term Efficacy, Adverse Events, and Tolerability of Recombinant Human Hyaluronidase -Facilitated Subcutaneous Infusion of Immunoglobulin G (FSCIG) in Patients Aged <18 Years with Primary Immunodeficiency Diseases (PID)

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Background: Recombinant human hyaluronidase (rHuPH20)-facilitated subcutaneous infusion of immunoglobulin G (IgG) (fSCIG; HyQvia) overcomes some of the limitations associated with intravenously- and conventional subcutaneously-administered IgG and can be administered at rates, volumes, and frequencies similar to intravenous Ig (IVIG) with better systemic tolerability. We report the efficacy, safety, and tolerability of fSCIG in patients <18 years treated for up to ~3.5 years in the pivotal phase 3 study and extension.
Design and Methods: Patients <18 years with PID received IVIG for 3 months, then fSCIG every 3–4 weeks for ~18 months followed by up to an additional 21 months. fSCIG was discontinued after up to ~3.5 years of exposure.

Results: A total of 19 of 26 pediatric patients (aged 2–17 years) completed the pivotal study; 15 patients participated in the extension study. Maximum fSCIG exposure was ~3.5 years (48.66 patient-years). No fSCIG -related serious AEs were reported. Infection rate with fSCIG was 3.02/patient-year. Of 706 fSCIG infusions, 96.7 % required no administration changes. Three patients developed binding anti-rHuPH20 antibody titers ≥1:160 on ≥1 occasion with no associated ARs (defined as causally and/or temporally associated AEs occurring within 72 hours); titers declined despite continued treatment. No anti-rHuPH20 antibodies were neutralizing.
Conclusions: In patients <18 years treated with fSCIG for up to ~3.5 years, infection rates were low and infusions were well-tolerated, despite infusion volumes and rates similar to IVIG. Data on pediatric patients are similar to the adult and total patient datasets.

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Local Adverse Reactions Decreased Over Time During Recombinant Human Hyaluronidase-Facilitated Subcutaneous Infusion of Immunoglobulin G (FSCIG) Treatment in Patients with PID

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Background: Recombinant human hyaluronidase (rHuPH20)-facilitated subcutaneous infusion of immunoglobulin G (fSCIG; HyQvia) can be administered at similar doses/volumes and dosing intervals as intravenous immunglobulin (Ig) (IVIG) but, similar to conventional subcutaneous Ig (SCIG), is associated with a lower risk of systemic and higher risk of local adverse reactions (ARs). We report local AR rates over time in patients with primary immunodeficiency disorders (PID) aged ≥16 years treated with fSCIG for up to ~3.5 years in the fSCIG pivotal phase 3 study and its extension.
Methods: Following a 3-month IVIG treatment period, patients initiated fSCIG on a 7-week dose ramp-up schedule and thereafter received fSCIG every 3 (Q3W) or 4 weeks (Q4W) for ~18 months, followed by up to an additional 21 months. Local AR rates were evaluated over time.
Results : Of the 63 enrolled patients aged ≥16 (16–78) years, 61 were administered fSCIG for up to ~3.5 years at the established dose. Rates of local ARs (defined as related and/or temporally associated adverse events) per infusion decreased over time: 0.28 (months 1–12), 0.15 (months 13–24), and 0.08 (months 25–33.6). The percentage of patients experiencing ≥1 local AR per infusion was highest during the dose ramp-up period (33.3–41.7 % [Q3W] and 29.2–37.5 % [QW4]), and rapidly declined over time. The rate of local ARs per patient-year declined from 4.40 in the first year, to 2.35 in the second year, and to 1.45 in the third year. Overall, the local AR rate per infusion was 0.19; discomfort/pain was the most commonly reported local AR.
Conclusions: In adults with PID treated with fSCIG for up to ~3.5 years, rates of local ARs per infusion and the percentage of patients experiencing ≥1 local AR markedly declined over time.

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Effect of Bay 41-2272, a Soluble Guanylate Cyclase Agonist, in Lymphocytes

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Background and aims: Our group has studying new therapies with potential therapeutic chemical components for Primary immunodeficiencies, which are disorders that predispose individuals to recurrent infections and other immune manifestations. Recently, our studies has been shown that BAY 41-2272, a soluble guanylate cyclase agonist (sGC), has proven to exert an effect in modulation of monocytes, leading to infection control. In T cells, activation of sGC by NO,increasing the levels of cyclic guanosine monophosphate (cGMP), selectively induces expression of IL-12β2 receptor or induced calcium influx and IL-4 production. Thereby, BAY 41-2272, and its pathway, has a potential for activation of T cells. Thus we evaluate the potential of BAY 41-2272 and its pathway as a tool for modulating of lymphocytes.
Methods: To this end, pharmacological treatments were performed with BAY 41-2272 to evaluate cytokine production by ELISA, cGMP and cAMP production and expression of CD69,
FOXP3 and RORγT.
Results: It was observed that BAY 41-2271, as direct activator did not induce the production of IFNγ and expression of CD69, FOXP3 e RORγT in lymphocytes ($p < 0,001$, ANOVA with Tukey post-test) (Figure 1 A, D, G, L). However, pretreatment for 24 hours with BAY 41- 2272, with subsequent activation with 90 nM of phorbol myristate acetate (PMA), has showed inhibitory effect on IFNγ production and expression of CD69 in lymphocytes ($p < 0,05$) (Figure 1 B, C, E, F), but did not interfere on expression of transcription factors FOXP3 and RORγT (Figure 1 H, K, M, N). We did not observe production of cGMP, but we visualied production of cAMP (Figure 1 O, P).
Conclusion: These results suggests a immunomodulator effect of BAY 41-2272 in a manner cGMPindependent but dependent on cAMP, inhibiting, thereby, lymphocytes.

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Hyaluronidase-Facilitated SCIG (HYQVIA [FSCIG]) for the Treatment of Primary Immunodeficiency

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Introduction: Intravenously administered immunoglobulin (IVIG) is used to treat primary immunodeficiencies (PID), but has limitations including the risk for systemic adverse reactions (ARs), need for venous access, requirement of a healthcare professional to perform the infusion, and time commitments for infusions. Subcutaneous administration of immunoglobulin (SCIG) therapy is effective, and offers the advantages of patient self- administration, scheduling flexibility, and a lower risk of systemic ARs. However, the volume of IG that can be administered SC in a single site is limited because hyaluronan, a component of the extracellular

matrix, causes resistance to bulk fluid flow. Thus, conventional SCIG necessitates multiple infusion sites and an increased frequency of administration compared with IVIG to achieve therapeutic dosage requirements. Recombinant human hyaluronidase (rHuPH20) mimics endogenous hyaluronidase causing local and transient increases in dispersion and absorption of SC-administered fluids and drugs. HyQvia is a rHuPH20–facilitated subcutaneous IgG 10 % (fSCIG) that provides a SC treatment option for patients with PID.
Objectives: To describe the mechanism of action of rHuPH20, and the pharmacokinetics and local AR profile of fSCIG in patients with PID.
Results: rHuPH20 facilitates infusion of large volumes into the SC space allowing for fewer infusion sites and decreased frequency of administration relative to conventional SCIG. The enzymatic activity of rHuPH20 is highly specific for the β1-4 linkage in glycosaminoglycans and does not degrade structural protein components in the skin or increase vascular permeability. rHuPH20 rapidly depolymerizes hyaluronan and the effects of rHuPH20 are completely reversible within 24–48 h of administration. fSCIG allows volumes up to 600 mL to be delivered in a single infusion site at infusion rates up to 300 mL/h/site—volumes and rates that are approximately 20-to 30-fold larger and 10- to 15-fold faster, respectively, than those of conventional SCIG. Repeated large volume infusions of fSCIG have shown no long-term effects on skin integrity with up to 3.5 y of treatment. fSCIG had a relative bioavailability to IVIG of 93.3 % (90 % CI, 91.4 %, 95.2 %). The concentration-time profile of fSCIG is similar to that of IVIG, but without the large peak; the peak to trough variation of fSCIG is more similar to SCIG than to IVIG. In clinical trials, the overall rate of local ARs was 2.65 per patient-year and the majority were mild or moderate despite faster infusion rates and larger volumes per site.
Conclusion: fSCIG is an attractive treatment option for patients with PID, enabling self-administration in 1 or 2 infusion sites with infusion intervals similar to IVIG and local AR profile similar to conventional SCIG.
Funding Source: This study was funded by Shire

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Efficacy Analysis of Subcutaneous Immune Globulin (HUMAN), 10 % (SCIG 10 %) Administered Intravenously or Subcutaneously in Patients with Primary Immunodeficiency Diseases (PIDD)

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Introduction: Most patients with PIDD are prone to recurrent bacterial infections and usually require lifelong immunoglobulin G (IG) replacement therapy. Intravenous IgG (IVIG) therapy has been the most common treatment of PIDD; however, subcutaneous preparations may be a safe and effective alternative to IVIG. Subcutaneous immunoglobulin (SCIG) is typically associated with fewer systemic reactions and higher serum IgG trough levels than IVIG.
Objectives: This multicenter, prospective, open-label study evaluated the efficacy, tolerability, and pharmacokinetics of a 10 % liquid IG product originally developed for IV administration when administered intravenously or subcutaneously in patients with PIDD. Efficacy was determined as the rate of validated acute serious bacterial infections (VASBI) per patient year, and the overall incidence of infections and protective specific antibody titers.
Results: Overall, 49 patients were enrolled and 47 were treated with SCIG 10 %. While receiving SCIG 10 %, the rate of VASBI was 0.067 per patient per year, with an upper confidence limit of 0.134, well below the established limit of 1 ASBI per patient per year. There were 3 episodes of acute serious bacterial pneumonia, none of which required hospitalization. The annualized rate of all infections during the SC phase of the study was 4.1 infections per patient (95 % CI: 3.2–5.1). SC infusions were distributed almost evenly over the seasons. Trough levels of specific antibody to *Haemophilus influenzae*, hepatitis B surface antigen, and tetanus were in the protective range for all patients regardless of therapy, with titers higher during the SC phase of the study for all 3 specific antibodies.
Conclusion: The efficacy of SCIG 10 % replacement therapy was confirmed by rates of infection that were comparable to that of other SCIG and IVIG products. Treatment with IVIG or SCIG 10 % conferred protective trough levels of specific antibodies to *Haemophilus influenzae*, hepatitis B, and tetanus within the protective levels.
Funding Source: This study was funded by Shire.

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Thrombosis Association with Administration of Intravenous Human Immunoglobulin in Patients with Primary or Secondary Immunodeficiencies

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Introduction: Intravenous administration of human immunoglobulin (IVIG) aims at the treatment of several autoimmune, inflammatory, infectious or immunodeficiency conditions. Although it is generally considered a safe therapy, serious adverse effects, such as thrombosis, may occur.
Objective: To evaluate the incidence of thrombosis in patients with primary or secondary immunodeficiencies who go through IVIG therapy monthly.
Methods: This case-control study was performed through a retrospective analysis of the medical records of patients in IVIG therapy at Hospital das Clinicas, University of Sao Paulo.
Results: The medical records of 150 patients in IVIG therapy for primary or secondary immunodeficiency were evaluated. Four patients (2.6 %) had thrombotic events after initiation of IVIG and 1 had a previous event (the latter had hypogammaglobulinemia associated with the use of immunosuppressants due to systemic lupus erythematosus and human immunodeficiency virus). The age at diagnosis of the thrombotic event ranged from 37 to 64 years. Among the 4 patients with thrombotic events after initiation of immunoglobulin therapy, 3 had infusion rates of 50 to 150 mL/h and 1 of 50 to 100 mL/h. Their reasons for IVIG were variable common immunodeficiency (3 patients) and hypogammaglobulinemia associated with monoclonal gammopathy (1 patient). Thrombotic events were arterial or venous, namely: acute coronary syndrome, stroke, lower limb venous thrombosis (2 cases), and venous thrombosis of intracranial vessels. Some associated thrombogenic factors were found, such as monoclonal gammopathy, colon adenocarcinoma, immobilization, and antiphospholipid antibody syndrome. The human immunoglobulin dose ranged from 0.35 to 0.75 mg/kg/28 days.
Conclusion: The presence of thrombogenic and atherogenic comorbidities may be associated to the increased risk of thrombotic events in patients taking immunoglobulin. Thrombotic events may occur even at low infusion rates and at low doses. The control of the associated factors is a way to reduce the risk of thrombosis.

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Treatment with Intravenous Immunoglobulin in the Brazilian Public Healthcare System: Analysis of the Datasus Database

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Introduction: Intravenous immunoglobulin (IVIG) replacement therapy is indicated for primary immunodeficiency (PID) diseases that result in antibody deficiency. The Brazilian government funds most IVIG treatment.
Objective: To examine IVIG treatment patterns for all indications and for PID in the Brazilian public healthcare system from 2008 to 2015.
Methods: Patients using IVIG for all indications including PID, Guillain-Barré, and idiopathic thrombocytopenic purpura in 2008 and 2015 were identified in the Brazilian national public healthcare system (Sistema Único de Saúde, SUS) using the DATASUS reimbursement database, which contains vital statistics, diagnosis, and financial data on every treatment provided by the Ministry of Health. Indications for IVIG were identified using ICD-10 codes. Number of patients, total volume of IVIG, number of infusions, and average dose were calculated for the period between 2008 and 2015 for all indications and for PID.
Results: IVIG volume increased from 2.54 tons in 2008 to 4.97 tons in 2015 (95 %) for all indications. Patients with PID comprised 26 % of IVIG treated patients for the overall period. The number of patients treated for PID with IVIG increased by 73 %. Of the 80,577 IVIG treatments reimbursed between 2008 and 2015 in the Brazilian public healthcare system, 61 % were related to PID treatment.

Table 1. All indications	2008	2015	Increase (%)
Number of treated patients	2541	4965	95
Number of infusions	13408	21470	60
Average dose, g/month	34	59	73
Table 2. PID	2008	2015	Increase (%)
Number of treated patients	1072	1858	73
Number of infusions	7066	13206	87
Average dose, g/month	26	39	49

Conclusion: In the Brazilian healthcare system public sector, IVIG use has increased substantially from 2008 to 2015 due to increased use for treatment of various conditions including PID.

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Pharmacovigilance of a Regional Intravenous Immunoglobulin: Update of Registry in Three Health Centers from Córdoba - Argentina, in the Period 2015-2017

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Introduction: Intravenous Immunoglobulin (IVIG) replacement therapy is of choice in all Primary Immunodeficiencies (PID) with Antibody Deficit. The development of this blood product from regional donors constitutes an improvement in product quality as recommended by WHO in its technical reports. These products are safe and effective but may cause adverse reactions in some patients. Pharmacovigilance is a fundamental multidisciplinary activity for detection and prevention.
Objective: To assess the occurrence of Adverse Drug Reactions (ADR) during the infusion of INMUNOGLOBULINA G ENDOVENOSA UNC™ in patients with PID treated at three health centers in Córdoba, Argentina, in the period 2015-2017.
Results: 242 IVIG infusions were analyzed in 15 children who received a total of 3,640 g with an average dose of 568 mg/kg/dose; 66 infusions in 07 adults who received a total of 2,316 g at an average dose of 504 mg/kg/dose. All infusions were performed with infusion pump and prior administration of antihistamines. Controls of vital and thermal signs were performed before, during and at the end of each infusion procedure, and normal values were found. The occurrence of ADR was recorded in 3 adult patients: 1 with arterial hypertension and 2 with headache. There were no adverse events during the administration of the drug in the other patients.
Conclusions: Excellent IVIG tolerance was evidenced in the studied population, demonstrating a satisfactory safety profile during each administration procedure. The rate of infusion was the main factor associated with ADR, so it represents an aspect of relevance on which to work. The training of the health team and the multidisciplinary work in this regard are fundamental actions for the prevention of ADR.

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Granulocyte Transfusion in Patients with CGD: an Effective Alternative for Severe Refractory Infections

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Introduction: Patients with chronic granulomatous disease (CGD) present severe and recurrent infections, granulomas and inflammatory diseases. Patients experiencing life-threatening infections, poorly or non-responsive to surgical and antimicrobial treatment can benefit from granulocyte transfusions (GT).
Objective: To report two male patients with CGD who received GT as adjuvant treatment for severe infections, unresponsive to conventional treatment.
Case Report: Patient 1- WOAS, diagnosed with CGD at the age of 3. When he was 10yo, he presented extensive pneumonia caused by *P. aeruginosa* and septic shock, requiring mechanical venti. lation (MV), vasoactive medications and hemodialysis. Despite broad-spectrum antibiotics and corticosteroids, pneumonia showed no improvement. On the 34th day of hospitalization he started 3 consecutive days of GT (10 ml/kg/day in 3 hours). As adverse event, he experienced hypertensive crisis, responsive to sodium nitroprusside. Two days after the last transfusion, he showed remarkable clinical, laboratory and radiological improvement, allowing endotracheal extubation and interruption of dialysis that same day. Patient 2- KRAS was hospitalized at the age of 5 for the treatment of pulmonary tuberculosis and osteomyelitis, initially assumed to be caused mycobacteria. At that time he was diagnosed with CGD. In the fourth month of hospitalization, despite treatment, he developed septic shock, acute renal failure and acute respiratory

distress syndrome. He developed a cervical abscess secondary to the osteomyelitis and the surgical drainage identified *Aspergillus fumigatus*. Despite multiple surgical interventions and broad-spectrum anti-infective treatment for 7 mo, the infection persisted. Granulocyte transfusion was indicated (20 ml/ Kg/d, total of 8 transfusions in 40 days) being fever the only adverse event. The patient showed progressive improvement of the infection.
Discussion: Although not definitively proven GT could be an adjuvant therapy for refractory infections in CGD. Concerns related to alloimmunization and its implications in a future hematopoetic stem cell transplantation may be overcome by its efficacy and safety in the setting of a life-threatening infection.

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Abatacept Therapy Improving Clinical Symptoms from LRBA Deficient Pediatric Patient: Case Report

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Introduction: Mutations in LRBA gene leads to a PID (Primary Immunodeficiency) characterized by lymphoproliferation, autoimmunity, and recurrent infections. This protein defect could compromise CTLA-4 function. In this scenario, abatacept, a CTLA4 analogous, could be effective in controlling the disease.
Case presentation: Eight years old girl born to consanguineous parents that presented at 8 months old a single severe pneumonia episode, followed by recurrent upper respiratory infections. At 4 years old she developed a severe autoimmune haemolytic anemia with partial clinical response to corticosteroids, cyclophosphamide and IVIG (Intravenous Immunoglobulin) demanding splenectomy at 6 years old, with anemia control. During anemia treatment, she developed a presumed fungal pneumonia successfully treated with voriconazole. At 4 years old she developed a profuse diarrhea, that required electrolytic replacement. Colonoscopy revealed signs of inflammatory disease without evidences of infection. Patient received mesalazine, followed by azathioprine without clinical response. Sirolimus was prescribed and partial control of symptoms was achieved but patient developed moderate stomatitis as an adverse reaction. During follow up, patient presented persistent low levels of serum immunoglobulins demanding IVIG replacement. Respiratory symptoms were mild, but persistent. Functional measures revealed impairment of FVC and FEV1 and chest CT showed ground-glass opacities and pulmonary nodules. Lung biopsy revealed interstitial infiltration of T and B lymphocytes. Infection and neoplasia were ruled out and granulomatous lymphoproliferative interstitial lung disease (GLILD) was characterized. The myriad of symptoms and laboratorial findings motivated genetic analysis that showed a homozigous mutation in LRBA gene (c.5903G > A:p.W1968X). Considering pathophysiological aspects of this disease, abatacept was the therapy of choice. Patient received 10 mg/kg IV infusion on days 1, 15, 29 and every 4 weeks thereafter. Diarrhea resolved and there was a mild enhancement in lung function. The patient tolerated medication without any complications.
Discussion: LRBA deficiency is a newly described disease in which targeted therapy is possible and effective. Abatacept significantly improved GI (gastrointestinal) and respiratory symptoms, with a good safety profile in our patient. This report illustrates how specific genetic diagnosis directly helped management in a PID patient.

PO - 145

Adverse Reactions During Immunoglobulin Infusions in Primary Immunodeficiency Patients

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Introduction: Endovenous immunoglobulin is the treatment of choice for primary immunodeficiencies (PID) with antibody depletion or function impairment. The infusion intervals are between 21 to 28 days and the rage dose is 400-600 mg/kg. Adverse reactions are associated with infusion rate, infection, first infusion and prolonged interval between infusions, as well as frequent change of product's trademarks. Most commom reactions are: lumbar/abdominal pain, nausea/vomiting, pruritus, flushing, paresthesia, hypo/hypertension. Rare symptoms include thoracic pain, dyspnea, renal failure, asseptic meningitis and neutropenia. In case of medical treatment necessity, the reactions must be notified to farmacovigilance.
Methods: Retrospective observational study of medical charts of patients with PID who were treated with immunoglobulin infusions from may 2016 to may 2017. The data were analysed with excel2010.
Objectives: Evaluate the incidence of adverse reactions and the frequency of the symptoms during immunoglobulin infusion in patients with PID.
Results: We analysed 221 infusions in 20 patients, 50 % of female gender. The velocity rate was the same in all patients. The mean age was 17,6 years (6 months-42 years). Most commom diagnosis was common variable immunodeficiency (10 patients). All but one pacient received only intravenous infusions. One patient received both intravenous and subcutaneous infusions. The trademarks utilized were: Immunoglobulin (33 %), Octagam (29 %), Flebogamma (18,6 %), Kiovig (6,8 %),Tegeline (5 %) and Privigen (0,9 %). There were no information regards the trademark in 15 infusions (6,8 %). We observed 8 reactions (3,6 %). The most frequent symptom were tremor (1,4 %), followed by fever (0,9 %), thoracic pain (0,9 %), irritability (0,9 %), dyspnea (0,5 %), pruritus (0,5 %), nausea (0,5 %), pallor (0,5 %). No reactions were observed during the subcutaneous infusions. There were more reactions in adolescents (12-18y). Three reactions ocurred after trademarks exchanged and 2 patients had flu symptoms and cough before the infusion. The other reactions didn't correlate with trademarks or previous symptoms.
Conclusion: Immunoglobulin infusion is a safe treatment, with a low rate of adverse reactions, mostly mild. We didn't observe any reactions during the use of subcutaneous immunoglobulin.

PO - 146

G-CSF Treatment in Stat1 Gain-of-Function Mutation with Chronic Mucocutaneous Candidiasis – Case Report

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Introduction: Chronic mucocutaneous candidiasis (CMC) is a challenging presentation of several immune defects. Candida infections usually persist, despite antifungal treatment. We report our experience with an adjuvant therapy in a patient with STAT1 gain-of-function mutation
Case report: 12yo boy, born to consanguineous parents. Adopted at the age of 15mo, unknown previous personal and family history. He had a

history of recurrent fungal infections, with oral thrush and diaper rash, onychomycosis with nail dystrophy, fungal osteomyelitis with sequelae in phalanx of the hands and feet. He also reported a history of suppurative otitis media, pyodermitis with cutaneous abscesses, sinusitis and recurrent pneumonia, requiring ICU admission in many occasions. In the initial evaluation, he had failure-to-thrive, general apathy, whitish plaques in the oropharynx, crusty lesions, thick and scaly lesions with well-defined borders and erythematous lesions on the gluteal and scalp area. Hyperkeratotic lesions, dystrophy and deformities in the nail and phalanx of the hands and feet were evidenced. Pulmonary auscultation with bilateral rales and rhonchi. Skin scraping found blastoconidia and pseudofilaments in addition to positive culture for *Trichophyton rubrum*. Laboratory workup revealed TSH 816.6 μIU/mL and T4 < 0.1 ng/dL. Screening for autoimmunity was negative, including anti-thyroid antibodies. He also had normal immunoglobulins, CD4, CD19 and NK cells below normal. Proliferative response to candida, tetanus toxoid and pokeweed mitogen was impaired. Thyroid hormone replacement was initiated and IV antifungal treatment prescribed. Functional assays showed increased phosphorylation of STAT1. Exome sequencing revealed a probable pathogenic heterozygous mutation in STAT1 gene (c.1061T>C), confirming our hypothesis of CMC due to STAT1-GOF. As IV fluconazole alone had previously failed, we added G-CSF as an adjuvant therapy (5 mg/kg subcutaneous G-CSF, 1x/week). The patient showed significant improvement of oral and skin lesions and had no new infections in the last year.
Discussion: Previous studies found that G-CSF enhanced TH17 immunity, an important immune mechanism against candida infections. Our patient had marked clinical improvement without any adverse reactions. G-CSF, a self-administered drug, can be used in the outpatient setting. Compared to other treatments of fungal infections it has a lower cost and represents a valuable adjuvant therapy in STAT1-GOF.

PO - 147

Clinical Features of Patients with Primary Immunodeficiency Under Immunoglobulin Replacement Therapy at the Hospital da Criança de Brasília José Alencar

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Introduction: Primary immunodeficiency disease (PID) comprises more than 300 clinical entities well characterized. Predominant antibody deficiencies (PAD) are the most common form of PID and, immunoglobulin (Ig) replacement is the standard treatment. Pulmonary complications are important causes of morbi-mortality in these patients.
Objective: To describe clinical, laboratory data and pulmonary imaging (chest computed tomography [CCT]) of patients with PID under Ig replacement therapy in a reference center in Brasília, Brazil.
Results: We reviewed 40 medical records, from January/2008 to September/2016. Male patients were predominant, $n = 26$ (65 %), mean age was 10 years old (1-22), and 24 patients (60 %) were younger than 12 years. PID diagnosisto indicate Ig therapy were: Specific Antibody Deficiency (SAD) in 17 (42.5 %) cases, within seven presented with associated genetic syndromes (Blaun = 1;Hyper IgE, $n = 4$; ALPS-like $n = 1$; and, Down, $n = 1$); Unclassified Hypogammaglobulinemia $n = 4$ (10 %); Common variable immunodeficiency $n = 4$ (10 %); Transient hypogammaglobulinemia of infancy (retrospective diagnosis) $n = 3$ (7.5 %); X-linked agammaglobulinemia $n = 2$ (5 %). One case of each PID were observed: Severe Combined Immune Deficiency, CD40L deficiency, Chronic Granulomatous Disease, PNP deficiency and X-linked lymphoproliferative syndrome. Patients with Ataxia-telangiectasia, $n = 3$ (7.5 %) and Kabuki syndrome associated with PID, $n = 2$ (5 %) were also noted. Not including patients with SAD, mean of IgG, IgM and IgA levels in mg/dL, at diagnosis and updated, were: 250/775; 59/59.5 and 55/44, respectively. Baseline lymphocyte subset (cell/mm^3) were: CD4+ 1502 (94-3123); CD8+ 894 (150-2634), CD19+ 697 (3-3296), mean (min-max). Pulmonary abnormalities were observed in 26 (65 %) patients, some of them had more than one alteration: Atelectasis $n = 10$ (38.5 %), Parenchymal nodule $n = 8$ (30.7 %); Bronchiectasis $n = 7$ (26.9 %); Air trapping $n = 6$ IUU (23 %); Peribronchial thickening $n = 4$ (15.4 %); Ground-glass opacity $n = 2$ (7.7 %); cystic adenomatoid malformation $n = 1$ (3.8 %).
Conclusion: Use of Ig therapy in PID patients was based on Brazilian guidelines and, SAD was the most common diagnosis. The high number of patients with pulmonary complications, in a cohort with predominance of children, highlight the importance of an early evaluation of lung diseasein PID patients.

PO - 148

Follow up During 6 Years of 52 Patients with Subcutaneous Immunoglobulin Treatment by Push as Replacement and Immunomodulatory Therapy

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Introduction: Several studies have shown that subcutaneous Immunoglobulin (SCIG) is as good as Intravenous Immunoglobulin (IVIG) preventing infections in primary immunodeficiencies (PID), also SCIG has been proposed as an alternative in the immunomodulatory treatment (IT) of many neurological diseases and other diseases and it seems to be as efficient as IVIG.
Objetive: To describe the follow up of 52 patients (p) with SCIG treatment during 6 years in a single center in Argentina.
Results: We reviewed the clinical history of two Groups (G) of patients followed in our center, G1: 44p with PID with IG replacement treatment, G2: 8p with IT for different diseases. Mean age: G1 19.4 yo (1.25 – 63.4), G2 43 yo (12.5 – 77.2). Among the G1 6p are under 5 yo (mean age 3.2) 23 are between 5 and 18 (mean 10) and 15 are over 18 yo (mean 40.2). The mean time of follow up was 2,98 years. Thirteen patients were follow for more than 5 years and 26 patients between 1 and 5 years. SCIG was administered at 1 or multiple injection sites by push, in each site a maximum of 20 ml in children and 35 ml in adults. G1: The mean dose was 144 mg/kg/w.G2: Dose was 300 mg/Kg/w.

G1: The mean serum IgG level was 1143 mg/dl. Levels were stable over the years. Efficacy: Among the G1 p, the annual rate of infection was 0,19 infections/patient/year. G2: All patients presented remission. Tolerance: 28,8 % presented mild episodes related with the injection site and only three p presented 3 systemic adverse reactions in a total of 10,449 infusions.
Conclusion: SCIG therapy is safe and effective for replacement treatment in PID patients, even in children under 5 years old. SCIG may be as effective as IVIG in the maintenance therapy in CIDP and other autoimmune diseases. Further systemic clinical studies are needed to better define combination therapy, optimal dosage and application intervals of SCIG.

PO - 149

Evaluation of the Response of Dendritic Cells in Coculture with Memory Lymphocytes T CD4+ Stimulated with Allergen of *Dermatophagoides Pteronyssinus* Group 1

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Introduction: The atopy is the IgE production in response to low levels of an allergen specific which lead to the development typical diseases such as, asthma, allergic rhinitis or eczema. This response is dependent of the allergen presentation to lymphocytes that development a Th2 differentiation. The dendritic cells (DCs) the main cell that is involved in communication between innate immunity and adaptative. It is known that the mother transfers IgG and IgA against mites for baby, but is not clear whether there is a mechanism for protection allergen.
Objective: To evaluate the protective effect of IgA and IgG specific to Der p 1 on responses of dendritic cells in atopic patients and non-atopic stimulated with allergen of mite *Dermatophagoides pteronyssinus* group 1 in coculture with memory lymphocytes T CD4+ autologous.
Results: Atopic patients and individuals controls were initially selected with skin prick test, immunoglobulin dosage specific to Der p 1 and evaluation clinical history. We observed that atopic patients showed higher production of IgE, IgG and IgA specific against Der p 1. The monocytes from atopic patients and non-atopic patients were derived the DCs stimulated with Der p 1, immunocomplex Der p 1-IgG or Der p 1-IgA in coculture with lymphocytes for cytokines evaluation. Thus, we observed that the DCs stimulated with immunocomplexes Der p 1-IgG or Der p 1-IgA showed lower release of IL-5, when compared with the cells stimulated only with Der p 1. Already non-atopic patients were not able to produce IL-5 stimulated with Der p 1 under all conditions.
Conclusion: Our results showed that atopic patients have higher levels of specific immunoglobulin against Der p 1. These antibodies seem to play a protective role, decreasing the Th2 response. In this way, IgG and IgA antibodies could be used to attenuate the Th1 and Th2 response, associating with drugs improving the treatment of atopic disease.

PO - 150

Successful Use of Tranexamic Acid in a Pregnant Women with Hereditary Angioedema with Normal C1 Inhibitor and FXII Mutation

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Introduction: Treatment of pregnant women diagnosed with hereditary angioedema with normal C1 inhibitor and FXII mutation (FXII-HAE) is a clinical challenge as a result of the unpredicted course of the disease during pregnancy with risk of worsening the symptoms due to hormonal changes, allied to the lack of clinical trials on prophylaxis and treatment of FXII-HAE.
Case presentation: Female patient, 20 years old (ys), diagnosed with FXII-HAE at 17 ys. Symptoms initiated when she started the use of oral combined anticonception at 16 ys, characterized by recurrent episodes of swelling affecting lips, hands, feet, genitals, eyelids, uvula, larynx and repeated abdominal pain attacks. She obtained good control of the angioedema attacks with the use of continued oral progestagens. At 19 ys, she stopped the use of the progestagen despite medical orientation and became pregnant. Symptoms then returned as recurrent and severe abdominal pain attacks, associated with vomits, lasting usually 3 days, with no relief with the use of regular pain medications. Other causes of abdominal pain were excluded through laboratory exams, obstetric evaluation and abdominal ultrasound, that revealed ascitic liquid simultaneously with the abdominal attacks. With 24 weeks, the patient was started on tranexamic acid (TA) 500 mg every 8 h and the patient reached total control of the HAE attacks. This medication was used until the day before labor. It was a vaginal delivery that occurred uneventfully and the baby was born healthy with no perinatal events. Oral progestagens were prescribed on the third day after delivery as HAE attacks prophylaxis. The patient remained with no attacks during the postpartum period.
Discussion: The patient achieved good disease control with the use of TA, without adverse effects and with no interference on the labor and the neonate health. This case report shows that TA could be a promising treatment option of pregnant women with HAE-FXII, although clinical trials are needed to establish safety profile and confirm efficacy.
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PO - 151

Subcutaneous Immunoglobulin Replacement Therapy for Primary Antibody Deficiency: Case Report

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Introduction: Over the past 3 decades, IgG has been broadly used as replacement therapy in patients of all ages with primary antibody deficiencies. Successful use of therapeutic IgG to prevent serious infections was first described in 1952 by Bruton in a boy with agammaglobulinemia. In Brazil the IgG can be administered intravenously (IVIG) or, more recently, subcutaneously (SCIG). The selection of route of administration should be based on the individual patient, the medical status of the patient, the availability of IV access, the tolerability of IVIG, the history of serious side effects from IVIG, and other factors.
Case Report: JP, male, born in 1997, diagnosed with probable Congenital Agammaglobulinemia at 5 years old, when he was hospitalized for a pneumectomy. Previous history revealed consanguinity, premature birth, meningoencephalitis when 2 months old after a live poliovirus vaccine with paraplegia for the lower members as a *sequelae*. Evolved with intermittent diarrhea, giardiasis and recurrent respiratory infections: otitis, mastoiditis, sinusitis, pneumonias and sacral bronchiectasis. Laboratory tests: IgG 170; IgM 7.18; IgA < 6; T lymphocytes: CD3 1451, CD4 706, CD8 676, CD4/CD8 1.04 and B-lymphocytes: CD19 400- 669 – 5-13 %. Evaluation of BTK gene or protein was not done. The restitution of IVIG with 400 mg/kg every 14 days and antibiotic prophylaxis achieved a good progress. In 2014 a catheter was implanted because the unavailability of peripheral IV access. Evolved with episodes of bacteremia and/or sepsis by infectious focus through the catheter. It culminated in pulmonary sepsis by *Mycobacterium fortuitum* and beginning of fever, chills and erythroderma with Octagam® and Tegeline®. In 2016 absolute indication for the use of SCIG. Satisfactory clinical and laboratorial progress with 150 mg/kg of Endobulin Kiovig 10 % once a week.
Conclusion: Therapeutic IgG can be given via IV or SC. Although both routes provide similar efficacy in preventing serious bacterial infections, each offers different advantages and disadvantages. One clear advantage of IVIG over SCIG is that it can be infused in a larger volume and less frequently. SCIG has grown in popularity for some reasons: short infusion time, low wear-off effects, a feeling of independence... The indications of SCIG on this patient was based on the unavailability of the IV access, the serious side effects like a sepsis with the use of an implanted catheter and the adverse reactions with IVIG.

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Transplantation of Hematopoietic Stem Cells in Human Severe Combined Immunodeficiency: Immune Reconstitution of 7 Mexican Patients

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Background: Severe combined immunodeficiency (SCID) is a fatal syndrome of diverse genetic cause characterized by profound deficiencies of T and B cell function and, in some types, also of NK cells and function.
Objectives: To describe the immune reconstitution of 7 patients with SCID
Methods: Descriptive, longitudinal cohort. On the postrasplant follow-up was measured periodically (1, 3, 6, 9 and 12 months) subsets lymphocytes, immunoglobulins, specific polysaccharide antibody and T cell proliferation.
Results: Seven patients with SCID were evaluated. Mean age at diagnosis of the 159 days. Median age at transplantation of the 11 months. Six of the seven had received pre-transplant conditioning. Two patients of them received HLA-identical sibling bone marrow, 2 of umbilical cord and 3 received T-cell depleted haploidentical. Immune reconstitution of NK cells and B cells was observed in the first month post-transplant, T CD8+ cells at 3 months. Normal levels of IgM and IgA from the 6th month post transplant. T-cell proliferation normol in all patients in the 6th month post transplant. Was suspended gammaglobulin in 4 patients. It was observed that the immunophenotype may influence immune reconstitution; as reported in other studies, TB-NK + SCID patients present additional resistance to the graft, because the presence of normal NK cells may contribute to a high rate of graft failure, due to defective repair mechanisms, which increases the incidence of HSCT complications, such as graft-versus-host disease and conditioning-related toxicity.
Conclusions: Immune reconstitution is very important from the first month post-transplantation because chimerism does not reflect the correct immune reconstitution of the cellular elements. Also allows us to perform interventions such as lymphocyte infusión, time to suspend administration of gammaglobulin and initiate vaccination.
Keyword: Severe Combined Immunodeficiency. Transplantation of Hematopoietic Stem Cells. Immune reconstitution.

PO - 153

The Use of Post-Transplantation Cyclophosphamide After Alternative Donor Transplantation for the Treatment of Primary Immunodeficiencies: the Brazilian Experience

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In the absence of an unaffected matched sibling, alternative donor(AD) transplantation maybe curative for a variety of primary immunodeficiencies (PID). The aim of this study is to analyze the outcome of children with PID submitted to AD transplantation using post-transplantation cyclophosphamide(PT-CY) as GVHD prophylaxis in Brazil.
Patients and methods: This is a multicenter, retrospective study of 42 patients(pts) transplanted between 2012 and 2017 in 8 Brazilian BMT centers. The median age was 1 yo and 79 % were male. PID diagnosis included: SCID (n = 21); Wiskott-Aldrich Syndrome (n = 9), CGD (n = 5); Kostmann Syndrome (n = 1); CVID (n = 1); LAD (n = 1); HLH (n = 2); IPEX (n = 1) and Chediak Higashi (n = 1). Alternative

donors included matched unrelated donors (n = 3), mismatched related donors (n = 1), or haploidentical related donors (n = 38). All pts received graft versus host disease prophylaxis that included PT-CY + a calcineurin inhibitor and mycophenolate. Most pts (93 %) received bone marrow grafts. 30pts were transplanted upfront and 12pts were rescued after a primary or secondary graft failure(GF) from previous transplants. Most pts had active infections, failure to thrive and severe auto-immune complications before transplant. Three pts were transplanted while receiving mechanical ventilation.

Results: 29pts are alive at a median of 1 year after HCT with an overall survival (OS) of 70 % at one year. We observed no difference regarding OS for SCID when compared to other PID (71 % *vs* 67 %; p = 0.9). When pts were transplanted upfront with a reduced intensity conditioning (RIC, n = 19), only 2pts had full donor chimerism. In this group, primary (n = 3) or secondary (n = 3) graft failure was observed in non-SCID pts and 4 out of these 6 pts received a 2nd HCT. When a busulfan-based regimen was used in upfront transplants (n = 11), full donor chimerism was detected in all but one patient and none rejected. Ten out of these 30pts died and causes of death included rejection (n = 4) and infections (n = 6). All 12pts that were transplanted after previous graft failures received a RIC regimen and 9 are alive, fully engrafted.

Conclusions: Allo-HCT using alternative donors and PT/Cy shows promise for curing PID and the use of PT-CY is feasible without the need of extensive T cell depletion. However, timing of transplantation is critical for a successful outcome and early referral to transplantation could change the prognosis of many children with PID.

PO - 154

Primary Immunodeficiency Disorders in Children in Kuwait (2004-2016)

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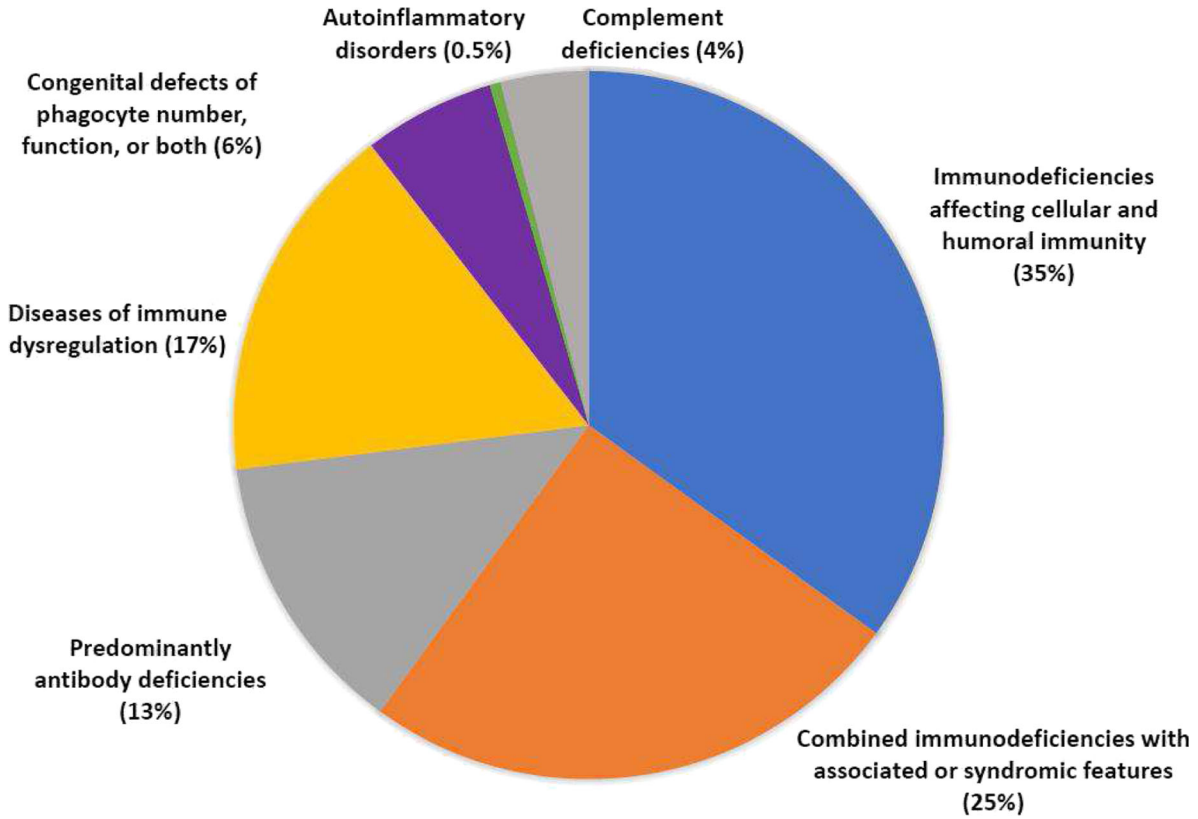
Introduction: Registries are important resources to study the epidemiology and characteristics of primary immunodeficiency disorders (PID).

Aim: To present details of PID in children (0-14 years) in Kuwait for the period of 2004-2016

Method: Data was retrieved from the Kuwait National Primary Immunodeficiency Registry and patients were classified according to the 2015 IUIS classification

Results: A total of 248 patients (132 males and 116 females) were registered during the study period. The distribution of these patients showed the following:



Parental consanguinity and family history of PID were reported in 81 % and 54 % of the patients, respectively. Genetic testing was performed in 187 patients (75 %) and a genetic defect was identified in 157 patients (63 %). There were 4 novel PID-causing genes identified during the study period (TFR1, HOIP, DOCK2 and TTC7A). IVIG was used in 50 % of the patients. Bone marrow transplantation was performed in 58 patients (23 %). There were 70 deaths (28 %) during the study period
Conclusions: PID are prevalent in Kuwait and show a peculiar pattern compared to patients from other geographic areas

PO - 155

Diagnostic Delay of Primary Immunodeficiencies at a Tertiary Care Hospital in Peru

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Abstract: Introduction: Delay in diagnosis of PID from the onset of symptoms contributes to delayed administration of specific treatments, increased morbidity (recurrent infections such as pneumonia or sinusitis), poor quality of life, and mortality.
Objective: The aim of the study was to assess the diagnostic delay in pediatric patients with primary immunodeficiencies (PID) at a tertiary care hospital in Peru.
Methods: A descriptive study was carried out in which patients from a third-level referral center in Peru were included. Those without a specific diagnosis of PID were excluded. Data was collected by reviewing the medical records and interviewing patients' family members.
Results: A total of 45 patients with a mean of 7.4 years (SD = 4.3) were studied. The most frequent diagnosis was predominant antibody defects (35.5 %), and the diagnostic delay had a median of 12.17 months (IQR 5.1–30.3).
Conclusions: The most frequently diagnosed group of PID was predominant antibody deficiency. The overall median diagnostic delays for PID and predominant antibody deficiency were 12 and 14 months, respectively. Even though early detection of PIDs is crucial for effective treatment, current available laboratory tests required for PID diagnosis are both complex and expensive. Early detection and management of these pathologies cannot be achieved without training non-specialist health professionals in the diagnosis of PID, as well as integrating multidisciplinary and multi-center cooperation at both national and international levels.
Table 1. Onset of symptoms and diagnostic delay of PID according to the IUIS classification in the CERNAAI

	Onset of symptoms (months)	Diagnostic delay (months)
PID Specific diagnosis	*n* = 36	*n* = 29
Diseases of immune dysregulation	61.3 (1.0-121.5)	51.8 (0.6-103.1)
Immunodeficiencies affecting cellular and humoral immunity	23.4(23.4-23.4)	18.1 (18.1-18.1)
Predominantly antibody deficiencies	18.7 (11.1-61.6)	13.8 (3.9-29.0)
Defects in Intrinsic and Innate Immunity	6.8 (2.1-17.4)	9.9 (6.7-45.9)
Combined immunodeficiencies with associated or syndromic features	6.7 (1.5-23.9)	20.2 (8.5-39.4)
Congenital defects of phagocyte number, function, or both	1.7 (0.0-2.9)	10.3 (4.0-17.9)
Total	10.4 (2.0-25.6)	12.2 (5.1-30.3)

Median and interquartilar range of time are shown from the onset of symptoms and the diagnostic delay in months
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Delayed Diagnosis of Comel-Netherton Syndrome In a 2-Year-old girl

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Introduction: Comèl-Netherton syndrome is a rare autosomal recessive disease that is characterized by congenital ichthyosis, bamboo hair and atopic symptoms. Other symptoms include failure to thrive, enteropathy and immunodeficiency. Bamboo hair is pathognomonic indicating a structural defect of the hair shaft[1].
Case Presentation: Female patient, born full term, since birth has difficulty to gain weight. With 40 days of life, she presented diffuse erytrodermia with peeling and skin pruritus. Several allergists and dermatologists evaluated the case, and atopic dermatitis and food allergy were the diagnoses. Moisturizers, cow's milk and egg exclusion diet as well as a soy based diet were prescribed but the skin lesions did not improved. She mantained these treatment for more than two years, needing hospitalization due to the worsen of the skin lesions. During this time, she did not present any infections but her hair never grew more than 1 inch and it would break when she lies down. Also, weight and height were always below the 3rd percentile. At age 2, she was referred to an immunologist and Comèl-Netherton syndrome was confirmed through capillaroscopy that showed bamboo hair. She has normal IgG, IgA and IgM, with high IgE levels (1.475 UI/ml). However, her IgG is decreasing: at age one it was 814 mg/dl and now at age 2 years is 567 mg/dl. She has normal response to protein vaccines and normal T-lymphocyte count. Response to polysaccharide vaccine was not evaluated because of her age. Replacement treatment with IVIG (500 mg/kg/month) was started due to the skin lesions. She has had 3 infusions so far and her skin erythema and pruritus showed improvement. Also, her weight is now on 10th percentile.
Discussion: Although this is a girl that doesn't have abnormalities on her blood tests, we decided to start IVIG because studies have shown that these patients can present clinical improvement as a whole, and not just of the immunodeficiency[2]. In the short period of time that she has received IVIG, it looks like her skin is improving.

References:
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A Systematic Review and Meta-Analysis on the Safety and Efficacy of Interferon Gamma as Added Treatment for Chronic Granulomatous Disease, as Compared to Antimicrobial Prophylaxis Alone

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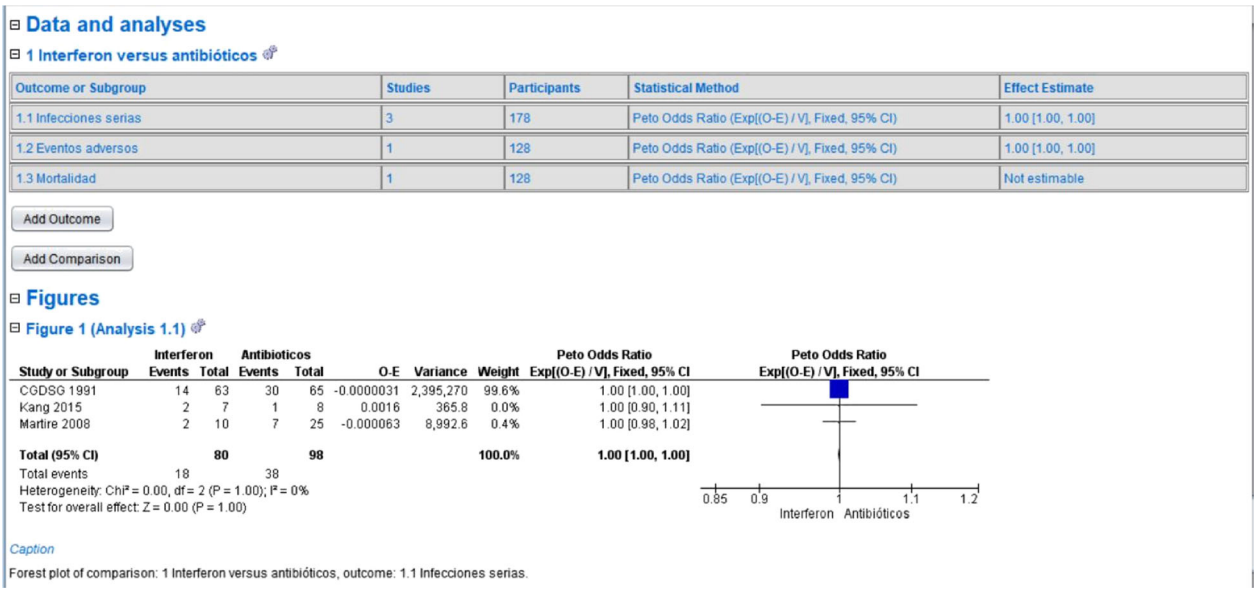
Introduction: Chronic granulomatous disease (CGD) is a primary immunodeficiency with increased susceptibility to several bacteria, fungi and mycobacteria, caused by defective or null superoxide production by the NADPH oxidase enzymatic complex. Accepted treatment consists mainly of antimicrobial prophylaxis. The role of human recombinant subcutaneous interferon gamma (IFN) is less clear: available clinical evidence on its safety and efficacy is scarce and conflicting.

Objective: We aimed to assess the efficacy and safety of IFN as added treatment for CGD, when compared to antimicrobial prophylaxis alone.

Methods: A literature search was conducted using the MeSH terms "Chronic granulomatous disease" AND ("interferon gamma" OR "interferongamma"), as well as *antibiotics, placebo, no therapy, clinical trial, trial*, on MEDLINE, EMBASE, LILACS, WHOs, CENTRAL, KOREAMED, The Cochrane Library, clinicaltrials.gov, and abstracts from meetings, from 1976 to 2015. We included clinical trials (CT) and prospective follow-up studies, and registered number of serious infections (requiring hospitalization and IV antibiotics) and deaths, adverse events and autoimmune complications in patients treated for CGD with antimicrobial prophylaxis plus IFN , versus antimicrobial prophylaxis alone. Statistical analysis was conducted on Review Manager (RevMan 5.3), by using a fixed effects model for combined data and Peto Odds Ratios.

Results: Out of 58 hits, we excluded: 12 duplicates; 7 studies by title; 9 after screening by abstract; and 24 full-text articles for content, model or design; to keep 6 studies: one randomized placebo-controlled CT, and 5 prospective follow-up studies, which had followed 324 patients (58 % X-linked) for 319 months. Risk of bias, as measured by RIB and STROBE was low or unkown. Only 3 of the studies had a control group. Only the outcome "serious infections" was amenable to meta-analysis, with an aggregate 3 studies and 178 participants; the OR was 1.00 (95%CI 1-1, see table and forest plot). Stratification by group was not possible.

Conclusion: This meta-analysis does not permit to recommend or discourage the use of IFN in the treatment of patients with CGD. We believe there is not enough clinical evidence. More clinical trials are needed to better assess the efficacy and long-term safety of IFN.



Data and analyses

1 Interferon versus antibióticos

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
1.1 Infecciones serias	3	178	Peto Odds Ratio (Exp[(O-E) / V], Fixed, 95% CI)	1.00 [1.00, 1.00]
1.2 Eventos adversos	1	128	Peto Odds Ratio (Exp[(O-E) / V], Fixed, 95% CI)	1.00 [1.00, 1.00]
1.3 Mortalidad	1	128	Peto Odds Ratio (Exp[(O-E) / V], Fixed, 95% CI)	Not estimable

Add Outcome

Add Comparison

Figures

Figure 1 (Analysis 1.1)

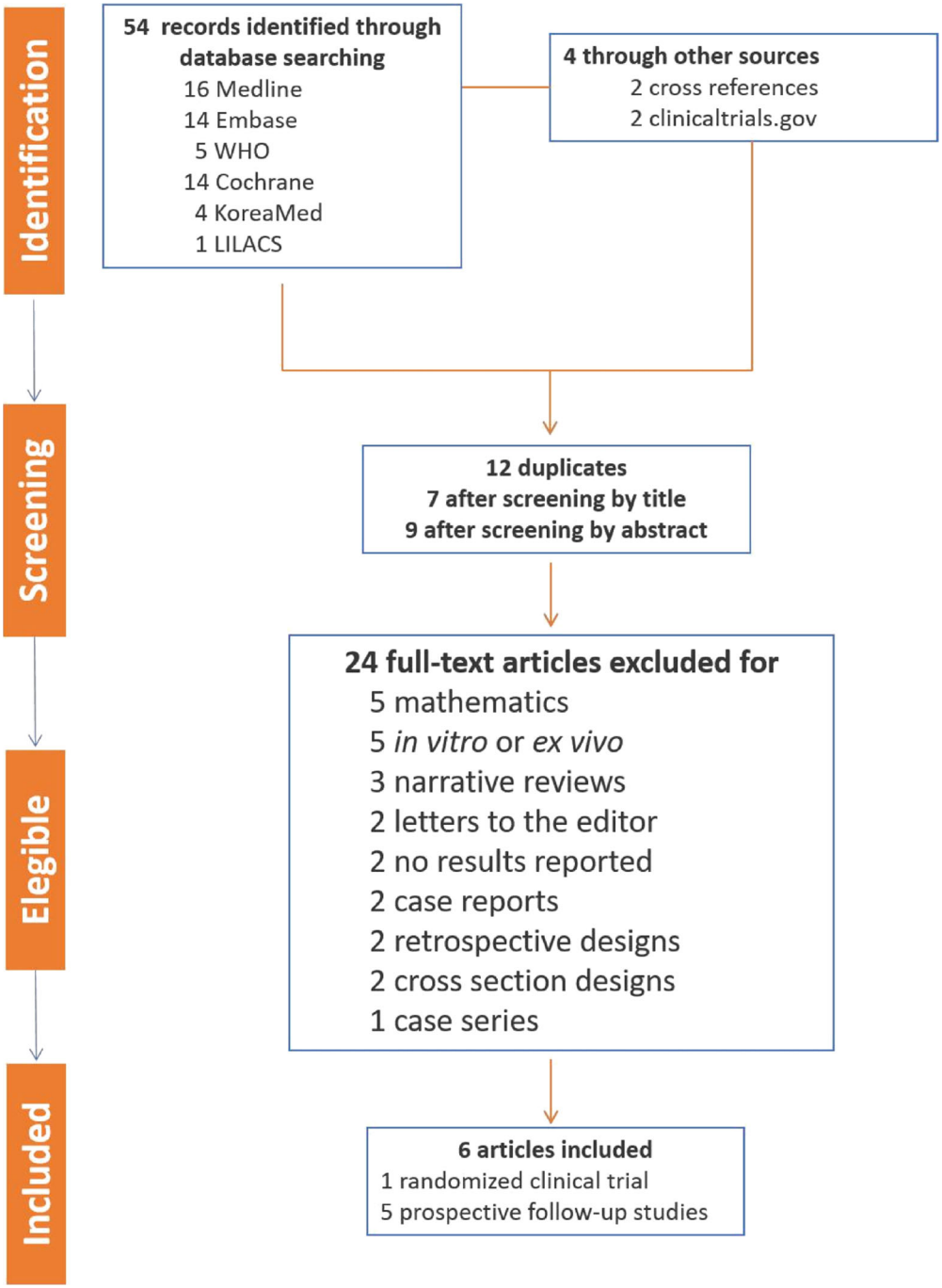
Study or Subgroup	Interferon Events	Interferon Total	Antibioticos Events	Antibioticos Total	O-E	Variance	Weight	Peto Odds Ratio Exp[(O-E) / V], Fixed, 95% CI
CGDSG 1991	14	63	30	65	-0.0000031	2,395,270	99.6%	1.00 [1.00, 1.00]
Kang 2015	2	7	1	8	0.0016	365.8	0.0%	1.00 [0.90, 1.11]
Martire 2008	2	10	7	25	-0.000063	8,992.6	0.4%	1.00 [0.98, 1.02]
Total (95% CI)		**80**		**98**			**100.0%**	**1.00 [1.00, 1.00]**
Total events	18		38					

Heterogeneity: Chi² = 0.00, df = 2 (P = 1.00); I² = 0%

Test for overall effect: Z = 0.00 (P = 1.00)

Caption

Forest plot of comparison: 1 Interferon versus antibióticos, outcome: 1.1 Infecciones serias.



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Primary Immunodeficiencies (PIDS): a Single-Center First Two Years Experience in Cali-Colombia

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At the Hospital Universitario del Valle (HUV) in Cali-Colombia, the Clinical Immunology service was established since August 2015, with an average of 5 to 8 patients weekly (outpatient and hospitalized patients) has been evaluated. Most of the cases are referred in the context of abnormal recurrent infection syndrome being the lung the most frequently affected organ.

The development of the Clinical Immunology service has enabled us to evaluate and follow up a total of 117 patients classified as: primary immunodeficiencies (PID) (39 %), secondary immunodeficiencies (16 %), severe immunological and rheumatological diseases (24 %), severe allergies (9 %), and others (12 %). According to the IUIS-2015 classification, 46 patients with PID were diagnosed: Immunodeficiency affecting cellular and humoral immunity 1 (2 %), combined immunodeficiencies with associated or syndromic features 4 (8.6 %), predominantly antibody

deficiencies 24 (52 %), diseases of immune dysregulation 1 (2 %), congenital defects of phagocyte number, function or both 1 (2 %), defects in intrinsic and innate immunity 2 (4 %), autoinflammatory disorders 4 (8.6 %), complement deficiencies 5 (10 %) and phenocopies of PID 2 (4 %).The mean age was 17,2 ± 15,1 years with a Male:Female ratio 24:22.
The Clinical Immunology service in Cali, Colombia has improved the diagnosis and follow-up of people with PID as well as patients with other immune diseases. In the short term, it is proposed to create a search program for primary immunodeficiency patients in line with Colombia's orphan diseases law, which will improve the quality of life of patients with PID and reduce costs in health care with a positive impact In the southwestern Colombian.

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Visceral Leishmaniasis and Primary Immunodeficiency: is There Relationship?

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Introduction: Visceral leishmaniasis (VL) is an infectious disease prevalent in some regions of the world and primary immunodeficiency (PID) is unknown by the majority of the population, including health professionals.
Objectives: The present study aimed to relate PID as a cause of serious diseases in children hospitalized at the Academic Hospital Clemente Faria, in the city of Montes Claros, Brazil, and to analyze the admission and discharge diagnosis, as well as the types of immunological tests performed.
Methods: A retrospective, descriptive, cross-sectional study was held based on the analysis of medical records of children from zero to five years old, who were admitted with severe infections in the pediatric section of an Academic Hospital, in the city of Montes Claros (Minas Gerais, Brazil), from February to December 2016, Ethics Committee number: 1976572. Until the present, 100 medical records analyzed, were collected from the Service of Medical Archives and Statistics, of the Academic Hospital Clemente de Faria. The following variables were included: sex, age, origin, diagnosis at admission, length of hospitalization, diagnosis at discharge, outcome, cause of death, complications, types of immunological, molecular or genetic tests performed. Children with cancer, AIDS and HIV positive were excluded.
Results: In this partial date, most of the patients evaluated were male (55 %). The age group that stood out was the closest to birth to the first year of life (0-1 year), totaling 47 %. The most commonly diagnosis obtained so far, totaling 51 cases, was Visceral Leishmaniasis, with diagnostic confirmation based on immunological exams (Kalazar Detect and IT-Leish) in 39 % of these cases and myelogram compatible with VL in 37 %. Pancytopenia was observed in 43 % of cases. The bases of treatment for VL were Amphotericin B and Glucantime. No specific biologic or genetic examination for diagnosis of PID was performed in these cases.
Conclusions: It will be necessary to deepen this study, as we do not find literatures specifics articles of PID and VL in children.

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Clinical and Genetic Characteristics of Patients with Wiskott-Aldrich Syndrome in Brazil

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Introduction: Wiskott-Aldrich Syndrome (WAS) is a rare X-linked primary immunodeficiency characterized by eczema, thrombocytopenia with small sized platelets and recurrent infections[1]. More than 300 types of mutations associated with the WAS gene have been described, including eight hotspots[2,3].The diversity of these mutations can lead to the appearance of great variation in the clinical presentations, which makes it difficult to predict the evolution of the disease based only on the initial symptons[4]. Furthermore, there is paucity of information on WAS from the Brazilian population. Objectives: To describe the clinical and molecular characteristics of Brazilian patients with clinical diagnose of WAS.
Results: Data from eighteen patients was analyzed (Table 1). Seventeen patients presented first symptoms within first year of age. Mean age for initiating symptoms was 4,5 months and mean time for diagnosis was 31,2 months. Three patients were diagnosed after 10 years of initiating symptoms. Seventeen patients (94.5 %) had eczema. The platelet levels ranged from 1,000 to 65,000/mm3 and only nine patients (50 %) presented microthrombocytopenia. Two patients (11.1 %) had macroplatelets. Sixteen patients (88.9 %) had hemorrhagic events throughout their lives, including intestinal, urinary and petechial bleedings. In relation to infectious manifestations, acute media otitis was the most frequent infection, reported by 13 patients (72.2 %), followed by skin infections (66.7 %). Three patients (16.7 %) had autoimmune manifestations including IgA nephropathy, ischemic stroke and vasculitis. Most patients (55.5 %) did not present alterations in IgG levels. Twelve patients (70.6 %) did not present alterations in IgA levels and elevated levels of IgA was only observed in 4 patients (23.5 %). Reduction of IgM levels was observed in 7 patients (38.9 %). Patients were classified according to a previously described clinical score[5]. Most patients presented scores of 3 (33.3 %) and 4 (27.8 %). Four patients were classified with score 5 due to autoimmune or neoplastic manifestations. Regarding genetic analysis, mutations were found in 10 patients (Table 2). Only three of mutations found in this study were previously described.
Conclusion: Clinical characteristics of Brazilian patients are similar to medical features seen in other populations, however genetic analysis showed yet undescribed mutations.
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Table 1- Clinical and laboratory characteristics of the 18 patients analyzed.

DIAGNÓSTICO					
	AVERAGE (months)	STANDARD DEVIATION (months)	MEDIUM (months)	MINIMUM (months)	MAXIMUM (months)
Age of onset of symptoms	4,5	6.1	1	0,03	24
Age at diagnosis	35,3	52,7	10,5	0,03	156
Mean time for diagnosis	31,2	53	6,5	0	156

FAMILY BACKGROUND	
Inbreeding	2 (11,1%)
Early death in Family	5 (27,8%)
Familiar diagnosis of PID	3 (16,7%)

CLINICAL MANIFESTATIONS		
	PRESENT	ABSENT
Eczema	17 (94,5%)	1 (5,5%)
Frequent infectious manifestations	13 (72,3%)	5 (27,7%)
Autoimmune manifestations	3 (16,7%)	15 (83,3%)
Allergic manifestations	6 (37,5%)	12 (66,7%)
Neoplastic manifestations	1 (5,5%)	17 (94,5%)

NÍVEL PLAQUETÁRIO				
AVERAGE (mm^3)	STANDARD-DEVIATION	MEDIUM (mm3)	MINIMUM (mm^3)	MAXIMUM (mm^3)
19.605	19944,64	8.500	1.000	65.000

PLATELET SIZE		
MICROPLATELETS	NORMAL	MACROPLATELETS
9 (50%)	7 (38,9%)	2 (11,1%)

HEMORRHAGIC MANIFESTATIONS	
Enterorrhagia	6 (33,3%)
Petechiae	6 (33,3%)
Hematuria	3 (16,7%)
Epistaxis	1 (5,5%)
Otorrhagia	1 (5,5%)

INFECTIOUS MANIFESTATIONS	
Acute media Otitis	13 (72,2%)
Skin infections	12 (66,7%)
Pneumonia	9 (50%)
Diarrheia	8 (44,4%)
Viral infections	5 (27,8%)
Sinus infections	5 (7,8%)

Table 2 – Description of found mutations.

PATIENT	EXON	gDNA	TYPE OF MUTATION	AMINOACID ALTERATION	CLINICAL SCORE
WA-02	7	g.10257 C > T	Nonsense	R211*	3
WA-04	11	g.12751_12752delCG	Deletion	L456Afs*38	3
WA-06	1	g.7358 C > T	Nonsense	R34*	3
WA-07	11	g.12767 C > T	Nonsense	Q461*	2
WA-08	11	g.10185G > A	Intron	Intron	4
WA-09	4	g.9175 G > A	Missense	E133K	2
WA-12	10	g.12427 G > T	Nonsense	G432*	5
WA-17	3	g.8998 A > G	Missense	Y107C	5
WA-19	10	g.12164_12165insC	Insertion	V345Cfs*150	5
WA-24	8	g.11504_11507delGAGT	Intron	Intron	4

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Registry of Primary Inmunodeficiencies Diseases in National Medical Center "La Raza" (IMSS)

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Background: The Primary Immunodeficiencies Diseases (PID) involve nearly 300 gene inborn errors of immunity. The most PID present at early age with infections, malignity, or disregulation in the immune response. The global prevalence is estimated at 1:5000 to 1:100 000. LASID Registry is a platform based in ESID Registry, until 2017 involve 122 centers in 15 countries, including Mexico.
Objective: To report patients diagnosed with PID in National Medical Center "La Raza" based on LASID Registry
Results: We analyzed patients of the National Medical Center "La Raza" with diagnosis of PID in LASID Registry database from 2012-2016. It was reported 140 patients with diagnosis of PID, 83 (59.2 %) are men and 57 women (40.1 %). It was found 104 (74.2 %) children (<18 years) and 36 adults (25.8 %). The mean age at report time was 13.2 years. It was documented a delayed in diagnosis from 0-35 years (mean 3.7 years). Based in the IUIS classification, the predominantly antibody deficiencies were the most frequent in 118 cases (84.2 %): 52 Common variable deficiency (44.1 %), 31 IgG subclasses deficiency (26.2 %), 17 (14.4 %) X-linked Agammaglobulinaemia (BTK), 10 (8.5 %) IgG specific deficiency, 4 (3.4 %) Selective IgA deficiency, 2 (1.7 %) unknown cause Agammaglobulinemia, 1 (0.8 %) transient Hypogammaglobulinemia of infancy, 1 (0.8 %) Unknown cause hypogammaglobulinemia. It was identified 5 (3.6 %) cellular PID cases, 1 SCID T-B- (20 %), 1 SCID T-B+ (20 %), 1 CD4- (29 %) selective deficiency and 40 % T-cell disorders not classified. 11 (7.8 %) congenital defects of phagocyte, 3 (27.3 %) Chronic granulomatous Disease of unknown cause, Griscielli Syndrome (RAB27A) in 3 patients (27.3 %) and other phagocytic disorders in 5 patients (45.5 %). Less frequent Complement deficiencies (1 case), identify selective deficiency (0.7 %). 2 (1.4 %) Unknown cause Wiskott - Aldrich syndrome. 3 (2.1 %) not classified IDP.
Conclusion: In México there are specialized PID centers that present problems for the diagnosis due to costs that limits the diagnosis and a correct treatment. However we must continue with PID Registry. Our report is like our literature research in Latino America even like a report of another Medical center in México, founding that predominantly antibody deficiencies was the most frequent, and of this, the majority are common variable deficiency. We consider that actual classification is practical and useful to promote the PID registration. We believe it´s important to mention that primary care professionals must be prepared to suspect PID, and with this way avoid the delayed diagnosis.
References:
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Chronic Granulomatous Disease in a Brazilian Patient Mimetizing Sarcoidosis

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Introduction: Sarcoidosis, multisystem disease, in which the most common cutaneous presentation are small papules on the face, often purplish red or brown. This lesion may mimic other diseases as facial chronic granulomatous disease (CGD), a rare inherited primary immunodeficiency characterized by recurrent infections due to defective phagocyte NADPH oxidase enzyme which can affect various organs and, unusually, skin.
Case presentation: A 10-year-old female with facial skin lesion history for 2 years and 4 pneumonia with hospitalizations since 8 months of age until 8 years old. She had nasal infiltration and erythematous-violet papules in bilateral-malar, knees and elbow area with cicatricial lesions, besides fibroelastic, mobile and painless cervical, axilar and inguinal lymph nodes. The patient also showed a discreet periungual erythema on her hands. The histopathology of skin biopsy from nasal papule showed epidermis with acanthosis and dermis with chronic inflammatory infiltrate, presence of necrosis with rare multinucleated cells called granulomatous dermatitis. The knee´s biopsy showed preserved epidermis and a deep dermis with intense inflammatory infiltrate, necrosis and some giant cells. The smear and culture examination excluded M tuberculosis, Leishmaniasis cutis or coccidioidomycosis. In the chest radiography and computed homography, the lung showed an elevation of the left dome, with adjacent parenchymatous atelectasias presenting an air bronchogram and bronchioloectasis of the right anterior base. The laboratory to leukocytes, for liver and renal function, electrolysis, autoimmunity were consistently within normal limits. All results of immunological tests, including serum immunoglobulin levels to answer serological responses to hepatitis, rubella, HIV were normal. However, the dihydrorhodamine (DHR) assay evaluated that production of oxygen peroxide in granulocytes was abnormal in patient (MFI: 4509) compared with healthy control (MFI: 224806).
Discussion: Based on the clinical records the patient received itraconazole, trimethoprim/sulfamethoxazol and prednisone for 1 month. We identified an adolescent patient with CGD with a clinical history suggestive of Sarcoidosis.

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Report of 8 years of Primary Immunodeficiencies in Two Centers in Argentina for Lasid Registry

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Introduction: In 2009 the Latin American Society of Immunodeficiencies, created the Latin-American (LA) registry of Primary Immunodeficiencies (PID). Represents a powerful tool to improve health policies, showing that are under diagnosed and should receive more attention
Objectives: Present the prevalence of PID, into a center of immunology in Argentina.
Results: In our center we have 1205 patients (p) with PID, with made retrospective study of medical records, up today we have registered 1097p (91 %). According to this record, these diseases are distributed in the following way: Predominantly antibody disorders: 837p (76 %), Predominantly T cell deficiencies:86p (7.8 %), Phagocytic disorders:41p (3.7 %), Complement deficiencies:26p(2.3), Other well PID:45p(4.1), Autoimmune and immune dysregulation syndromes:8p(0.7 %), Unclassified immunodeficiencies:54p(4.9 %). As different reports in different countries, predominantly antibody deficiencies are the most common PID, which comprise more than half of our all p. These group is represented by: Specific IgA deficiency (SAD):330p, Specific IgG deficiency:163p, Transient hipogammaglobulinemia:205p, Common Variable Immunodeficiency (CVID):96p, Agammaglobulinemia linked X:33p, Agammaglobulinemia unknown causes:8p, Secondary hipogammaglobulinemia:22p, Selective IgM deficiency:1p, subclasses deficiency:10p, CD40L deficiency:7p, Hyper IgM unknown causes:2p, Other hyogammaglobulinemia:2p. Among them, Selective IgA is the most common PID. In our cohort of unclassified immunodeficiency, we have 25p with auto inflammatory syndrome, such as Family mediterranean fever, Hyper IgD syndrome and Candle like- syndrome and 6 p with NK deficiency. In all our PID 238 p, are under replacement gammaglobulin (gg)treatment, 167p use intravenous gg and 71p use subcutaneous gg.
Conclusion: We want to demonstrate, the kind of PID in our center. Although the number of patient diagnosed with PID, is growing. Many physicians still know little about these disorders. More data are needed to define the exact prevalence of PID to avoid underestimation of these diseases due to under reporting.

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Development of Patient-Centred Application Supporting Self Care for Immunoglobulin Replacement Therapy

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Introduction: Due to defect in immunoglobulin production, replacement therapy has provided the best option for patients with primary immune deficiency (PID) affecting antibody production. It is a life-long therapy and still susceptible to risks, which demands constant supervision of symptoms. The chronic nature of PID claims a particular model of medical attendance with improved adherence of patient to the treatment. Promoting self-care is a way to improve treatment adherence and engage patient, family and community. An individual aware of the illness' details may collaborate in the decision-making process and, also, serve to instruct finer practices to the caretakers. Therefore, a mobile health system has been developed to empower patients with real comprehension of the disease and grant tools to manage their follow up.
Objectives: The aim has been the development of a free mobile application to promote self-care for PID patients dependent on immunoglobulin replacement therapy (IRT).
Results: As a software engineering method, every aspect of the design was increasingly carried out in meetings with experts and patients, from the initial product vision to models, diagrams and processes. The design of the dataset has been drawn for the collection of patient information, symptoms, manifestations, side-effects and his activities in the therapy. The clinical workflow would not be replaced by the application, in fact they operate in parallel, assisting the PID treatment without changing the health professional's role. Based on the design, the App has been released for either the patient, parent, responsible or family as a remote self-care tool with the following features: record card, lab tests control, pondostature, infusion log, diary of symptoms, deliver results and calendar. The system is available as a beta test in Google Play Console.
Conclusion: We developed an App as a solution to properly guide a continuous treatment for PID, bringing patients to play an active role in their treatment, holding and supplying the data. Additionally, the features make possible to remotely build the treatment history, get a better comprehension of the treatment and increase adherence to the therapy.

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A Survey Study of Medical Knowledge About Primary Immunodeficiency Diseases Among Physicians of Several Specialties from a Tertiary Hospital

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Introduction: Primary Immunodeficiency Diseases (PIDs) are disorders of the immune system that affect its function and/or development, predisposing the affected individuals to an increased rate and severity of infections, allergy, malignancy and autoimmunity. Early diagnosis is essential to promote morbidity and mortality reduction, better quality of life and outcome.
Objectives: Evaluate the knowledge about PIDs among physicians of different specialties from the Hospital Federal dos Servidores do Estado.
Methods: We conducted an observational study applying questionnaires with the following questions between April and June 2017: "Are you familiar with PIDs diagnosis?", "Do you know the warning signs of PIDs?", "Have you ever seen any patient with suspicion or diagnosis of PIDs?"
Results: We evaluated 142 questionnaires answered by physicians (67.6 % female) from many specialties that work with adults (64.8 %) or with children (35.2 %). Most of them were less than 30 years old (56.3 %). Questioned if PIDs are familiar disorders, half answered NO (50.7 %). About knowing the 10 Warning Signs of PIDs from Jeffrey Model Foundation, half answered YES (57 %); however, only 49.3 % had already seen a patient with suspicion or diagnosis of PIDs. Pediatricians are better aware of warning signs than the total of other specialties (88 % versus 44 %), are more familiar with diagnosis (73 % versus 39 %) and have more patients with suspicion or diagnosis of PIDs (75 % versus 38 %).
Conclusion: Over the last 65 years, the field of PIDs has advanced greatly. With the advent of cutting-edge genetic technology, more than 240 PIDs have been discovered and the number continues to increase. Estimates of PIDs prevalence from registry data are 5.38/100000 in France, 5.6/100000 in Australia; however they were much lower than the estimates based on the data from Boyle and Buckley's survey (86.3/100000). The LASID registry identified 7095 PID patients until June 2017. Upper estimates suggest that 6 million people may be living with PIDs worldwide, where only 27.000 to 60.000 have been identified to date. We believe that many PIDs patients die before diagnosis because the lack of awareness among the physicians. This survey demonstrated that medical specialties, with the exception of pediatrics, are not familiar with PIDs even in a tertiary hospital. It is necessary more information among general practitioners who will the first physician to attend those patients. It is important that Healthy Ministry develops strategies of continuous education and professional capacitation.

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Case Report Of Hereditary Angioedema

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Introduction: About 10 % to 20 % of people worldwide will develop an episode of angioedema at some point in their lifetime. Angioedema is characterized by localized temporary swelling, which can affect the skin or the walls of viscera, such as the oropharynx, respiratory system, or the gastrointestinal tract.
Case Presentation: Patient M.A, female, 8 years old, diagnosed with HAE and her regular medication was Tranexamic Acid. She was admitted to hospital for face and upper extremities swelling, pruritus following an acute difuse abdominal pain. She had nausea and vomiting, but denied fever.
Her laboratory examination revealed hemogram with leukocytosis of 8.560, ESR 30 mm, RCP negative and a normal urine routine. By day 2, patient evolved with CRP of 24, leukocytosis of 12.520 and a fever (38.5 ° C). During the physical examination, the patient was with a constant abdominal pain, but now localised to the right iliac fossa and blumberg's signal positive. The diagnosis was appendicitis and the decision was made to perform a laparotomy with a view to undertake an appendicectomy. She had an uneventful postoperative recovery and 2 months further on remains well.
Discussion: Abdominal pain associated with angioedema may manifest as severe acute onset abdominal pain, or as chronic recurrent abdominal pain of moderate severity. The abdominal pain is described as cramping or colicky and is rated as severe to excruciating in 87 % of patients. Vomiting and diarrhea occur in 78 % and 65 %, respectively, of patients with abdominal symptoms. Although rare, hereditary angioedema is associated with episodic attacks of edema formation that can have catastrophic consequences. Laryngeal edema can result in asphyxiation; abdominal angioedema attacks can delay in diagnosis, as well as to narcotic dependence due to severe pain; and cutaneous attacks can be disfiguring and disabling.
Conclusion: Patients experiencing angioedema with abdominal involvement often present with a history of recurrent episodes or acute onset of abdominal pain. A careful history and physical examination, imaging studies, laboratory assessments can help the clinician order appropriate tests to explore the differential diagnosis.
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Primary Immunodeficiencies Follow Up After Haematopoietic Stem Cell Transplantation

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Introduction: Primary immunodeficiencies (PIDs) are a group of heterogeneous genetic disorders that affect innate and acquired immunity, commonly leading to lethal complications. Haematopoietic stem cell transplantation (HSCT) offers a curative approach for many of these disorders including severe combined immunodeficiencies (SCID), several T-cell immunodeficiencies, Wiskott-Aldrich syndrome, phagocyte disorders such as leucocyte adhesion deficiency and chronic granulomatous diseases, haemophagocytic syndromes such as familial lymphohistiocytosis, Chediak-Higashi syndrome, Griscelli's disease, and X-linked lymphoproliferative syndrome.
Objective: To present the after HSCT follow up of the patients diagnosed at the Immunology Service of the Clinical Hospital of Federal University of Minas Gerais.
Results: The specialized service in primary immunodeficiencies of the Clinical Hospital of Federal University of Minas Gerais emerged in 1989. In 1999 an exclusive clinic was created for the diagnosis and treatment of these patients. Currently we have more than 300 patients affected by PID in follow-up. Hematopoietic stem cell transplantation (HSCT) was performed in 10 patients from 2012 to 2016 aged 1-9 years. All transplants were performed belatedly because of diagnostic delay and the difficulty of finding compatible donor and transplant center. Four transplants were realized in the Clinical Hospital of Federal University of Minas Gerais., with these diagnosis: Wiskott-Aldrich syndrome, Chediak-Higashi syndrome, chronic granulomatous disease and Revesz's syndrome. At the Albert Einstein Hospital in São Paulo four transplants were performed, two patients were affected by SCID, one patient with Griscelli's disease and one with chronic granulomatous disease. At Pequeno Príncipe Hospital, in Curitiba, two transplants were performed, one patient with SCID and one Leaky SCID. Of the ten patients transplanted, only two patients died, one affected by Revesz's syndrome, which resulted in CMV pneumonitis and sepsis three months after transplantation and one patient with SCID eleven months after transplantation due to sepsis of probable fungal focus. Only one patient presented graft failure, remaining affected by chronic granulomatous disease.
Conclusion: Most of the transplanted patients had a favorable outcome and are currently being followed up both in the outpatient clinic of PID and in the outpatient clinic exclusively for patients transplanted from the hematology department.

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Hereditary Angioedema with Normal C1-inh: Features in a Brazilian CohorT

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Objective: To describe demographic and clinical features in a cohort of patients with Hereditary Angioedema (HAE) with normal C1-INH followed up at a Reference Center in Rio de Janeiro, Brazil.
Material and Methods: A descriptive cross-sectional study with prospective data collection of 31 patients with HAE with normal C1-INH followed up at a Brazilian Outpatient clinic specialized in HAE, from 1989 to 2016. The following parameters were evaluated: sex, age, age at onset of symptoms, age at diagnosis, familial history and severity of HAE attacks.
Results: From a total of 138 patients, 107 had HAE with C1-INH deficiency (77.5 %) and 31 had HAE with normal C1-INH (22.5 %). Data from the 31 patients from 6 unrelated families were analyzed. The FXII mutation was identified in all of them (exon 9 - Thr309Lys, previously described). Twenty-five were female (80.6 %) and 6 were male (19.4 %). Mean age was 42.4 ± 16.4 (range: 13-77 years). Mean time between first symptoms and diagnosis was 15.0 ± 13.7 years. Most of them (61.3 %) had moderate or severe attacks, including a young boy. Eight were asymptomatic (25.8 %).
Conclusion: We have found an important frequency of HAE-FXII, showing us that probably HAE-FXII is more prevalent in our country than in

others. The severity of HAE attacks and the delay in diagnosis were important characteristics outlined. Screening of family members, including asymptomatic individuals, is critical to early diagnosis and management.

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Hair Analysis as a Diagnostic Challenge for Primary Immunodeficiency Associated with Albinism: Case Report of a Probable Brazilian Hermansky-Pudlak Syndrome (HPS) Patient and a Brief Review of Literature

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Introduction: Primary Immunodeficiency is a large group of disorders characterized by genetic mutations, usually monogenic, that drive any alterations in the immune system leading impaired function to control allergic antigens, infection control and homeostasis in self-reactive and neoplastic cells.
Case presentation: D.A.M., 52 year old male, entered the emergency department with acute respiratory distress syndrome, requesting mechanical ventilation and broad-spectrum antibiotics in the ICU department. During the hospitalization, generalized albinism with nystagmus, independent of the actual clinical condition was observed. Laboratory analysis showed low immunoglobulin levels and a persistent lymphopenia. There was history of neonatal generalized albinism and mental retardation was observed in the first years of life, always treated as schizophrenia. Patient has had recurrent infections (four pneumonias in the last year) and recurrent untreatable skin cancer. The family lives in Brazil but is of Italian descent. The patient's father, has first degree consanguinity. Heredogram construction showed two brothers with generalized albinism and nystagmus but no mental retardation or history of recurrent infections or skin cancer. All albino individuals have normal growth development. Due to the suspicion of primary immunodeficiency, the patient received intravenous immunoglobulin with an excellent response. All albino individuals were submitted to hair analysis to differentiate Griscelli (GS) from HPS.
Discussion: In this case, we describe an patient with autosomal dominant albinism associated with nystagmus and recurrent infections. The association of albinism in primary immunodeficiencies is restricted to a small group of diseases, as revised by Al-Herz et al, Frontiers in Immunology, 2014: GS, HPS and P14-LAMTOR2 immunodeficiency. Hair analysis in these patients is essential to guide the diagnosis without the genetic approach since specific alterations can be found especially in GS´s hair. In this related case, we made the hair analysis and it is fundamental when occurring in suspected primary immunodeficiency and albinism.

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CMV Infections in Patients with Wiskott-Aldrich Syndrome

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Introduction: Wiskott-Aldrich Syndrome (WAS), including X-linked thrombocytopenia (XLT), is a complex disorder with a wide range of clinical severity and unique hematological and immunological manifestations which are assessed on a score (1-5). Based on this complexity, several treatment approaches are available including symptomatic treatment, splenectomy, gene therapy (GT) or hematopoietic stem cell transplantation (HSCT). This is a retrospective study analyzing the impact of cytomegalovirus infection in patients with Wiskott-Aldrich Syndrome in a tertiary pediatric care center.
Objectives: To assess the frequency of complications related to *Cytomegalovirus* (CMV) infection and the outcomes of those infections based on the severity of the WAS phenotype.
Methods: We reviewed all the patients' charts, and molecular laboratory. CMV infection was defined by positive serology (IgG and/or IgM) and positive PCR viral load above 1000 copies/ml. WAS score includes the following features: thrombocytopenia, small platelets (defined by diameter below 7 FL), eczema, infections, autoimmunity (cytopenias) and/or malignancy.
Results: 31 patients with WAS gene mutation followed at Hospital Garrahan from 1987 to 2017. Were included 11 patients had a WAS score of 3 and 13 patients scored 5 (WAS score was not available in 7/31 patients). CMV infection was documented in 16 patients. Thirteen positive had IgG and 3 positive had positive IgM. Three patients presented positive PCR viral load and 1 had positive CMV in bone marrow. Ten patients underwent allogenic HSCT (6/10 in our center). Patients were followed weekly with quantitative PCR for CMV before and after HSCT. Ganciclovir, Foscarnet and Valganciclovir were used to treat or prevent CMV infection. Five (83 %) patients died after HSCT (4 due to reactivation of CMV infection and 1 due to other infections). One patient is alive post-HSCT and never experienced CMV infection to date.
Conclusion: This study describes the proportion and complications related to CMV infection in a cohort of WAS patients with or without HSCT. We found that the 51,6 % had CMV infection. Reactivation occured in 66,6 % of those with HSCT resulting in 100 %. Mortality white is higher when compared with other centers that use other therapeutic approach such as celular therapy.
Key words: Wiskott-Aldrich syndrome, thrombocytopenia, cytomegalovirus, autoimmunity.

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Epidemiological Report of Primary Immunodeficiencies at the Jeffrey Modell Reference Center in Colombia: 1987-2017

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Introduction: Primary immunodeficiencies (PIDs) result from mutations in that affect the development and function of the immune system, leading to a wide spectrum of clinical manifestations.
Objectives: To describe the epidemiological characteristics of Colombian patients affected with PIDs and diagnosed at the JMC-UdeA in Medellín, Colombia.
Methodology: This cross-sectional study included data from clinical records collected from 1987 to June 2017. Statistical frequency measures were established for qualitative variables. The clinical and laboratory definition was based on diagnostic criteria established by the European Society for Immunodeficiencies (ESID). All diagnoses were catalogued based on the subgroups as defined by the classification of the Committee on Primary Immunodeficiency of the International Union of Immunological Societies (IUIS).
Results: A total of 891 patients (59.5 % males and 40.5 % females) have been diagnosed with a PIDs from 1987 to 2017, from which 70 have died of various causes. Diagnosis was established in 79.4 % before the age of 19 years. The percentages of diagnostics are as follows: 74.4 % for predominantly antibody deficiencies, 5.7 % for defects of innate and intrinsic immunity, 3.7 % for Immunodeficiencies affecting cellular and humoral immunity, 8.6 % for combined immunodeficiencies with syndromic features, 4.3 % for congenital defects of phagocytic cells, 2 % for diseases of

immune dysregulation, 0.7 % for complement deficiencies and 0.6 % for autoinflammatory diseases. The number of cases diagnosed annually at the JMC-UdeA has increased by 60 % in the last 7 years; from these, 12 % have confirmed molecular diagnosis. The distribution of cases by region show that 85 % come from Antioquia, followed by Cundinamarca with 3.9 %, Caldas with 3.7 %, and the remaining 7.4 % from the rest of Colombia.
Conclusions: These results show significant progress in the diagnosis of PIDs in Colombia in recent years. In addition, to promote registration of patients throughout the country, we created The National Network of Nodes for PIDs (IDPNet) that currently is operating 6 registering centers in 7 cities. The LASID registry currently has a total of 1.031 Colombian patients registered until June of 2017. Assuming that this reflects the number of diagnostics per Country and with a global estimated prevalence of 1:5.000, our percentage of registered patients is currently 12.76 %, from which 71.1 % come from the JMC-UdeA. This positions the JMC-UdeA and the IDPnet in the third place for registration of patients in Latin America, only after Argentina and Costa Rica. However, if the Colombian population is of approximately 49 million inhabitants, we estimate that the number of affected individuals with a PID might be around 9.800 people. Hence, we remain determined to improve diagnosis and registration for the benefit of all PID patients in Colombia.

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Survey on Resources and Needs for Diagnosis and Treatment of Primary Immunodeficiencies Among SLaai Members

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Introduction: Despite global advances in diagnosis and treatment for PID, there are several gaps which prevent reaching a greater number of patients, especially in our region; still lacking of diagnostic facilities, appropriate treatments and trained health professionals. The LASID has been working in the last 2 decades to improve this reality. The Latin American Society of Allergy and Immunology (SLaai) is formed by most of all national Allergy societies in the region. We conducted an open survey via e mail to all SLaai members in order to learn about their needs and basic resources to treat and diagnose PID.
Methods: We directed an online open survey, for basic resources and needs for diagnosis and treatment of PID via e mail trough the SLaai mailing list and social media.
Results: We received 106 complete responses. Eighty-five percent of responders approach to a patient with possible PID at least once in a month and 21 % do it every day. Most of them (92 %) consider themselves capable of conduct diagnosis workup. Only 17 % always receive support from their centers to do so, 63 % sometimes and 19 % never. Forty percent may send their patients to another center because of lack of support/resources. A majority (97 %) considers that more education in PID is needed; they also consider that their centers or societies should devote more resources in this regard. Roughly 80 % of responders have access to white blood cell counts and serum immunoglobulin levels. Seventy percent specific antibodies. Eighty-four percent flow citometry. Twenty percent lymphocyte proliferation assays and 16 % TRECs. Eighty-six percent of responders have access to immunoglobulin preparations for treatment. Forty-eight percent have access to 10 % presentation. Forty-two percent have access to subcutaneous formulations and 14 % do not have any product available. Only 19 % have HSCT available for all SCID patients and 45 % do not have a local donor bank.
Discussion and conclusion: Approaching to a patient with a possible PID is common among responders but a big proportion of them consider that there is neither enough support nor education for this endeavor. Basic diagnostic tests are available but more access to advanced techniques for diagnosis must be achieved. A small but alarming proportion mentions lack of access to Immunoglobulin therapy and a large majority of responder does not have early diagnosis for SCID or HSCT available. From this small and limited survey we learned that the efforts to increase education in PID should be reinforced everywhere. We also learned that access to diagnosis and treatment, even if improved in the region during the last decade is not enough. There are several gaps in order to improve PID perspectives in the region and the LASID should keep a major role in this regard.

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Hereditary Angiedema in Infant: Case Report

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Introduction: Hereditary angioedema (HAE) is caused by a quantitative and/or functional deficiency of C1 esterase inhibitor (C1INH), becomes clinically manifest as attacks of angioedema. C1INH is the main inhibitor of the complement system. Poor control of a local activation process of this system at the site of the attack is believed to lead to the formation of bradykinin (BK), which increases local vasopermeability and mediates angioedema on interaction with BK receptor 2 on the endothelium. Is an dominant autosomal disease with a prevalence of 1:50.000. Case presentation: JS, brazilian, male, 18-month-old caucasian infant with a history of edema of the extremities and knees in May 2017, associated with abdominal pain, diarrhea and erythematous spots on the hands and feet. No cardiorespiratory symptoms. The edema regressed spontaneously after 72 hours. He presents a family history of Type I HAE (father, grandfather and paternal aunt). Therefore, a laboratory investigation was performed, which showed serum complement C4: 8 mg/dL, quantitative C1INH: 8 mg/dL, confirming the diagnosis of Type I HAE. It also performed abdominal ultrasound without alterations. Patient presented one new crisis of angioedema restricted to extremities, in July 2017. To date, there have been no new seizures of angioedema and, therefore, no need for prophylactic drugs.
Discussion: HAE accounts for about 2 % of all cases of angioedema. First manifestation symptoms occurring during the second decade of life and most attacks are associated with trauma or infections. The most commonly affected regions are the face, limbs, distal extremities and genital region. Gastrointestinal symptoms are frequent and can mimic acute abdomen. However, within its manifestations, the most feared is glottal edema, associated with a high mortality rate due to delayed diagnosis and inadequate treatment. Serpinous erythema may be a prodromal manifestation of seizures, which lasts about 2 to 5 days, with spontaneous resolution. The case reported above, evidences Type I AEH, with quantitative deficiency of C1INH and manifestations in the first two years of life. Since the crisis only affected extremities, prophylactic treatment is not necessary until now. The patient is followed up at the Pediatric Allergy and Immunology outpatient clinic.

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Primary Immunodeficiencies (PIDS) in Tucumán- Argentina: Five Years' Experience

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Introduction: PIDs diagnosis is increasing worldwide. Prompt identification of PID is important for prognosis. In 2012, the Immunology Unit was

officially established in Hospital del Niño Jesus (HNJ), Tucumán, and the Garrahan Hospital Immunology Laboratory became the reference center for diagnostic and follow-up studies for that Unit. The Flow Cytometry Laboratory was established in Tucumán in 2015. In 2016, Immunology Working Group in HNJ were formed, to improve the diagnosis and diffusion of the signs of PIDs. It consists of an interdisciplinary team, formed by 5 members (Pediatric Immunologist, Pediatric Rheumatologist, Clinical Pediatrician and 2 Biochemists). Annual meetings are organizated since 2013.
Objectives: To report patients (p) with PIDs diagnosed in our center from 1899 to 2017. Available data of patients were collected . IUIS-2015 Classification. Unclassified PIDs, transient hypogammaglobulinemia, Neutropenias were excluded.
Results: 93p have been registered. 21p were diagnosed until the end of 2011 and 72p from 2012 to 2017. Combined Immunodeficiency (CID): 2p (2 %),CID with associated or syndromic features: 32p (34 %). DiGeorge anomaly 17p, Ataxia-telangiectasia 4p, Hyper-IgE Syndromes 11p
Predominantly antibody deficiencies: 33p (35 %). CVID 5p; Selective IgA deficiency 24p; Specific antibody deficiency 3p; Hyper IgM syndrome 1p Diseases of immune dysregulation: 11p (12 %). ALPS 5p; APECED 1p; HHL 4p; Type I interferonopathies 1p Congenital defects of phagocyte: CGD 3p (3 %).Chronic mucocutaneous candidiasis: 6p (6 %). STAT1 gain- of-function 4p; IL17RA 1p; not defined 1p Autoinflamatory disorders: 6p (6 %). FMF 3p; CINCA 2p; not defined 1p
Conclusion: The availability of a Pediatric Immunologist in our Center along with collaborative interchange with a reference center result in an important improvement for PID detection, thus explaining the sharp increment in the number of PIDs diagnosed in Tucumán as of 2012.
Primary immunodeficiencies, registry, early detection

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T-Cells Subsets Profile in Kidney Transplant Recipients, Preliminary Results

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Introduction: Several limitations have been identified for the success of solid organ transplantation including acute rejection, chronic allograft injury and comorbidities such as obesity, dyslipidemia, hypertension, diabetes, which are related to the type of immunosuppressive therapy[1]. The immune tolerances is regulate by a balance between effector and regulatory T-cells[2].
Objectives: The aim of this study is to characterize T-cell subsets in kidney transplant recipients with acute renal rejection in order to identify differences between immunosuppressive therapies.
Results: We have designed a cross-sectional study, for the moment we have recruited fifteen kidney transplant (KT) recipients when they present an acute reject event. They are classified by immunosuppressive therapy (sirolimus, tacrolimus and cyclosporine A) and T-cells subsets are evaluated (TH9, TH17, TH22, and Tregs) by flow cytometry, we are generating a healthy control (HC) group too, for a reference values. In this partial analysis, HC group has shown a tendency of higher percentages from all cell lines (TH9 = 6.16, TH17 = 0.78, TH22 = 0.10, and Tregs = 0.28) respect to KT group (TH9 = 3.04, TH17 = 0.35, TH22 = 0.02, and Tregs = 0.09). There are no previous reports including all these T-cells subsets, Li *et al.* reports higher levels of Th17 cells and lower of Tregs cells associated to calcineurin inhibitors respect to healthy controls.
Conclusion: Study of Th17 cells and Treg cells balance in KT is a field that need to be explored, in order to define its contribution to renal allograft rejection.

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Profile of Patients Sent for Primary Immunodeficiency Investigation: Why They are Referred and by Whom

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Introduction: Primary immunodeficiencies (PIDs) are a heterogeneous group of immune system defects. Although relatively rare, they are increasingly known among general pediatricians and specialists. Repetitive infections are the main cause for diagnostic suspicion among these professionals.
Objective: To describe the profile of referral of children and adolescents to an immunology service.
Methods: Retrospective study, with data collection in medical records of patients attended in the period from 2013 to 2016. We analyzed the following data: origin and reason of the referral, diagnostic hypothesis formulated and final diagnosis.
Results: Of the 217 patients evaluated, 93 were referred by doctors from different pediatric specialties (68.8 % from the institution and 31.2 % from the outside) and 124 from general pediatricians (59.7 % from the institution and 40.3 % from outside). The most frequent referrals were recurrent infections (n = 100; 46.1 %), severe infections (n = 21; 9.7 %), recurrent fever (n = 14; 6.5 %), and angioedema without urticaria (n = 14; 6.5 %). Among recurrent infections, the most common was pneumonia (n = 31; 34.44 %). Of the 146 patients whose diagnostic investigation was completed, the diagnosis of PID was excluded in 65 % (n = 95), with the majority being referred for recurrent pneumonia. In 51 patients (35 %) the diagnosis was confirmed, being repetitive infections, angioedema without urticaria and alterations in the levels of immunoglobulins the main reasons for referral in these cases. Of the patients referred by general pediatricians, the diagnosis of PID was confirmed in 28.6 %, whereas by other specialists in 34.7 % and 76.9 % of cases, by immunologists. The diagnostic hypotheses formulated were confirmed in 23 patients, 8.3 % (n = 7) of those referred by general pediatrics, 11.1 % (n = 7) by non-immunologists, and 69.2 % (n = 9) by immunologists.
Conclusions: The diagnosis of PID has not been confirmed in most cases, as seen in other studies. Most referrals are made by general pediatricians, although they do not fit the diagnostic hypothesis in most cases. Immunologists are still responsible for most diagnostic confirmations.

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Primary Immunodeficiencies in Chile: Whole Exome Sequencing in a Cohort of Chilean Patients with Undiagnosed PIDs

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Introduction: Chile is divided into 15 regions, and most clinical immunologists are based in the capital city of Santiago. The health system is covered 75 % by public and 25 % by private insurance. Within the public system, primary care facilities refer patients to larger hospitals, and in turn those centers refer more complex patients to Santiago. Immunologists in Chile are scarce but have increased over the last 5 years. Primary immune deficiency (PID) awareness has improved during the last five years contributing to an increase in PID referrals. However, no genetic testing is available locally, and in most cases diagnosis is based on clinical presentation and functional flow cytometry studies, which are only available only in Santiago and Temuco. Therefore, genetic causes for most of PID patients in Chile remain unknown. We hypothesized that due to the unique geographical characteristics and cultural admixture of Chile, novel PID causing genes would be identified using an unbiased sequencing approach..
Objectives: We report a cohort of Chilean patients with unknown PIDs in which whole exome sequencing (WES) was performed.
Results: More than 30 family trios (proband and parents) with undiagnosed PIDs and strong heterogeneous proband phenotypes were referred to the Center for Human Immunobiology at Texas Children's Hospital in collaboration with the Center for Mendelian Genomics for genomic analysis. Nine patients in this cohort fulfilled criteria for hemophagocytic lymphohistiocytosis (HLH). Other common phenotypes included were hyper-IgE syndrome (n = 4) and combined immunodeficiency (n = 3). Analysis has been completed for 19 trios. A known genetic cause of PID was found in 6 patients; 5 of which correspond to either an expanded or a blended phenotype. A strong novel candidate gene was identified in at least 3 families (5 patients), one of which has been functionally confirmed.
Conclusion: The epidemiology of PIDs in Chile is currently unknown, and genetic diagnostic testing is not currently available. Our results showing diagnosis, phenotypic expansion and potential new genetic causes of PID suggest WES is a useful tool for both diagnosis and identification of new PID genes in Chile. Further analysis of this cohort may contribute to understanding the underlying pathways of known and novel PIDs.

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Characteristics of Patients in Primary Immunodeficiency Investigation: Why They Are Referred and by Whom

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Introduction: Primary immunodeficiencies (PIDs) are a heterogeneous group of immune system defects. Although relatively rare, they are increasingly known among general pediatricians and specialists. Repetitive infections are the main cause for diagnostic suspicion among these professionals.
Objective: To describe the profile of referral of children and adolescents to the immunology service.
Methods: Retrospective study, with data collection in medical records of patients attended in the period from 2013 to 2016. We analyzed the following data: origin and reason of the referral, diagnostic hypothesis formulated and final diagnosis.
Results: Of the 217 patients evaluated, 93 were referred by doctors from different pediatric specialties (68.8 % from the institution and 31.2 % from the outside) and 124 from general pediatricians (59.7 % from the institution and 40.3 % from outside). The most frequent referrals were recurrent infections (n = 100; 46.1 %), severe infections (n = 21; 9.7 %), recurrent fever (n = 14; 6.5 %), and angioedema without urticaria (n = 14; 6.5 %). Among recurrent infections, the most common was pneumonia (n = 31; 34.44 %). Of the 146 patients whose diagnostic investigation was completed, the diagnosis of PID was excluded in 65 % (n = 95), with the majority being referred for recurrent pneumonia. In 51 patients (35 %) the diagnosis was confirmed, being repetitive infections, angioedema without urticaria and alterations in the levels of immunoglobulins the main reasons for referral in these cases. Of the patients referred by general pediatricians, the diagnosis of PID was confirmed in 28.6 %, whereas by other specialists in 34.7 % and 76.9 % of cases, by immunologists. The diagnostic hypotheses formulated were confirmed in 23 patients, 8.3 % (n = 7) of those referred by general pediatrics, 11.1 % (n = 7) by non-immunologists, and 69.2 % (n = 9) by immunologists.
Conclusions: The diagnosis of PID has not been confirmed in most cases, as seen in other studies. Most referrals are made by general pediatricians, although they do not fit the diagnostic hypothesis in most cases. Immunologists are still responsible for most diagnostic confirmations.

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Stem Cell Transplantation for Adenosine Deaminase Deficiency: Two Case Reports

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Introduction: Adenosine deaminase (ADA) deficiency is a rare inherited disorder of purine metabolism characterized by the accumulation of metabolic substrates that lead to abnormalities of immune system development consistent with severe combined immunodeficiency (ADA-SCID) and function and a variety of systemic defects. Without treatment, the condition is fatal in the first year of life. Hematopoietic stem cell transplantation (SCT) from matched siblings donors (MSD) is de preferred treatment. However, <25 % of infants have a suitable HLA-matched related donor available, making HLA-matched unrelated donor (MUD) transplant an acceptable alternative. Gene therapy (GT) are other treatment options are available for ADA-SCID.
Objectives: Data from a total of 53 patients whit SCID (9 ADA-SCID). We report on the most recent HSCT at two patients ADA-SCID deficiency.
Results: P1: female. Male sibling died at 3 months of age due to lung infection by Adenovirus. At 3 months of age, she suffered from meningitis caused by Listeria monocytogenes. She received HSCT (1y.1 m), with incompatibility major of groups and factors. GVHD prophylaxis with cyclosporine and tacrolimus. P2: male. At the age of one month he suffered pneumococcal suppurative otitis and Enterobactercloacae

meningitis. HSCT (3 m), GVHD prophylaxis with cyclosporine and methotrexate. Both patients had absolute lymphopenia, severe T lymphopenia and hypogammaglobulinemia. They both received myeloablative conditioning regimens (Flu/Bu/ATG). In addition, the patients had received PEG-ADA to stabilize their clinical condition before HSCT. HSCT from MUD donor, male, compatible 10/10 for both patients. P1: immunological reconstitution after HSCT was complete six months later (at +41 day for B cells and six months for T cells and chimerism Dr). P2: immunological reconstitution after HSCT was complete six months later (at +50 day for B cells and six months for T cells and chimerism D), reconstitution is shown in both cases.

Conclutions: Data on immune recovery suggest that both patients normalize absolute lymphocyte and T-cell numbers. Although gene therapy or HSCT from matched siblings donors (MSD) are the treatments of choice, in the cases reported since there is no availability of any of them, matched unrelated donors (MUD) was an option of curative treatments.

Palabras claves: Adenosine deaminase deficiency, llogeneic hematopoietic stem cell transplantation, pegylated bovine ADA.