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ABSTRACTS

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IMMUNOGLOBULIN CLASS SWITCH RECOMBINATION DEFICIENCIES

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Ig class switch recombination deficiencies (CSR-D), previously named hyper-IgM syndromes, are rare diseases (1/500,000 births), characterized by normal or increased serum IgM levels, and drastic decrease or complete lack of other isotypes (IgG, IgA and IgE). Besides CSR-D due to impaired T :B cooperation, analysis of CSR-D caused by an intrinsic B cell defect was essential for a better understanding of the complex mechanisms underlying antibody maturation in humans : description of Activation-induced cytidine deaminase (AID)-deficient patients revealed the master role of this molecule in both CSR and somatic hypermutation (SHM). The description of a CSR-D caused by mutations in *Uracil-N glycosylase* gene was a strong argument for a DNA editing activity supported by AID. Molecules involved in DNA repair have been shown to play a role in CSR through analysis of CSR-D patients (Ataxia Telangiectasia Mutated, Mismatch repair, Non homologous end joining).
Through our patients'analysis, we identified a new factor involved in CSR, INO80, which is a key protein of an evolutionary conserved chromatin remodeling complex. Although little is known on its precise function, it has been shown to play a role in histone exchange activity, transcriptional regulation. DNA replication and repair. Two CSR-deficient patients were found as carrying bi-allelic hypomorphic mutations in *INO80* gene and hypersensitivity of patients' fibroblasts to high doses of γ-radiation was corrected by transduction of INO80wt. INO80 knock-down in the CH12-F3 cell line led not only to defective CSR but also to impaired chromatid sister cohesion, indicating a role for INO80 in cohesin activity. Moreover, INO80 and cohesin were both found located on switch (S) regions during CSR. Our working hypothesis is that INO80 enhances cohesin activity during the S-S synapsis which is required for DNA repair during CSR.
PI3K-d gain of function mutations have been recently shown to be responsible for combined immunodeficiency named APDS (activated PI3K-d syndrome). Sequencing of this gene in a large cohort of patients revealed that as much as 10% of CSR-deficient patients do carry the heterozygous gain of function PI3K-d mutation. Moreover, we found that these patients are prone to develop B cell lymphomas. Our observation emphasizes the broad spectrum of APDS.

CONVENTIONAL AND NOVEL GENETIC APPROACHES TO PID

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The identification of single gene defects involving genes that play crucial roles in adaptive or innate immunity is not only important for confirming a PID diagnosis, but may contribute to optimal therapy, and contribute to genetic counseling, carrier identification and pre-natal diagnosis.
To accomplish this, the diagnostician has to consider the inheritance of these disorders: X-linked, autosomal recessive, autosomal dominant and the type of mutation: loss of function, hypomorphic, dominant negative or gain of function. Conventional techniques to screen for single gene mutations include flow cytometry to measure disease-specific expression of proteins (cell surface, cytoplasmic or nuclear) or to analyze relevant signaling pathways (e.g. STAT5B phosphorylation via the IL-2R; pSTAT3 via the IL-10 receptor); and Sanger sequencing of mRNA or genomic DNA using Dye-Terminator sequencing. Next generation sequencing ("by synthesis") has been refined, and is being used increasingly to study families with multiple affected members with an atypical PID phenotype, or to explore consanguineous families with one member affected. Whole exome sequencing requires less data analysis, compared with whole genome sequencing, but may miss intronic or regulatory elements. The challenge of whole exome/genome sequencing is to confirm that the multiple variants identified by these techniques are causative for the clinical phenotype of the study patient. However, with increasing experience, next generation sequencing will become a standard procedure for the identification of genetic defects responsible for inherited diseases, including PID.

PID PATIENTS WITH NEUTROPENIA: DIFFERENTIAL DIAGNOSTIC ALGORYTHMS

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The phagocytic system is an essential part of the host immune defense and is the main component of the innate immune system. The most commonly encountered phagocytic defect is a decrease in the absolute number of circulating neutrophils. Impaired production, peripheral destruction, and abnormal distribution of neutrophils may lead to low numbers of circulating granulocytes. Although neutropenia could occur in most primary immunodeficiency diseases (PIDs), as a result of either recurrent infection or autoimmunity, some may suffer the congenital form of this hematological abnormality. These disorders consist of several inborn diseases ranging from isolated form of neutropenia such as severe congenital neutropenia and cyclic neutropenia to complex inherited disorders associating neutropenia. Chediak-Higashi syndrome, Griscelli syndrome type 2, Hermansky-Pudlak syndrome type 2, and p14 deficiency are a group of PIDs with neutropenia and oculocutaneous hypopigmentation, whereas exocrine pancreatic insufficiency in

Shwachman-Diamond syndrome and warts in WHIM syndrome could be the prominent findings. CD40 ligand deficiency, which is usually characterized by hypogammaglobulinemia and increased or normal IgM level could also present with neutropenia. Cartilage hair hypoplasia, glycogen storage disease Ib, Barth syndrome, dyskeratosis congenital, and Cohen syndrome are some other diseases which could be associated with neutropenia. Early diagnosis and appropriate treatment are the keys in the management of the patients to avoid complications and even death in the affected individuals.

NOVEL ADHESION PROTEIN DEFICIENCIES

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Leukocyte adhesion deficiency was described more than 30 years ago in patients with recurrent infections, delay separation of the umbilical cord, defective wound healing and marked leukocytosis, mainly neutrophilia. This is an autosomal recessive disease due to mutations in the gene encoded the β subunit of the integrin with is crucial for firm adhesion of the leukocytes to the endothelium. Up to now hundreds of patients were described and the only curative way is HSCT. 10 years later the second LAD syndrome was reported. This LAD II is very rare (less than 10 patients) and is due to mutation of the fucose transporter from the cytoplasma to the Golgi apparatus, where fucosylation of glycoproteins take place. This will lead to absence of the CD15 the ligand for the selection, essential for the first phase of the adhesion cascade the rolling phase.
The third LAD syndrome was found to be due to a general defect in all integrins activation leading to LAD I like symptoms associated with increase bleeding tendency. Using animal models was found that LAD III is due to mutation in Kindlin 3, an integrin cytoplasmic tail-binding adaptor. Up to now, several dozen of patients were reported and also here HSCT is the treatment of choice.
Very recently an interesting case of hyperadhesion state was described but its genetic defect is unkown.

LIFE-THREATENING INFECTIOUS DISEASES OF CHILDHOOD: SINGLE-GENE INBORN ERRORS OF IMMUNITY?

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The hypothesis that inborn errors of immunity underlie infectious diseases is gaining experimental support. However, the apparent modes of inheritance of predisposition or resistance differ considerably between diseases and between studies. A coherent genetic architecture of infectious diseases is lacking. We suggest here that life-threatening infectious diseases in childhood, occurring in the course of primary infection, result mostly from individually rare but collectively diverse single-gene variations of variable clinical penetrance, whereas the genetic component of predisposition to secondary or reactivation infections in adults is more complex. This model is consistent with (i) the high incidence of most infectious diseases in early childhood, followed by a steady decline, (ii) theoretical modeling of the impact of monogenic or polygenic predisposition on the incidence distribution of infectious diseases before reproductive age, (iii) available molecular evidence from both monogenic and complex genetics of infectious diseases in children and adults, (iv) current knowledge of immunity to primary and secondary or latent infections, (v) the state of the art in the clinical genetics of non-infectious pediatric and adult diseases, and (vi) evolutionary data for the genes underlying single-gene and complex disease risk. With the recent advent of new-generation deep resequencing, this model of single-gene variations underlying severe pediatric infectious diseases is experimentally testable.

HYALURONIDASE FACILITATED SUBCUTANEOUS IMMUNOGLOBULIN (SCIG)

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Immunoglobulin (Ig)-replacement therapy represents the mainstay of treatment for patients with primary antibody deficiency and is administered either intravenously (IVIg) or subcutaneously (SCIg). Recent developments using a high-purity recombinant human hyaluronidase have allowed the longer term repeated use of this enzyme to facilitate the delivery of immunoglobulin and other molecules including antibiotics, local anesthetics, insulin, morphine and fluid replacement into the subcutaneous space. Hyaluronidase facilitated SCIg (fSCIg) has helped overcome the limitations on the volume which can be delivered into the subcutaneous tissues by enabling dispersion of SCIg and its absorption into lymphatics. The rate of facilitated SCIg infusion is equivalent to that of IVIg, and the volume administered at a single site can be greater than 700 mL, an enormous increase over conventional SCIg, at 20–40 mL. The use of fSCIg avoids many of the systemic side effects of IVIg, and has higher bioavailability than SCIg. Over three years of safety data are now available for this approach though longer term safety data and information on anti-hylauronidase antibodies and their relevance will be required. fSCIg could aid several areas of patient management in both primary antibody deficiency and immunomodulatory indications. Key factors influencing how it will be used in future are long-term safety data and cost–benefit analysis.

ACTIVATED PHOSPHOINOSITIDE 3-KINASE δ SYNDROME

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Activated PI3K-δ Syndrome (APDS) is a novel primary immunodeficiency caused by a dominant gain-of-function mutation E1021K in the p110δ protein, the catalytic subunit of phosphoinositide 3-kinase δ (PI3Kδ), encoded by the *PIK3CD* gene. To date, we found E1021K in 33 patients from seventeen unrelated families, but not among 3,346 healthy subjects. APDS is characterized by recurrent respiratory infections, progressive airway damage, lymphopenia, increased numbers of circulating transitional B cells, increased IgM and reduced IgG2 levels in serum and impaired vaccine responses. APDS patients have high risk of developing lymphomas. The E1021K mutation enhanced membrane association and kinase activity of p110δ. Patient-derived lymphocytes had increased levels of phosphatidylinositol 3,4,5-trisphosphate and phosphorylated AKT protein and were prone to activation-induced cell death. Selective p110δ inhibitors IC87114 and GS-1101 (Idelalisib) reduced the activity of the mutant enzyme *in vitro*, suggesting a new therapeutic approach for patients with APDS.

IMMUNODEFICIENCY DUE TO CD19 MOLECULE

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CD19 molecule is expressed in early stage of B cell differention in bone marrow and we commonly used CD19 molecule to identify the B cells in peripheral blood. Nine patients with CD19 deficiency were reported up to

date after the CD19 deficiency was firstly described in a Turkish girl in 2006. The patients with CD19 deficiency had normal B-cell differentiation in bone marrow, normal absolute number of B cells in peripheral blood and normal BCR repertoire. Also, the patients had normal stimulation via the BCR, normal proliferation response upon antigen stimulation but reduced memory-B-cell compartment in peripheral blood. The CD19 deficiency leads to hypogammaglobulinemia and impaired antigen-specific humoral immune responses after vaccination. We had described thirty carriers in relatives of our two patients with CD19 deficieny and also showed that the MFI value of CD19 and CD21 expressions were lower in the carriers than in controls. During the last five years, it was also showed that the mutations of the other coreceptors of B cells such as CD81 and CD21 caused antibody deficiency.
In conclusion, the description of CD19 deficiency reminds the importance of the molecules on B cells and contribute to identify new genetic defects (CD81, CD21), and it was showed that coreceptors could affect the expressions and the functions of each other.

CLASS SWITCH RECOMBINATION DEFECTS AND UNIQUE CASES OF CD40 AND CD40L DEFICIENCIES

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Ig class switch recombination deficiencies are rare PIDs (1:500,000 births) with normal or elevated serum IgM and low IgG, IgA and IgE levels, defective or normal somatic hypermutation, defective T/B cooperation (50%), intrinsic B cell defect (50%), susceptibility to bacterial infections begining from the first year of age (impaired B cell immunity) and lack of germinal centres in secondary lymphoid organs. We present a CD40L defective case with clinical findings such as recurrent otitis media, recurrent upper and lower respiratory tract infections, sinusitis, arthritis, relapsing polychondritis , EBV-associated cervical lymphoproliferation, CMV infection, bronchiectasis, liver and spleen enlargement, multiple nodules in the liver, chronic diarrhea due to persistent *Cryptosporidium parvum*, fungal pneumoniae, osteoporosis, and schwannoma. This case is remarkable with low IgM levels and normal CD40L ezpression on activated T cells although he had a novel mutation in CD40L gene (a novel missense mutation in CD40LG (c. C139T), leading to an a. a. change from histidine to tyrosine at position 47 (H47Y) at the start of the extracellular domain). In addition, we present two cases with CD40 deficiency with normal CD40 expression on B cells.Both of these cases had homozygous-CD40-mutation leading to a longer protein due to deletion of stop-codon.
In conclusion; CD40 molecules although non-functional in B cells, may be normally expressed on cell surface. These CD40 molecules are unable to trigger signal, because CD40L + IL4 activation leads to complete lack of proliferation. Evaluation of CD40 or CD40L expression by flow cytometry may lead false results. Study of CD40L + cytokine (or CD40+ cytokine)-induced B cell proliferation appears as a useful tool for these diagnosis.

PROGRESSIVE DEGENERATIVE DAMAGE OF THE CENTRAL NERVOUS SYSTEM IN X-LINKED AGAMMAGLOBULINEMIA PATIENTS

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The Ural Regional center of clinical immunology, which based on Children clinical hospital number one (№1) in Yekaterinburg, observe patients from different territories of Ural region and neighboring areas. It consists of laboratory department, consultative department, vaccination and treatment rooms, beds and boxes in special departments in the Regional children hospital. The close collaboration with J-Project started in 2009.
This is an example of such collaboration. In Patient A. an international consilium was diagnosed a progressive neurodegenerative disease as a manifestation of Primary Immunodeficiency: X-linked agammaglobulinemia with B-cell deficiency. MRI results: unspecified leukodystrophy — a rapidly progressive multifocal brain lesions with demyelinating, generalized cerebral atrophy, III degree, signs of periventricular leukomalacia in the anterior horns of the lateral ventricles. The brain biopsy was recommended in order to clarify the nature of the defeat of the pathological process and define the role of the immune mechanisms of its development (held in the neurosurgical department with subsequent histological and immunohistochemical studies). Histological and immunohistochemical study of the brain tissue of the right frontal lobe: a signs of productive meningoencephalitis in brain tissue with vasculitis, perivascular and focally moderate diffuse infiltration of mononuclear (accumulation of mononuclear CD45RB+, vimentin+), most of which are CD8 + lymphocytes with granules of granzymeB. Around - dystrophy and necrobiosis neurons, intracellular edema, small focuses of gliosis - there are isolated myeloid cells (myeloperoxidase +) and plasma cells with cytoplasmic expression of immunoglobulin light chains lambda and kappa; cells and the extracellular matrix of brain tissue expressing CD56 antigen and S100 protein.
Virological and bacteriological studies of brain tissue and liquor: connection of progressive degenerative changes and infectious process weren't obtained
Verified acknowledgments of an infectious or autoimmune process has not been received. Search for a genesis of cytotoxic process in the brain continues.

CHANCES AND LIMITATIONS OF IGG REPLACEMENT THERAPY IN CVID PATIENTS

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The essential role for IgG replacement therapy (IgGRT) for Common variable immunodeficiency (CVID) has been demonstrated in many studies and meta-analyses. While patients with „infection only“ reach a nearly normal life expectancy - though still not quality - under IgGRT, CVID patients with additional manifestations like inflammatory lung, bowel or liver disease, lymphoproliferative and/or autoimmune disease often require additional immunosuppressive treatment. There is little consensus on the form of immunosuppressive regimen, once steroids have failed, with possibly the one exception of Rituximab treatment for autoimmune cytopenia. Additional studies are essential to guide therapeutic algorithms.
Some of these patients suffer from late onset combined immunodeficiency (LOCID). As in classic forms of combined immunodeficiency, IgGRT can be only a part of the treatment strategy, which needs to additionally address the cellular immunodeficiency of the patients. Therefore a retrospective survey was performed on patients diagnosed with CVID who underwent hematopoietic stem cell transplantation. The results of this study are currently in revision. In summary, IgGRT is the baseline therapy for CVID but does not address sufficiently the immune dysregulation in a subgroup of patients. Better predictive markers have to be identified for the selection of patients for additional, potentially even definite forms of treatment in order to prevent the morbidity and mortality associated with these secondary manifestations of CVID.

IVIG TREATMENT OF PATIENTS WITH CVID AND AGAMMAGLOBULINEMIA

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The first department of primary immunodeficiencies in Russia was established on the basis of the Institute of Immunology in 1980, when 3 patients with PID were registered. Currently, 327 patients with PID are followed in the Department of immunopathology in adults. 65% of PID adult patients have PID with immunoglobulin deficiency. Analysis of this group of adult patients showed that the diagnosis of PID, on average has a delay of 10-15 years from the first symptoms. In 88% of cases, there is an infectious clinical phenotype, 32% - combined infectious-lymphoproliferative phenotype, 27% - infectious and enteropathy. The study of immunophenotyping of B-lymphocytes for the degree of maturation in this group of patients was begun. 13 patients are currently included in this study. 2 patients showed complete absence of B-lymphocytes, 11 - the reduction of B-cells, 2 patients of those have a normal amount switched memory B cells (MBC), 9 people - a decrease amount of switched MBC. 8 persons of the group with decreased amount of switched MBC had an expansion of transitional MBC. At present, a clear link of immunophenotypes with specific clinical phenotypes in not found, but this may be due to small sample of patients at the moment, the investigation continues.

For the treatment of this category of patients only intravenous immunoglobulins are available in Russia. We use drugs in various concentration of Russian and foreign production. The availability of immunoglobulins for the adult patients unfortunately is not sufficient in Russia, so the recommended pretransfusion level of IgG is not achieved in about 70% of patients.

CLINICAL AND IMMUNOLOGICAL EFFICACY OF SUBCUTANEOUS IMMUNOGLOBULIN TREATMENT OF CHILDREN

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Our work presents the experiences of our center with the subcutaneous form of immunoglobulin therapy (SCIG). We have 64 patients on such therapy. The youngest child is 7 months old. The largest group consists of CVID patients, next-XLA patients. We also substitute children diagnosed with the DGS and accompanying hypogammaglobulinemia and some children with subclasses deficiency as well as secondary hypogammaglobulinemia. In most cases we start therapy with intravenous preparates, but there have been some children to whom we proposed the subcutaneous form at the initial stage of the therapy. The main factors which made us change the mode of the drug application were adverse reactions to IVIG, poor vein access and the parents` wish. The administration of SCIG is very rarely complicated by severe adverse reactions (the risk of their incidence amounts to about 0.3%). Even patients with serious side effects to previous immunoglobulin therapy and/or blood transfusion can be safely treated with SCIG. The most common side effects are local reactions but their incidence decreases during following substitutions. We can observe swelling, redness, induration, soreness. But we should remember that more severe side effects are also possible, for example: the first CVID patient presented with fever, weakness, difficulties in breathing during the 3 following infusions. Changing the brand of the drug turned out to be a sufficient method of getting rid of side effects. The second patient, also with CVID, suffered from nausea, headache, meningismus. We changed the drug brand, slowed down the infusion rate and introduced premedication with an antihistaminic drug. The third patient – a girl with DGS and hypogammaglobulinemia, after having been operated on for hypoplastic left heart syndrome, responded to infusions with high fever, muscle and joint pain, skin changes (erythrodermia). We introduced premedication, changed the drug brand and slowed the infusion rate, yet without any positive effects. In two patients we observed adverse reactions after preparates at a concentration of twenty percent. There were: weakness, chills, fever, headache, and very intense pain in the place of injection. During the subcutaneous treatment of XLA patients, we observe significant reduction in the number of infections and days of school absence. Despite that, all our patients with XLA suffer from chronic sinusitis. Similar results occurred in CVID patients, but the severity of infections was the same. The use of SCIG results in more stable and higher IgG through levels especially in XLA patients. In our practice, we had only a few cases in which IV form appeared to be better than SC one. In the case of two boys with HIGM syndrome, we observed recurrent enthesitis of the first patient and progression of lung fibrosis of the other. IVIG was better to control platelets levels in the girl with CVID and thrombocytopenia. It has also occurred that parents refuse to allow us to start subcutaneous therapy, giving two main reasons: they feel safer under frequent doctor`s control and they are afraid of making mistakes in procedures. As for the youngest children (below 7) – their fear of needle is independent of its size, which is the third reason.

In conclusion, we would like to emphasize that education programmes implemented by doctors and nurses are essential to make this form of therapy easier, safer and more satisfying for patients and their parents.

AN OPEN, PROSPECTIVE TRIAL INVESTIGATING THE PHARMACOKINETICS AND SAFETY, AND THE TOLERABILITY OF ESCALATING INFUSION RATES OF A 10% HUMAN NORMAL IMMUNOGLOBULIN FOR INTRAVENOUS INFUSION (IVIG), BT090, IN PATIENTS WITH PRIMARY IMMUNODEFICIENCY DISEASE

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Keywords: Intravenous immunoglobulin (IVIg); infusion rates; primary immunodeficiency disease (PID)

Summary: The pharmacokinetics and safety, and the tolerability of escalating infusion rates of a 10% human normal immunoglobulin for intravenous infusion (IVIg), BT090, were studied in patients with primary immunodeficiency disease (PID). Overall, the pharmacokinetic characteristics of BT090 were found to be comparable to those of other IVIgs. In particular, the pharmacokinetics of BT090 were comparable to those reported for Intratect®, demonstrating that the higher immunoglobulin G (IgG) concentration of BT090 (10%) compared to Intratect® (5%) does not result in relevant differences in the clinical pharmacology of these products. Moreover, the safety profile for BT090 was consistent with that for other IVIgs including Intratect®. Escalation of infusion rates was well tolerated, allowing the identification of the individual patient's maximum tolerated infusion rate. When treated at subsequent infusions, all patients could tolerate their individually defined maximum infusion rate: 17 patients (68.0%) tolerated infusion rates of 6.0 or 8.0 mL/kg/h at

subsequent infusions and only 4 patients (16%) had maximum tolerated infusion rates of <4.0 mL/kg/h at subsequent infusions. Escalation of infusion rates shortened infusion time from a median of around 2.5 hours to around 1.6 hours. Shortening infusion time may reduce overall health care spending, e.g. nursing time needed, and also minimize disruption of patients' daily routine, especially for those patients in work or school settings.

NIJMEGEN BREAKAGE SYNDROME: LONG-TERM OUTCOME AND TREATMENT

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The Nijmegen breakage syndrome (NBS) is an inherited genetic disease that belongs to the group of chromosome instability disorders characterized by combined immunodeficiency of both cellular and humoral arms of the immune system and a high predisposition to lymphoid malignancies.
The disease occurs worldwide with increased prevalence in Eastern and Central Europe and the largest group is registered in Poland.
The profile and severity of immunodeficiency, clinical manifestations, including infections, autoimmunity and malignancies were shown. The need for searching for predictive factors helpful in the prognosis of outcome and early selection of NBS patients for HSCT was highlighted.
Summary of the outcome of NBS patients after stem cell transplantation and propose which patients should be qualified for the procedure were presented.

CVID – FROM T CELL DYSFUNCTION TO B CELL DISORDER

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Despite intensive investigation into the nature of CVID, the exact molecular defect(s) and pathogenesis of disease remain unknown. Our aim was to evaluate the role of T cells in the mechanisms of CVID development. Additionally the impact of some innate and adaptive immunity related genes (HLA, cytokine gene polymorphism, MBL genes) was investigated. Based on previously observed by us constellation of shared immunogenetic profiles a comparison of T-cell phenotype of CVID patients, and elderly/young healthy individuals was performed. Ten patients with CVID were enrolled (4 male, 6 female; average age – 42,9 years) presented mainly with pulmonary infections, followed by bronchoectasis and splenomegaly. Our study demonstrated multiple T- and B-cell abnormalities in CVID patients such as: decreased CD4+, increased CD8+ T cells and low CD4/CD8 ratio, loss of naïve and early differentiated T cells, expansion of terminal effectors (CD8 + CD45RA + CD62L-) T cells, memory/effectors (CD8 + CD28-CD27-) and terminally differentiated (CD8 + CD57+) T cells. Excessive T-cell activation reflecting the prevalence of activated T cell phenotype was also detected, due perhaps to an antigen-driven process. The very low numbers of circulating mature (CD21 + CD24+) and class–switched memory (IgM-IgD-CD27+) B cells were pathognomic for our patients and could be used as an additional diagnostic criteria in the national guidelines. Furthermore high level of non-class switched (IgM + IgD + CD27+) B memory cells and suppressed NK cell count was observed. Decreased responsiveness to polyclonal stimuli *via* CD3 and CD28 pathway correlated with the loss of CD28 expression which was more pronounced in the treatment – naïve CVID patients. These findings were further discussed in the context of the similarities that exist along with markers for immune senescence (lack of CD28 or expression of CD57). Increased frequency of IFN-γ polymorphisms associated with low expression level found could indicate genetically predisposition to high activation of TH2 lymphocytes in CVID and consequently support the concept of impaired TH1-type responses**.** In conclusion our study provided new insight into the pathogenesis of CVID.
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INCIDENCE OF MOREAU STRAIN BCG DISEASE IN 62 SCID AND IN OTHER POLISH PID PATIENTS - 30 YEARS OF EXPERIENCE

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BCG vaccination at birth is the constant element of vaccination programmes in Poland. High reactogenic BCG Danish vaccine has been replaced in 1955 , by BCG Moreau vaccine. Frequency of disseminated BCG infection, in children with primary immunodeficiencies after BCG Moreau vaccine manufactured by Biomed, Poland were estimated. One thousand five hundred sixty three cases of primary immunodeficiencies were diagnosed in the Department of Immunology, Children's Memorial Health Institute in Warsaw between 1980 – 2013. Among patients with T cell predominant deficiency, group high risk of BCG infection, SCID was recognized in 62 children. Mendelian susceptibility to mycobactarial diseases (MSMD) was detected in four patients: IFGR1 deficiency and IL12 deficiency - equally in two patients, and NEMO - in one. In the group of primary immunodeficiencies regarded to be less prone to Mycobacterium infections, CGD was diagnosed in52, HIES in 20 patients, and XL-HIGM in 4 patients. Disseminated BCG infection was recognized in 10 SCID patients, 2 of them died, because of BCG diseases. All 4 patients with MSMD developed BCG infection, one with IL-2 deficiency died. During nearly 30-year-follow-up, no case of tuberculosis or disseminated BCG infection have been diagnosed among CGD , HIES and XL-HIGM patients. Early anti –Tb drug prophylaxis and usage of wide range of antibiotics in therapy is crucial for cleaning of BCG infection.

SCID BEFORE AND AFTER NEONATAL BCG VACCINATION IN SLOVAKIA

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Objectives: Severe combined immunodeficiency (SCID) is a group of disorders due to more than 15 genetic defects, characterized by increased susceptibility to severe infections and early life death. The diagnosis is supported by the demonstration of low absolute T lymphocyte count variably associated with numerical defects of B and NK cells. Patients are very heterogeneous regarding clinical course, immune parameters and clinical outcome. BCG (Bacillus Calmette-Guerin) vaccine, a life attenuated vaccine was the part of Slovak Immunization Program, administered at birth until 2011. A comparison of clinical course of BCG exposed (BCG+) and non-exposed (BCG-) SCID patients in Slovakia in period of past 10 years are given.
Results: Incidence rate of diagnosed and treated SCID in Slovakia was calculated to 1:87.000, meaning 1,5 cases per year. In total 10 cases represent 4 ADA patients, 2 IL2RG deficiencies, 1 case of complete del22q11 and in 3 cases genetic defect was not found by analysis of

RAG1/2, IL2RG, Artemis, IL7RA, JAK3 and ADA genes. All patients were confirmed absent TREC (T-cell receptor excision circles) copies in a retrospective neonatal Guthrie card analysis. Seven out of these 10 patients underwent HSCT, in 5 the HSC source was a MUD. Favorite outcome was achieved in 6 of them. Half of our patients have been exposed to a live BCG vaccine during neonatal period. Patients vaccinated with BCG faced severe complications and organ damage due to generalized skin and organ abscess formation, requiring prolonged (up to 18 months) hospital care and complex antibiotic therapy with more than four types of anti-mycobacterium drugs, for more than 2 years. Average length of hospital care for BCG exposed patient was 10,8 months vs. 2,7 months in non-exposed group ($p < 0,05$). No statistical difference was found between the time of recognized first symptoms, and time of diagnosis in BCG + and BCG- group. The clinical presentation of non-BCG vaccinated patient differs in the initial symptoms when failure to thrive and pneumonia at 4 months was the most common finding. Post-transplantational recovery in BCG- group was less complicated.

Conclusions: Two major improvements for the outcome for SCID patients in Slovakia have occurred in past 10 years. Early life vaccination for tuberculosis has been retreated and improvements in diagnostics for severe T cell defects have been made, including flow cytometry phenotyping and genetic testing within the middle European countries cooperation, the J-Project. BCG and late diagnosis prolongs time for hospital care, immune reconstitution and carries severe complications, consequently it increase the costs of health care and decrease the quality of patients' life. The perspective of newborn screening for SCID would be the next major step in improving the outcome of SCID patients.

A-PROJECT : A CLINICAL TRAINING FOR AFRICA

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In Africa, primary immunodeficiencies are still largely undiagnosed, with no cases reported in 40 of 54 countries. Though the African Society for Immunodeficiencies (ASID) already organized 3 International Meetings and 5 training schools, their impact outside the hosting country is still insufficient. At this time, only a few PID patients are reported in Africa (less than 2000 patients), the majority of whom are in North Africa and South Africa.

So, ASID propose the A-Project, a training program based on the J-Project. Some issues prevent effective training for PID in Africa: diversity of languages, only a few are initiated to PID, lack of resources for travel expenses, difficulty to access to care and shading by the HIV pandemic.

A-Project is designed as a one-day training by an African PID expert in a small group of motivated caregivers. This project is adapted to the African context, as it only requests minimum funding and can reach more people. Each A-Project will be co-organized by ASID and a local committee, and shall lead to some commitments to be realized by locals, in particular the establishment of a registry, a network between physicians and scientists and creation of a patient association. Moreover, each A-Project will be done in the medical language used in the country (English, French or Portuguese).

The first A-Project was already done in Benin, and five more are already planned for 2014. Our goal is to reach all 40 countries where no patient were reported in 3 years. This clinical program will raise PID awareness in Africa and can potentially discover new aspects of the immunity.

PRIMARY IMMUNODEFICIENCY DISEASE AS AN EVOLVING AREA OF MEDICAL RESEARCH IN INDIA

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Till very recently Primary Immunodeficiency Diseases (PIDs) were not being frequently recognized in India. However, the scenario has changed over the last 5 years or so. The Indian Society for Primary Immune Deficiency (ISPID) was founded in 2010-2011. Over the last 4 years the ISPID has organized 2 International Conferences (at New Delhi and Mumbai), 2 National Conferences (at Chandigarh and Varanasi) and 2 Continuing Medical Education Programmes (at New Delhi and Lucknow). These meetings have served to act as catalysts for the cause of PIDs and have resulted in increasing the awareness about these conditions amongst paediatricians and physicians in our country. Several centres now have the clinical skills and the technical wherewithal to perform laboratory investigations for these patients. The repertoire of tests includes nephelometery, ELISA based tests and flow cytometry. Facilities for molecular diagnosis of PIDs are also being developed at some of these centres. A lot more, however, needs to be done.

The clinical phenotype of several PIDs in India is likely to be different from that in the West[1]. Further, the type of infections in these patients is also likely to be different. This is because of the differences in the micro- and macro- environment to which these patients exposed in developing countries. These differences have been well brought in the recent publication on chronic granulomatous disease from our centre[2]. Further, the genetic background of the Indian population is diverse and several new mutations are likely to be identified amongst these patients.

The Indian Council of Medical Research has taken up the lead in this regard and is proposing to set up 2 Centres for Advanced Research (CARs) in PIDs – 1 each at the Post Graduate Institute of Medical Education and Research, Chandigarh and the Institute of Immunohematology, Mumbai. The Foundation for Primary Immunodeficiency (FPID), USA has also been closely involved in these efforts and has helped facilitate the development of these 2 CARs.

The field of PID research in India is wide open and we are likely to witness new and exciting scientific developments in the coming years.

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DEVELOPING PID CARE IN CENTRAL ASIA: THE J CENTRAL ASIA PROJECT

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The opportunity to improve the life quality of patients with primary immunodeficiency (PID) in the Republic of Kazakhstan and reducing the morbidity and mortality rate from PID are the main objectives of the J – project realization in the Republic of Kazakhstan. Successful project execution provides the improvement in detecting and diagnosing of PID,

the prevention of PID's complications, the improvement of the health care of patients with PID, the creation of the Registry of the patients with PID, the implementation of the finance regulations for detection and treatment of patients with PID diseases in public health facilities, the training and professional development of medical professionals in this field.

Objective: To improve the detection and diagnosis of PID diseases and the life quality of patients with PID in the Republic of Kazakhstan.

Undertaken activities for realization of the project:

1. Professor. L. Marodi visited Kazakhstan in October 2012 and the meeting was held in Ministry of Health of the Republic of Kazakhstan, p*resentations were given at the international conference* held in National Research Center for Maternal and Child Health, the negotiations with Heads of the National Medical Holding' clinics and Scientific Center of Pediatrics and Pediatric Surgery were held.
2. Primary immunodeficiency Center in the Republican Diagnostic Center of the National Medical Holding was established in November 2012.
3. International symposium "Diagnosis and treatment of primary immunodeficiency" was held in October 2013. Master-class of "Diagnosis and treatment of PID" with the invitation of the leading specialists from Kazakhstan.
4. The creation of the Registry for the patients with PID.
5. The development and publication of PID diagnostic protocols and guidelines in Kazakhstan in 2013.

Conclusion: The number of patients with PID significantly increased every year.

The J- project realization in the Republic of Kazakhstan allows to update the PID problem, to raise the **availability** of early diagnosis of PID, to improve the life quality of patients with PID by providing substitution therapy and as a result, the infant mortality and disability rate has been reduced.

PRIMARY IMMUNODEFICIENCIES IN MALAYSIA 1986-2013. A 28 YEAR EXPERIENCE

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Two hundred and sixty three (263) suspected PID (primary immunodeficiencies) cases were referred to clinical immunologist led clinics in Malaysia from 1986 -2013. Patients referred were from all states of Malaysia and seen at the institute of Pediatric, Hospital Kuala Lumpur and university associated Hospitals in North and Central Peninsular Malaysia

The initial PID patients were seen by - 1 pediatric immunologist between 1986-2006 followed by another 2, beginning in 2007 followed by the other in 2012. There were 168 (68.7 %) patients with at least 1 abnormality on the immune prameter recorded and regarded as probable PID. However 153 (62.7%) were recorded as PID based on existing criteria. (WHO Scientific Committee 1986, IUIS Scientific Committee, primary immunodeficiency disease.1999)

Our population were mainly children, 83% below 10 years and 36 % below 1 year. Only 3 were above 18 years. PID were classified as; predominant Antibody deficiencies 34 %, combined immunodeficiencies 19.3 %, other cellular immunodeficiencies 14.7 %, phagogocytic defect 11.3%, immunodeficiency associated lymphoproliferative disorders 2 %. Our data differed from most classification where predominant antibody deficiency is most frequent as high as 65 %, (Steihm, 2004). Of the specific 153 PID recorded, X linked a gammaglobulinemia (XLA) 19, hyper IgM syndrome (HIGM) 11, common variable Immunodeficiencis (CVID 7), selective IgA deficiencies 7 severe combined Immunodeficiencies (SCID) 17, Di George syndrome (DGS)12,chronic granlomatous Disease (CGD) 14, hyper Immunoglobulin E syndrome (HIGE) 14, primary CD4 deficiencies 6, ataxia telangiectassi 3 %

Malaysia comprises of multi ethnic groups with a population of 29.6 million in 2013. PID amongst them showed, Malays at 61.4%, Chinese 11 %, Indians 23.7 % and others 5.2 % whilst the male predominate over female at a ratio of 2.8:1. Family history of affected sibling or in first degree relative, or early death with suspected infant dying of infection was positive in 53.3 % which is higher than in most reports eg Egypt 23.4 % (Reeda 2009). This could be due to high consanguinity in the population. Alternatively the symptomatic sibling of affected patients is more likely to be referred to the clinical immunologist. SCID records the most varied organism from the positive microbiological isolate viz bacteria 4, fungus 2, virus 1, parasite 2. *Chromobacterium violaceum* was seen in 3 CGD patients in which 2 deteriorated with eventual death. As in many national registries diagnostic delays remains prominent. In our series the mean diagnostic delay was o 3.61 ± 4.82 years. In comparison Thailand stands at 2.1 ± 2.6 years, while France, a median of 1.3 years.

Malaysia remains committed to provide better diagnostic services and improved care of the PID patients through research collaboration with foreign partners with a drive for creating subspecialty training. Patient groups aligned to IPOPI is now closer to its formation with the creation of its protem committee ensuring that patients' interest will always be guarded

Aknowledgement. The authors thank all who had contributed directly or indirectly, especially medical officers, nurses, consultant pediatricians especially Dr Kamarul Azhar, Institut of Pediatrics HKL, laboratory scientists especially Dr Shanaz Murad of the IMR Kuala Lumpur

HUMAN TYPE I INTERFERONOPATHIES

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Although the concept of grouping Mendelian disorders associated with an up-regulation of type I interferon (IFN) has not been previously recognised in the medical literature, our past and current work argues that this concept has scientific validity and clinical utility. I will discuss the possibility that such conditions can usefully be considered to represent a novel set of inborn errors of immunity, and that the recognition of diseases as type I interferonopathies will have significance for the development of targeted therapies, as well as informing our understanding of viral and retroelement biology, and the pathogenesis of some forms of autoimmunity.

INHERITED HUMAN OX40 DEFICIENCY UNDERLYING CLASSIC KAPOSI SARCOMA OF CHILDHOOD

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Classic Kaposi sarcoma (KS) is exceedingly rare in children from the Mediterranean Basin, despite the high prevalence of HHV-8 infection in this region. We hypothesized that rare single-gene inborn errors of immunity to HHV-8 might underlie classic KS in childhood. We report here autosomal recessive OX40 deficiency in an otherwise healthy adult with childhood-onset classic KS. OX40 is a costimulatory receptor expressed on activated T cells. Its ligand is expressed on various cell types, including endothelial cells. The mutant OX40 protein was poorly expressed on the cell surface and failed to bind OX40 ligand, resulting in complete functional OX40 deficiency. The OX40-deficient patient had a low proportion of effector memory $CD4^+$ T cells in the peripheral blood, consistent with impaired $CD4^+$ T-cell responses to recall antigens *in vitro*. The proportion of effector memory $CD8^+$ T cells was less diminished. The proportion of circulating memory B cells was low, but the antibody response *in vivo* was intact, including to a vaccine boost. Together, these findings suggest that human OX40 is important for $CD4^+$ T-cell memory, but redundant for immunity to most common pathogens, with the notable and surprising exception of HHV-8.

NOVEL STAT1 GOF MUTATIONS IN ECE PATIENTS WITH CMCD

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The chronic mucocutaneous candidiasis disease (CMCD) is characterized by persistent or recurrent infection of skin, nails, oral, or genital mucosae with *Candida albicans*. IL-17-mediated immunity has been concerned in host defense against *Candida* on body surfaces. We have investigated nine patients with chronic mucocutaneous candidiasis disease (CMCD) and signal transducer and activators of transcription 1 (STAT1) mutations. The novel c.537C > A (N179K) and c.854A > G (Q285R) mutations in the coiled- coil domain (CCD) and the c.1154C > T (T385M) mutation in the DNA-binding domain (DBD) of STAT1 are gain-of-function (GOF) for γ-activated factor (GAF)-dependent cellular responses to STAT1. Low proportion of IL-17A- and IL-22-producing T cells, lower levels of intracellular IL-17A and IL-22 by T cells and impaired *Candida*-induced secretion of IL-17A and IL-22 by leukocytes from CMC patients compared to that in healthy controls were found. The c.820C > T (R274W) mutation affecting the CCD and the c.1154C > T (T385M) mutation affecting the DBD of STAT1 and resulted in gain-of-phosphorylation and GOF. These mutant alleles enhanced the cellular responses to cytokines via STAT1 signalling pathway. These data provide further insight into the mechanism of host defense against Candida.
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DIFFERENT SEVERITY OF PHENOTYPES IN PATIENTS WITH GOF STAT1 MUTATION

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Heterozygous gain-of-function STAT1 mutation is known as a major etiology of chronic mucocutaneus candidiasis. GOF mutation affecting the STAT1 coiled-coil domen (D165G) was initially discovered in 13-year boy with CMC. GOF mutation of DNA-binding domen (T385M) was found in the second our patient with CMC. Both patients have early manifestation of recurrent or persistent infections of the skin, mucous membranes, and nails with *Candida albicans. They also have skin infections with dermatophytes. Patient 1 presented from the first months of age with severe recurrent sinopulmonary infections. Recurrent pneumonia and chronic bronchitis complicated by bronchiectasis,* which resulted in cor pulmonale and congestive heart failure. *Patient 2 suffered from recurrent HSV infection, recurrent aphthous stomatitis, has several episodes of bacterial skin infections. He* also has chronic bronchitis and several episodes of pneumonia, but does not have bronchiectasis. Both boys developed esophageal stricture, patient 2 necessitating Nissen fundoplication in the age of 5 years. The patients have mild autoimmune features: uveitis (P1) and alopecia (P2). Immunological investigation revealed different impairment of immune system: more severe, similar

to combined immunodeficiency in P1, which declines with age. The P2 does not have changes in lymphocyte number and immunoglobulin's, but impaired antibody production to pneumococcal antigens. Western blotting performed with nuclear extracts of lymphocytes of both patients showed stronger STAT1 phosphorylation after stimulation with cytokines IFNγ, IFNα, IL-27. Mononuclear blood cells from both patients released much smaller amounts of IL-17A and IL-22 than Candida-exposed cells from healthy control. Conclusion: the patients with different gain-of-function mutation of STAT1 (CCD and DBD) demonstrated different clinical and immunological phenotype.

GAIN-OF-FUNCTION STAT1 MUTATION IMPAIRS STAT3 FUNCTION PREDISPOSING TO CHRONIC MUCOCUTANEOUS CANDIDIASIS

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STAT3 activation triggers transcription of interleukin (IL)-17 which is crucial for mounting protective immune responses against fungi. Several mutations affecting the STAT3/IL-17 pathway have been reported, resulting in selective susceptibility to fungal (*Candida*) infection, a hallmark of Chronic Mucocutaneous Candidiasis (CMC). In patients with autosomal-dominant (AD)-CMC we previously reported defective Th17 responses and identified an underlying gain-of-function (GOF) STAT1 mutation leading to hyperphosphorylation of STAT1. How this affects STAT3 or leads to decreased IL-17 remains to be determined. In patients with AD-CMC, we assessed how GOF-STAT1 mutations affect STAT3 activation, DNA-binding, gene expression, cytokine production and the effect of epigenetic modification. We show that stimulation of STAT3 in the presence of GOF-STAT1 mutations leads to significantly reduced transcription of STAT3-inducible genes (RORC/IL-17/IL-22/IL-10/c-Fos/SOCS3/c-Myc). This was not due to impaired STAT3 phosphorylation, altered nuclear translocation nor sequestration of STAT3 into STAT1/STAT3 heterodimers. DNA binding to a STAT-consensus binding site construct (hSIE) was intact but binding to an endogenous STAT3 DNA target was impaired. The reduced STAT3-dependent gene transcription could be normalized by inhibiting STAT1 activation by fludarabine or enhancing acetylation with histone deacetylase (HDAC) inhibitors trichostatin A or ITF2357. Silencing HDAC1, HDA2 and HDAC3 indicated an important role for HDAC1. Impaired STAT3-dependent gene transcription likely underlies decreased Th-17 cytokine production, susceptibility to fungal infections and other pathology seen in AD-CMC patients and could be a new target for defining novel therapeutic approaches for this potentially lethal disease.

REGULATORY T CELLS IN A FAMILY WITH IPEX-LIKE MANIFESTATIONS

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Autoimmune features have been long thought as association with immunodeficiency disorders, but are now viewed as a crucial component of some diseases attributed to the breakdown of self tolerance or defects of immune regulators.
It had been previously established that a single gene defect of the Foxp3 gene (FOXP3 in humans) caused widespread autoimmunity in both humans and mice. The clinical syndromes observed in both scurfy mice and humans suffering from IPEX are similar to those observed in experimental models in which Treg are selectively depleted. In 2003, three groups demonstrated that these diseases were indeed the result of a regulatory cell deficiency.
Around one third of the patients with clinical manifestation closely resembling IPEX syndrome, FOXP3 is not mutated, these patients are referred to as IPEX like.
Here we present a case; a female patient 13 years with multiple autoimmune manifestations; DM, Coeliac disease and ulcerative colitis with marked decrease in the percent of CD4 + CD25 + FoxP3+ cells. As she has a siblings suffering from DM; the whole family was investigated. The father and the mother had 0% CD4 + CD25 + FoxP3+ cells. The siblings had marked decrease in CD4 + CD25 + FoxP3+ cells (0.1%). CD25 gene sequencing of the patient was done at University of degli Studi di Firenze, department di Scienze per la Salute Della Donna e Del Bambino, Florence, Italy showing no sequence variation with pathogenic significance.
Conclusion: Whole Exome sequencing may reveal new mutations in such patients.

HYPERIMMUNOGLOBULINEMIA D SYNDROME IN TWO ALBANIAN CHILDREN

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Background: HIDs is an autosomal recessive disease, first recognized as a separated entity at 1984. In patients with HIDS, the activity of mevalonate kinase is reduced to 5–15% of normal levels. HIDS is caused by mutations in the mevalonate kinase gene (MVK), located on the long arm of chromosome 12 (12q24). It is manifested by cyclic attacks of fever initiated usually during first year of age. The frequency and severity of attacks tend to decrease later in life.
Materials and method: A retrospective analysis of medical history , clinical course and laboratory findings of two Albanian children with periodic fever , diagnosed with hyper IgD syndrome.
Results: Case presentation 1: An 5-year-old boy admitted to the hospital because of periodic fever spikes, which occurred every 3-4 weeks and lasted 3–5 days, presented since the first year of life and coincided with the beginning of immunization. He had a tonsillectomy and adenoidectomy at the age of 3. The fever attacks were associated with chills, malaise, and abdominal pain without gastrointestinal signs. Between attacks the patient was free of symptoms. From his family history, recurrent febrile episodes during childhood were reported to his father. Physical examination showed normal findings, except for a cervical lymphadenopathy. Laboratory: Marked increase of erythrocyte sedimentation rate and CRP. WBC- ranged from 5.710 to 12 000/mm^{3}, high ASTO. Serum IgD was repeated several times and was always elevated

(mean value: Serum IgD 122 IU/mL). The mutation V377I is found from the genetic examination done for gene mutations in chromosome 12 (12q24). He repeated attacks after initial treatment with corticosteroid ,than is suggested. The second case was a four-year-old girl hospitalized five times because of prolonged fever, and diagnosed as pneumonia, tonsillitis, acute otitis media and sinusitis, treated by antibiotics. Her laboratory findings were not remarkable except for increased acute inflammatory responses. Serum Amyloid A (SAA) 1100 μg/l (8 μg/l) and IgD was extremely high 181.9 IU/ml. Genetic examination for two mutations were negative, but reduced mevalonate kinase activity in white blood cells was demonstrated in more thorough investigations. Treatment regime: colchicine

Conclusions: Auto inflammatory syndromes always pose diagnostic and therapeutic challenges to the clinicians. The clinical description of the diversity of periodic fever syndromes is helpful in the assessment and management of these patients. Although HIDS is predominantly identified in populations from northern European areas, it has to be considered in children with periodic fever.

LUNG AND BRAIN ASPERGILLOSIS IN PATIENT WITH AUTOSSOMAL RECESSIVE CHRONIC GRANULAMATOUS DISEASE

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Background. Aspergillus is an actual pathogen in chronic granulomatous disease responsible for about 20% of all infections. In 70-80% lungs are involved and in 5% - CNS.

Case. We report a case of combined loci in 9-years old female patient with AR CGD. The child was born from III pregnancy, II delivery on 37th week of gestation with body mass 2750g. She received BCG vaccination at 4^{-th} day of birth. At 3 months the local inflammation in site of BCG with regional lymphadenitis developed which was treated with isoniazid for 3 months. Then bilateral purulent cervical lymphadenitis developed at 6, 9 and 11 months treated with wide spectrum antibiotics. Culture from pus was negative. PCR for mycobacterium tuberculosis complex was negative. At18 months systemic infection without loci occurred with fever, lymphadenopathy, hepatosplenomegaly, loss of weight, progressive anemia, inflammatory changes in blood for almost 6 months. Bacteriological cultures were negative. Treatment with wide spectrum antibiotics was insufficient for 3 months. Disseminated BCG infection was suspected and 4-compound AMB treatment was started *ex juvantibus* with positive effect: the fever has stopped, the sizes of lymph nodes, liver and spleen have decreased, the weight of a body normalized. The child suffered from recurrent pyogenic infections, underwent disseminated salmonellosis. At the age of 5 years blood samples were tested at the Laboratory of Human genetics of Infectious Diseases, INSERM (Paris, France). An absence of p22^{phox} protein expression detected by western blot conferring a complete defect in CYBA due to compound of geterozigous mutations in 16q24. At 6 years primary tuberculosis complex of right upper lobe (MBT –) was diagnosed. At the age of 7 during the unexplained fever multiple formations were identified in the liver, biopsy showed caseosis suspected the mycobacterial nature of lesions but MBT (-). At the age of 9 years because of shade in the left upper lobe and ineffective standard antibiotic treatment the tuberculosis again was suspected. Due to ineffective antimycobacterial treatment for 8 months multi drug resistant tuberculosis was considered. Anti-TB drugs II line was appointed without clinical response. Fever persisted. MRI of brain revealed mass lesion in the left parietal lobe. Because of suspected tumor the brain biopsy was done and the pus was obtained. Microbiological studies revealed Aspergillus fumigatus. At the same time subcutaneous tumor-like infiltrate 40 x 20 mm appeared on chest in a proection of lung lesions. The pus was obtained during thoracentesis. Result of microbiological studies: *Aspergillus fumigatus*. Drainage of abscesses and intravenous Voriconazolum led to dramatic clinical improvement and normalization of blood parameters.

Conclusion. Features of our case is spread lesions of aspergillosis with relatively slow progression of infection. High incidence of tuberculosis in Ukraine leads to a high suspicion regarding this infection. Diagnosis of TB is mainly based on instrumental studies. Radiological and histological differential diagnosis between tuberculosis and other infections with granulomas in CGD is difficult. High suspicion of tuberculosis led to late diagnosis of aspergillosis.

HAEMATOPOIETIC STEM CELL TRANSPLANTATION (HSCT) FOR SEVERE AUTOIMMUNE AND AUTOINFLAMMATORY SYNDROMES IN CHILDREN

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Even following the introduction of biologic disease modifying antirheumatic drugs (DMARDs), a small number of children suffering from severe, refractory autoimmune (AI), rheumatic and/or autoinflammatory disorders will not get into clinical remission (CR) and will potentially further suffer from multiple side-effects of combined and long-term immunosuppressive and anti-inflammatory therapies, in particular severe infections (Marodi L, Casanova JL. *JACI* 2010; Abinun M. *Ped Health* 2010).

Whilst autologous T cell depleted HSCT following the immunosuppressive conditioning regimen achieved complete clinical remission in majority of children with severe juvenile idiopathic arthritis (JIA) (de Kleer IM et al. *Ann Rheum Dis* 2004), infection-related mortality remains significant (Abinun M et al. *Mol Immunol* 2009). Therefore, following the success of allogeneic HSCT in treating 6 children with immunodysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome (Nademi Z et al. *BMT* 2014), we treated further 10 children with different severe AI (ALPS, autoimmune lymphoproliferative syndrome (n = 3); complex AI disorder (n = 1)), rheumatological (jSLE, juvenile systemic lupus erythematosus (n = 1); JIA (n = 2)) and autoinflammatory disorders (MKD, mevalonic kinase deficiency/ TRAPS, TNF-receptor associated periodic fever syndrome (n = 1); EOC, early onset colitis (n = 2)). Overall, 14 of the 16 children are alive (follow up 1-11 years), 12 in complete and 1 (complex AI disorder) in partial CR, original disease (ALPS) relapsed in 1, and 2 children died (1 each with ALPS and EOC). 2 children had significant, but transient acute (grade 3-4) and chronic (limited) graft vs. host disease (GvHD), 3 experienced multiple virus reactivation(s), and remarkably we saw significant secondary AI diseases post-HSCT (transient nephritic syndrome (n = 2) and cytopaenias (n = 1); psoriasis, n = 1; and thyroid disorders (Grave's thyrotoxicosis and hypothyroidism), n = 2).

Our data add to the positive experience and evidence acquired over the last 10-15 years (Daikeler T et al. *BMT* 2009; Snowden JA et al. *BJH* 2012) to propose the allogeneic HSCT as a viable treatment option for the small group of children suffering from severe autoimmune disorders.

NOVEL AND RECURRENT WASP MUTATIONS IN EASTERN AND CENTRAL EUROPEAN PATIENTS WITH WAS

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The Wiskott–Aldrich syndrome (WAS) is an X-linked primary immune deficiency disorder characterized by thrombocytopenia, microthrombocytopenia, recurrent, mostly respiratory tract infections, eczema and increased risk of autoimmune disorders and malignancies. WAS is caused by mutations in the WASP gene which encodes WASP, a 502-amino acid protein. WASP plays a critical role in actin cytoskeleton organization, signalling and different functions of immune cells. We present here the results of genetic analysis of patients with WAS from eleven Eastern and Central European (ECE) countries, Turkey, Iran and Azerbaijan. Clinical and laboratory information of 116 affected males and 63 carrier females from 106 WAS families were collected. The WASP gene was sequenced from genomic DNA of patients with WAS, as well as their family members to identify carriers. In this large cohort, we identified 77 unique mutations including 23 novel sequence variants. The mutations were scattered throughout the WASP gene and included single base pair changes (20 missense and 14 nonsense mutations), 8 small insertions, 22 deletions, and 12 splice site defects.

FUNCTIONAL AND MOLECULAR CHARACTERISTICS OF 100 CGD PATIENTS FROM TURKEY

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Background: Chronic granulomatous disease (CGD) is a rare primary immunodeficiency disorder of phagocytes. resulting in impaired killing of bacteria and fungi. A mutation in one of the four genes encoding the components $p22^{phox}$, $p47^{phox}$, $p67^{phox}$ and $p40^{phox}$ of the leukocyte NADPH oxidase leads to autosomal recessive (AR)-CGD. A mutation in the *CYBB* gene encoding $gp91^{phox}$ leads to X-linked recessive CGD.
Methods: We report here the results of genetically and functionally characterized 100 patients with CGD from 83 Turkish families in Turkey.
Results: Most of the families (62%) have an AR genotype (%28 $p22^{phox}$, %20 $p47^{phox}$ and %14 $p67^{phox}$) and 38% have an X-linked genotype. Patients with $A22^0$, $A67^0$ and $X91^0$ phenotypes with oxidase null activity (DHR stimulation index of ≤1.5) were found in 73 patients. However, in $p47^{phox}$ deficient cases and in 7 other AR cases with high residual oxidase activity (DHR stimulation index ≥3) were found in 27 patients.
Conclusions: Residual oxidase activity is similarly lack in the $X91^0$, $A22^0$ and $A67^0$ phenotype except 7 AR cases with missense mutation. In our cohort, the percentage of AR-CGD was different from European and USA registries (in comparison with %5, %5 and 30% of $p22^{phox}$, $p67^{phox}$ and $p47^{phox}$ deficient AR-CGD cases, respectively) with the higher percentage of patients with $p22^{phox}$ (28%) and $p67^{phox}$-deficent (14%) phenotypes, and the lower percentage of patients with $p47^{phox}$-deficient (20%) phenotype. The basic difference in our results from those reported is the higher percentage of patients with AR-CGD (%62), which was lower than in the European and USA registries, probably because of the higher prevalence of consanguineous marriage in Turkey.

MITOCHONDRIAL DISTURBANCES IN PATIENTS WITH SCHNITZLER SYNDROME

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Introduction: Schnitzler syndrome is an autoinflammatory disorder of unknown etiology. At least some of its clinical presentation is mediated through an activation of inflammasome and release of IL-1, as was repeatedly demonstrated by a prominent therapeutic effect of IL-1 blockade. Recent reports bring an evidence of an important role of mitochondria in inflammasome activation and in a pathogenesis of autoinflammatory diseases. We have therefore investigated mitochondrial function and structure in patients with Schnitzler syndrome.
Materials and methods: Activity and amount of oxidative phosphorylation complexes (OXPHOS) were analysed by spectrophotometry, histochemistry and imunoelectrophoretic methods in fibroblast cell lines derived from skin biopsies of three adult male patients with Schnitzler syndrome. Ultrastructure of mitochondria, mitochondrial network and reactive oxygen species (ROS) were analysed by fluorescent and electron microscopy.

Results: The activities and amount of OXPHOS complexes I, III and IV were decreased in patients with Schnitzler syndrome. Interindividual differences in the degree of impairment (from severe to moderate) in analyzed mitochondrial parameters were found. Content of ROS, previously suggested as main inducers of inflammasome, were not significantly increased in cells with Schnitzler syndrome. We, however, did find consistent and prominent changes in mitochondrial structure of all three patients. Disturbed mitochondrial network and mainly abnormal, partially swelling mitochondria with unusual and sparse cristae were characteristic for all patients. We did further notice marked accumulation of neutral lipids in all tested fibroblasts.
Conclusion: Severe structural damage of mitochondria associated with milder functional changes represented a consistent feature found in all tested Schnitzler syndrome patients.
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POSTERS

UPDATE OF PID ACTIVITIES IN IRAN

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Along with progress in basic and clinical immunology worldwide, the knowledge and activities in the field of primary immunodeficiencies (PIDs) have developed during last two decades. In 1997, a group of junior doctors and students joined seniors in this filed to establish Iranian Primary Immunodeficiency Registry (IPIDR). Several national and international research projects have been done so far which led to lots of publications, while improving the diagnosis of patients with PIDs, construction of Iranian Primary Immunodeficiency Association (IPIA), and establishment of Research Center for Immunodeficiencies were other activities which lead to better management of the patients. Organizing annual meeting on Clinical Immunology and Immunodeficiencies, celebrating PI week annually and active participation in the international congresses were all helped in to increase knowledge of physicians in the country. The overall activities in the field of PIDs led to an increased trend in recognition of more patients in the recent years, which was associated with decreased delay in diagnosis. Based on recent report of the registry, published recently in the J Clin Immunol, more than 730 new patients with PID, in addition to previously 930 reported patients, were presented. Predominantly antibody deficiencies were the most common form of disease, followed by combined immunodeficiencies, congenital defects of phagocytes, and other well-defined syndromes with immunodeficiency. The rapid progress in identification and registration of the patients with PIDs is important not only as of epidemiological aspect, but also as of timely diagnosis and appropriate treatment of the patients.

THE SPREAD OF THE J PROJECT

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The J Project physician education and clinical research collaboration program was launched in 2004 in Eastern and Central Europe (ECE). In less than 10 years, it has achieved remarkable success. This project aims to increase knowledge in the field of primary immunodeficiency disorders (PID), and to improve the diagnosis and treatment of patients worldwide, particularly in countries with limited economic resources, which currently report fewer such patients than expected. In most ECE countries, gene sequencing, which can provide a definitive diagnosis of PID, still remains unavailable. By contrast, such technology is used elsewhere to detect the more than 200 PID-causing genes that have been discovered in the last three decades. Thus, PID awareness programs like the J Project remain critically important, to improve diagnostic facilities and treatment and to promote clinical research collaboration. This paper highlights the achievements of the J Project and the spread of its concepts and spirit to the countries of Western Asia.
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POLISH REGISTRY OF PRIMARY IMMUNODEFICIENCIES

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Primary Immunodeficiencis (PID) are rare genetically determined diseases , occurring with an incidence of 10 per 100 000 inhabitants. It is heterogeneous group of disorders, from quite commonly found and usually asymptomatic IgA deficiency (1 in 600), to a very rare diseases such as Chediak - Higashi (1 in 2 000 000 inhabitants). In 2005, within the framework of a government research project No. PBZ-KBN-119/P05/2005 - " Development , improvement and implementation of highly specialized diagnostic procedures for immune-mediated diseases", a network of cooperating national centers for diagnosis and treatment of PID, named Polish Working Group on Primary Immunodeficiencies (PGR PNO) was founded. As a result of joint efforts of the Group as well as an implementation of three EU grants [EURO- PID - NAS QLRT -2001-0274 (2001-2004) , EURO- POLICY - PID SP23 -CT- 2005- 006411 , EURO- GENE – SCAN (223, 293)] the number of centers actively working in the diagnosis and treatment of primary immunodeficiencies increased. Up to – date PGR PNO includes 15 pediatric centers , and since 2012 - 11 centers for adults. Development and dissemination of new diagnostic and therapeutic standards contributed significantly to the increase in detection PID. With early diagnosis of the disease - the implementation of appropriate treatment, including gamma globulin replacement therapy together with quality of life has improved.
In spite of all efforts recognition of PID in Poland is very rare and currently is 1.44 to 100 000, what is almost 10 times smaller than in Europe (www.ESID.org).
At the moment, a nationwide registry of children and adults with PID consists of 3 368 patients. In September 2013 PGR - PNO summarized in the annual report the current status of the substitution therapy with intravenous and subcutaneous immunoglobulin therapy in children and adults with PID in Poland. On the basis of available information, half of all patients (1 684 children and adults) were diagnosed to have antibody

deficiency. These data are similar to the register of a European database ESID , where the percentage of patients with PID with a predominance of antibody deficiency is more than 56% (www.ESID.org)
Development and dissemination of new diagnostic and therapeutic standards as well as a national cooperation contribute significantly to the increased detection of PID. Early diagnosis of the disease is followed by earlier implementation of appropriate treatment, including gammaglobulin replacement therapy together with improvement of quality of life.

EPIDEMIOLOGICAL AND GENETIC FEATURES OF PID PATIENTS IN RUSSIAN CHILDREN`S CLINICAL HOSPITAL (20YEARS EXPERIENCE)

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Background. The main clinical manifestations of Primary Immunodeficiency Diseases (PID) are infections, autoimmune and oncology presentations.
Design and method. Disease manifestations were analyzed 738 and mutations of underling genes were analized in 195 PID patients observed in Clinical immunology department of Russian Children's Clinical Hospital (November 1992 - February 2014).
Results. Mutations was identified in 188 PID children and in 41 heterozygote relatives among 195 PID patients and 43 relatives analized.
Family history was positive in 72 cases: SCID-20, XLA-11, AR-AG-1, CVID-3, NBS-3, WAS-19, AT-4, HIGM1-2, CGD-9. Consanguineous marriage – in 2 families.
Mutations of *Btk* was identified in 40 of 42 evaluated XLA patients: missens - 18, splice-site mutation – 5, deletions - 12, insertion – 5. Deletions and insertions lead to stop-codon in 9 cases. Frequently mutations occur in 10,12,17 exons of *Btk*.
In HIGM1 patients most often occur nucleotide deletions in 1 and 5 exons of *CD40L*.
Mutations of *WAS* were identified in 38 WAS boys and in 10 heterozygote mothers. Frequently genetic damages occur in 1,2,7,10 exones and 6,8 introns: deletions (11), splice-site mutation (9), missens (12), insertions (6). Deletions and insertions lead to stop-codon in 7 cases.
31 NBS patients were homozygous for 657del5 mutation and one - heterozygote for 657del5 had 681delT
X-CGD: deletions (10) and nonsens (6) mutations in different exons of *CYBB* were observed most often.
In 33 families was performed prenatal diagnosis: X-SCID–4, HIGM1-4, XLA-2, WAS-6, NBS-6, A-T-4, CGD-5, XLP-1, DNAlig4-1. Healthy children – 31.
Recurrent severe complicated infections developed in 90% of PID patients. Antibody deficiencies: bacterial infections – 100%, enteroviral - 17%, tuberculosis 2 cases, atypical mycobacteriosis – 1 case. Combined PID: bacterial infections - 100%, fungal -40%, viral - 37%, opportunistic (*Pneumocystis jiroveci)* - 48%, mycobacterial - 70% (24 - complication of BCG vaccination, 5 - tuberculosis or atypical mycobacteriosis). CGD: bacterial - 62% (*Staph.aureus, E.coli, B.cepatia, Salmonella spp., Klebsiella spp.*), mycobacterial - 75% (85% BCG origin, 15% - tuberculosis), aspergilosis -30%
Immune disregulation syndromes (XLP1 [10] and ALPS [41]): bacterial infections - 20%, viral - 8% (EBV).
Autoimmune violations were observed in 56% of all PID cases: 5% of combined PID, 35% of antibody deficiencies, 65% of other well defined syndromes, 100% of autoimmune syndromes. Cytopenias developed in 68%, vasculitis – in 15%, ulcer colitis – in 14%, arthritis – in 11%.
Oncology diseases developed in 4% of patients: mainly in NBS, A-T, WAS and CVID: T- and B-leukemia's, lymphomas, solid cancer.

PRIMARY IMMUNODEFICIENCIES IN CHILDHOOD AND ADULTS: THE SIBERIAN PID REGISTRY

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The study of primary immunodeficiency is a unique model for studying the molecular basis of immunity. Question about intravital PID verification is still relevant. A regional center of clinical immunology was established in 1986 at the Regional Children's Clinical Hospital №1, Yekaterinburg. The Regional Clinical Hospital №1 joined the center in 2013. Institute of Immunology and Physiology, Ural Branch of the Russian Academy of Sciences carries scientific management of the center. The Centre works closely with foreign counterparts in the international project J Project and it has been one of the centers of JMF since 2013.
Over 28 years we formed a regional register of patients with Primary Immunodeficiency, comprising 309 patients: 224 children and 85 adults. Analysis of the regional register allows to investigate the causes of deaths in patients with PID. Infectious syndrome mortality - sepsis, generalized mycobacterial infection - 22 patients, proliferative process - 4 patients, dominate the mortality structure.
Creation of specialized immunological centers permit to raise the educational level of the medical staff, precisely identify nosological forms of PID among different groups of patients, to prevent the birth of children with PID, increase the length and quality of life such patients and take part in the collaboration with international experience in the PID.

FREQUENCY AND CHARACTERISTICS OF PATIENTS WITH CVID OVER 18 YEARS OF AGE

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Introduction: The aim of this retrospective study is to determine the frequency, and demographic, clinical and laboratory features of adult CVID patients referred to our clinic.
Materials and Methods: We retrospectively evaluated 26 adult patients (9 female (%34,6), 17 male (%65,4); aged 18 to 67 years: median 27 years) who were diagnosed as CVID according to ESID and PAGID criteria during a 4 year period (January 2010-March 2014).
Results: The median current age of 26 patients was 27, and the median CVID diagnosis age was 22,5 years. The diagnostic delay in patients with CVID was 4,5 years (median). CVID patients presented lower levels of IgM (12 patients, 46,1 %), IgA (16 patients, 61,5 %) and IgG (16 patients, 61,5 %). According to lymphocyte lmunophenotypes of CVID patients, CD4 (15 patients, 57,6 %), CD19 (13 patients, 50 %) and CD4/CD8 (13 patients, 50 %) values were observed the most lower ones.
Discussion: We found that both of the patients with bronchiectasis showed lower levels of immünoglobulins and lower imunophenotypes of B cell than the others that do not have bronchiectasis. In our patients CD4, CD19 and CD4/CD8 values have got enough priority to be mentioned about an immun deficiency. In conclusion, despite recent improvements in diagnostic tools, the diagnosis of mild or moderate CVID is often delayed. However, it seems that the diagnosis of CVID is delayed especially in adulthood on account of the fact that the lack of awareness of these illnesses among the medical professionals all over the world.

EDUCATION AND PID AWARENESS AMONG MEDICAL STUDENTS

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Primary immunodeficiency disease is important in Turkey because of the high rate of consanguineous marriage. The lack of awereness about immunodeficiency can cause late-diagnosis and severe complications. The objective of this study was to assess PID awereness before and after clinical immunogy education among medical students. One hundred and thirty-two questionnaires 0 with 71 items (1) were distributed to seventh somestre medical students and 116 (88%) completed questionnaires were evaluated before (first) and after (second) their education about clinical immunology courses for 6 hours. Questionnaire Scores (QS) were detected as total correct answers. The mean of the first QS was 37.4 ± 3.7 and second QS was 42 ± 4.3 ($p < 0.05$). There was no statistically difference in gender (60 M and 56 F). Of 69 questions, there were 39 related with PID directly. The correct responses rate less than 50% before education were 10 of 39 questions. All participants corrected their responses after education. The best improvement was detected in the responses of the clinical signs related with PID. It was remarkable that the participants have known the family history related with PID excellent before education. The majority of the participants (80%) believed that a lymphocyte count of 2500/mm3 was related to immunodeficiency. NBT and CH50 test were not found to be related with PID before education. It is also important to increase the awareness of PID among the physicians during their education in medical school and more comprehensive education in PID appears to be useful for medical students.

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CLINICAL AND GENETIC FEATURES OF CGD IN EASTERN AND CENTRAL EUROPEAN COUNTRIES

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Chronic granulomatous disease (CGD) is a rare primary immunodeficiency with mutations in NADPH oxidase enzyme complex which causes failure of phagocytic cells to produce superoxide and subsequent intracellular killing of microorganisms. We retrospectively analysed medical records of patients diagnosed with CGD in the last 35 years from immunological diagnostic centres from 9 central and eastern European countries (Estonia, Poland, Belarus, Ukraine, Czech Republic, Slovakia, Hungary, Serbia and Slovenia) and Russia. Genetic sequencing from patients' DNA was performed in genetic centres in Ljubljana, Belarus and Netherlands for mutations in known genes involved in CGD pathogenesis: CYBB, CYBA, NCF1, NCF2. We included 104 patients with CGD in our cohort, 7 were female. The mean age at presentation of the disease was 12 months and at diagnosis 3,9 years. Lymphadenitis (43%), dermatitis (16%), enteritis (16%), pulmonary infections (13%), liver abscesses (4%) and septicaemia (6%) were the most common clinical presentation. Complications of BCG vaccination (28%) were the most common presenting infection. In total 917,4 years of follow-up in our cohort, the patients suffered 834 different severe infectious episodes (0.9 per year). Respiratory (25%), Lymph node (25%) and gastrointestinal tract (18%) infections represented the most prevalent severe infections. We identified 87 different mutations out of 104 genes tested. In 78 patients we identified different mutations in CYBB gene, 2 unrelated patients had the same mutation in CYBA gene and in 5 patients had typical deletion in NCF1 gene. In our cohort we observed high incidence of BCG infections as a presenting symptom. Apart from high BCG infections patients included in our study had similar frequencies of infections and infecting microorganisms as patients described in previous series.

PREVALENCE OF MEFV GENE MUTATIONS IN APPARENTLY HEALTHY POPULATIONS IN BALKAN AND CENTRAL EUROPEAN COUNTRIES

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Introduction: Familial Mediterranean fever (FMF) is an autosomal-recessive disorder characterized by recurrent attacks of fever and serositis common in eastern Mediterranean population. Over 160 mutations have been identified in *MEFV* gene responsible for FMF. The most common mutations in *MEFV* gene are E148Q, M694I, M694V, V726A and M680I. The distribution pattern of *MEFV* gene mutation along the Mediterranean Sea is not uniform; eastern populations have the highest number of carriers (20-39%), whereas western Mediterranean populations are practically unaffected.
Objectives: The aim of this study is to determine the carrier rate in healthy controls from Central European and Balkan region.
Methods: We screened more than 500 healthy subjects from 5 countries in the region. Exon 2 and 10 was PCR amplified and subsequently sequenced with ABI prism 310 genetic analyzer.

Results: Heterozygous mutations were found in 4% of apparently healthy Hungarians, 7% of Slovenians, 8% of Bosnians, 11% of Serbians and in 16% of apparently healthy Macedonians. Mutations found in Hungarian population were as follows: V726A (1), K695R (3). Mutations found in Slovenian population were: V726A (1), K695R (5) and E148Q (1). Mutations found in Bosnian population were: V726A (1), K695R (6) and F756C (1). Mutations found in Serbian population were: E148Q (6), K695R (5). Mutations found in Macedonian population were as follows: E148Q (8), K695R (7) and M694V (1).
Conclusion: We found higher than expected carrier rate in screened populations, from 4% to 16%. It is interesting to note that more than half (60%) of detected carriers in all analyzed populations has K695R mutation.

THE EXPANDING SPECTRUM OF PID: DATA FROM THE SLOVENIAN PID REGISTRY

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Progress in the field of primary immunodeficiencies (PIDs) is reflected in national PID registries. Data from Slovenian PID registry were analyzed. Patients' data were collected retrospectively before 2007 and prospectively afterward. Patients were classified according to international classification and updated regularly.
Data of 193 patients with 45 different PIDs were analyzed. Interestingly, complement deficiencies are the most common, accounting for 23% of all entries. Second most common are antibody deficiencies with 19%, followed by well-defined syndromes (16%), immune dysregulation (13%), neutrophil defects (12%), combined deficiencies (9%), autoinflammatory disorders (6%) and defects of innate immunity (2%).
Prevalence of diagnosed PIDs in Slovenia has changed in the last 5 years; less complement deficiencies and more antibody deficiencies were diagnosed in comparison to previous decades. The number of new PID cases has been gradually increasing, a more prominent increase has been noted in the last 10 years. The prevalence increased most for combined immunodeficiencies, CVID and autoinflammatory disorders. The spectrum of PID entities has also widened in the last decade. Three patients with SCID were diagnosed and successfully treated in the last three years (incidence - 1:25.000 births).
High prevalence of complement deficiencies reflects early implementation of good complement diagnostic facilities and awareness among infectologists. This group of patients was prospectively collected from 1987. Combined immunodeficiencies, CVID and autoinflammatory syndromes were all probably underdiagnosed before due to lack of awareness among physicians. Distribution of PID groups is more consistent with ESID registry in the last five years. Identification and successful treatment of SCID patients in the last years is an important quality marker.

PID IN BULGARIA: RESULTS OF THE BULGARIAN ASSOCIATION OF CLINICAL IMMUNOLOGY INITIATIVES

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Bulgarian Association for Clinical Immunology was set up in 2005 aiming to get together all specialists working in the field of clinical immunology. One of the important objectives of the association was to raise the public awareness and attract attention of specialists, National health system, government and other related societies in order to improve the diagnosis and access to treatment for children and adults with PID. Efforts of immunologists led to the following results:

1. Consensus on the diagnosis and treatment of the basic PID groups was created by the PID national working group that was established in 2010, and specific guidelines were disseminated as well.
2. Register for PID patients has been set up in Bulgaria that allowed the collection of data on the incidence and prevalence of PID and the negative effect of these conditions on the population.
3. Educational program to improve the qualification of the physicians and provide available resources to general practitioners and raise the public awareness were introduced.
4. Collaboration with patient's organizations was developed.
5. Treatment of PID patients has been fully covered by the public health system since March 2013.

All these steps made it possible to advance the diagnosis and management of PID in our country.

PEDIATRIC PID PATIENTS CARE – SINGLE CENTER EXPERIENCE

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J-project in Bulgaria started in 2005 and up to now we have elaborated programme with diagnostic criteria, well equipped laboratory, established some mutual connections with foreign colleagues, held regional meetings, conferences; created clinical standards for treatment and ensured an immunoglobulin treatment and replacement therapy.
Here are examples of some of the problems we face:
1. Seven-years old boy with hypogamaglobulinaemia (normal number B-Ly with abnormal function). IVIG had some initial effect, but lately we noted very fast deceleration in the overall health status with possible need of lung transplantation. The case is posing a question what more could we do, could we have prevented this rapid worsening.
2. Ten-month old girl with SCID with severe BCG infection after first vaccination, referred relatively late to our center, but successfully transplanted. The case is posing a question about timing of BCG vaccination and of referral to specialized center.
3. Nine-years old girl with unidentified immune deficiency, normal immunological follow up but clinical course as an immune deficiency with very favorable effect of IVIG according the parents. The case is posing the question should we stop or should we continue IVIG, despite failing to find immunological defect, based on the good clinical response.
Unfortunately PIDs are not very well recognized and sometimes the patients are referred late. Sometimes poverty and lack of knowledge of patients leads to miscalculation and neglecting of their conditions by themselves, or refusal for specific tests for clarifying the diagnosis.

PRIMARY IMMUNE DEFICIENCIES – EXPERIENCE AND ACTIVITY FOR DIAGNOSTICS AND RESEARCH AT THE BIGGEST BULGARIAN HOSPITAL

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Background: Although rare, Primary immune deficiencies (PID) are manifested with high rate infections as well as with autoimmune and malignant disorders that are treated hardly and inefficiently. PID are not only immunological problem; they require close collaboration between immunologists, pediatricians, ENT, lung and gut specialists, dermatologists, hematologists, oncologists, patients and administration. The aim of this study was to summarize the activity on registration and replacement therapy of PID patients in Plovdiv region at the University Hospital "St. George"-Plovdiv for 1 year (03.2013-02.2014).
Methodology: Children with PID of humoral immunity hospitalized at the Clinic of Pediatrics, and adults with Hereditary angioedema (HAE) were included in the study using immunological and other lab tests, clinical follow up and treatment: IV and SC Ig for children with PID and C1 esterase inhibitor (Ruconest, Berinert) for HAE patients.
Results: Three national workshops and a national conference on PID were hosted and organized in Plovdiv since 2005. Well established university hospital immunological laboratory, detecting serum immunogloblins, blood lymphocyte populations and subpopulations and complement proteins; Clinic of Pediatric and Genetic Diseases and an Information center for Rare diseases and Orphan drugs function in Plovdiv. An Expert center for diagnosis and treatment of PID was created at the University Hospital. It is a team of two competent pediatricians, an immunologist and an allergist. The targets are hospitalized PID children, outpatient PID children and HAE adults. The Center introduced regular replacement therapy with IV and SC IV and C1 Inhibitor, reimbursed by the National Insurance. Together with ICRDOD the experts provide education for patients and parents how to perform SC Ig application as well as consultations of patients and relatives about PID.Since March 2013 indicated reimbursed replacement therapy with IV Ig – Octagam, started regularly in 5 hospitalized PID children with Bruton hypogammaglobulinemia, CVID, Omenn syndrome or IgG1 ID. These patients, aged form 4 to 12 years, had 2 to 6 hospitalizations for one year. Four outpatient children with Omenn syndrome or IgG1 subclass deficiency were subjected to SC Ig – Gammanorm, and 7 HAE type 1 outpatients had good response for replacement C1 inhibitor therapy as follows: Conestat alfa (Ruconest) – in 5 HAE adults (150 IU/ml weekly), and Berinert (20 U/kg b.w. weekley) – in 2 HAE adult patients.
Conclusions: The Expert PID Center in Plovdiv University Hospital provides competent diagnosis, therapy, education and consultations for pediatric and adult PID patients from Plovdiv region. The recent introduction of reimbursed replacement therapy for PID patients (hospitalized or outpatients) allows regular immunological and clinical follow up of the diseases.

ADVERSE EVENTS FOLLOWING INTRAVENOUS IMMUNOGLOBULINS (IVIG) TRANSFUSION IN EGYPTIAN CHILDREN

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Background: Intravenous immunoglobulins (IVIGs) are scarce biological products used in a broad variety of disorders. Tolerance to infusions is usually good but adverse events, including some serious ones, have been reported.
Methodology: A cohort study aimed for detection of adverse events that occur during and following intravenous immunoglobulin (IVIG) infusions at Cairo University Children Hospitals [Patients were recruited at Neonatal Intensive Care Units (NICU), Pediatric Intensive Care Units (PICU), general and specialized inpatient wards] over a time period of six months, from April through September, 2013. The study included 62 transfusions for different disease conditions in 55 patients.Three maltose-stabilized intravenous immunoglobulin products were administered to patients. Assessments were done before, during and after the infusions.
Results: There were 22 symptoms and 26 laboratory changes of adverse events during IVIG transfusions, with some patients experiencing more than one adverse reaction. Adverse events were noted to occur most frequently within 1 to 6 h from onset of IVIG infusion (n = 9, 39.1%). First hour after infusion onset was the most common timing for symptoms of adverse reactions (n = 5, 21.7%).
Patient characteristics of those with adverse reactions: Adverse reactions occurred in 37.1 % of the infusions (n = 23) with the majority belonging to the 6-9 years old age group (n = 10, 43.5%), with variable diagnostic categories. Ten patients observed during 14 infusions (60.9%) had one or more risk factors for complications, while 6 patients observed during 9 infusions (39.1%) had no risk factors. The commonest risk factor was administration of nephrotoxic drugs (n = 8, 34.7%), followed by presence of a suspected autoimmune disorder (n = 7, 30.4%) and preexisting renal insufficiency (n = 5, 21.7%).
Using regression analysis, the predicting variables for each complication were noted .For example ,fever and chills were related to infusion rate and dose whereas the predicting variables for pallor were infusion rate and presence of existing risk factors.
Conclusions: Clinicians should be aware of the high need for special monitoring while infusing IVIG to patients with primary immunodeficiency disorders, autoimmune hematological disorders and sepsis.

IMPORTANCE OF DEFINITE DIAGNOSIS OF PRIMARY IMMUNODEFICIENCY DISEASES

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Certain diagnosis of a Primary immunodeficiency disorders (PID) is most confirmedly performed by investigation of a gene defect, allowing genetic counseling and screening. Molecular diagnosis helps both parents and index PID patient by carrier detection and pre-implantation testing for selecting appropriate reproductive decisions. Furthermore, for confirmation of diagnosis and establishment of the inheritance pattern genetic analysis is necessary. This survey in all PID cohorts should be considered for long-term planning such as bone marrow transplantation of a PID infant at birth. The result of this testing also is important for screening of newborns and for those in specific family or ethnic groups. The prevalence of PIDs has been estimated to be more than 1/600 worldwide. Based on the total population of Iran reported in 2010 (76,424,000), the expected prevalence of PIDs in Iran would be more than 127,300 individuals. However, because of the high rate of consanguineous marriages in Iran and an increased risk for development of disorders with an autosomal recessive pattern of inheritance, this prediction is likely to be an underestimation. To date, 2247 clinically diagnosed patients of PIDs have been reported in Iran, and a definite diagnosis, defined by mutation analysis, was made in 790 individuals. As a result, 1.76% of the expected PID patients have been identified, and among these, 35.2% have been diagnosed at a molecular level. The proportion of genetically definite diagnosis varied between 84.5 and 0% in the different disease categories. This wide spectrum might be due to unknown underlying genetic defects or modifying genes, especially in patients with predominantly antibody

deficiency. On the other hand, the latter patients also had the lowest percentage of clinically diagnosed cases.

CROATIAN PID DATABASE

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Croatia is a small country with 4 267 889 inhabitants . According to expected prevalence of PIDs we expected approximately four hundred patients with PID. For the past few years University Hospital Center Zagreb is the reporting center for ESID registry. It is also the national center for diagnosis and treatment of PIDs, including haematopoietic stem cell transplantation.
Current PID database is running manually, with the exception of patients reported to ESID registry. Most of them are of pediatric age, reffered to the hospital from all over the country. The PIDs patients are classified according to international classification (IUIS- International Union of Immunological Societies). There are 121 PIDs patients included in the database at the moment. The majority of them have antibody deficiency. Combined immunodeficiency and well defined syndromes appear in equal distribution. Other types of PIDs are reported in small numbers. Although no consanguinity was reported, we noticed the geografic distribution of severe combined immunodeficiency patients (SCID) mostly in 2 regions, Istra and Podravina. It can be explained with genetic isolation.
The establishment of National Online PID registry is in process. The aim is to improve the diagnosis od PID specially in adult patients, who are not included in present database, with exception of the patients diagnosed in childhood.
Primary immunodeficiency disorders are underdiagnosed in Croatia, specially in adults. Establishing National PID registry will improve the physicians awareness of PIDs, which is particularly important for adult patients. We expected the number of diagnosed PID patients will rise. This will give the opportunity to make progress in diagnosis and treatment, and the opportunity for further epidemiological and clinical studies.

MACEDONIAN REGISTRY OF PID

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Background: Primary immune deficiency diseases (PID) are a heterogeneous group of rare, inherited disorders with unique genetic defects in the immune system. Besides the susceptibility to recurrent infections, they have a wide spectrum of clinical manifestations including autoimmune diseases, unregulated inflammation and predisposition to malignancies.
Aim: To present the register of pediatric patients with PID in Macedonia.
Material: The patients with suspected immunodeficiency disorders, investigated, diagnosed, treated and followed up at the Department of pediatric immunology at the University Clinic for Children`s Diseases in Macedonia (unique Center for PID in Macedonia) between 1976 and 2013 year are presented. Most of the patients have confirmed diagnosis for PID.
Results: Different PID are diagnosed in 107 patients.
With predominantly antibody deficiencies are 59 patients: 30 have selective IgA deficiency; 18 have transient hypogammaglobulinemia of infancy; 7 have X-linked agammaglobulinemia; 2 have common variable immunodeficiency and 2 have isolated IgG2 subclass deficiency. Another 25 patients have well defined immunodeficiency syndromes from which: 11 are with Di George anomaly; 2 with Wiskott-Aldrich syndrome; 4 with ataxia-teleangiectasia; 4 with Hyper IgE Syndrome; 1 with Schimke Syndrome and 3 are with Nijmegen Breakage Syndrome. In early nineties, two (2) of our patients had chronic mucocutaneus candidiasis. 3 patients are registered as X-linked SCID and 1 with X-linked lymphoproliferative syndrome (XLP). 1 patient has chronic granulomatous disease; 3 have severe congenital neutropenia and 5 have hereditary angioedema. 2 patients are with WHIM Syndrome. 6 patients are with anti-inflammatory disorders: 1 has Hyper Ig D Syndrome (HIDS) and 5 have Familial Mediterranean Fever.
Conclusion: 107 patients with PID in Macedonia are presented. 85 patients have definitive diagnoses. 35 of them have confirmed diagnose of PID with genetic analysis for PID on molecular level in referent immunology laboratories.
The patients with HLA, with replacement therapy are in good condition with controlled infections. 2 patients with PID had developed autoimmunity. There is no one case with developed malignancy. 10 of the patients with PID had died.

DEVELOPING PID CARE IN CENTRAL ASIA: THE J CENTRAL ASIA PROJECT

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Introduction: The opportunity to improve the life quality of patients with primary immunodeficiency (PID) in the Republic of Kazakhstan and reducing the morbidity and mortality rate from PID are the main objectives of the J – project realization in the Republic of Kazakhstan. Successful project execution provides the improvement in detecting and diagnosing of PID, the prevention of PID's complications, the improvement of the health care of patients with PID, the creation of the Registry of the patients with PID, the implementation of the finance regulations for detection and treatment of patients with PID diseases in public health facilities, the training and professional development of medical professionals in this field.
Objective: To improve the detection and diagnosis of PID diseases and the life quality of patients with PID in the Republic of Kazakhstan.
Undertaken activities for realization of the project:

6. Professor. L. Marodi visited Kazakhstan in October 2012 and the meeting was held in Ministry of Health of the Republic of Kazakhstan, p*resentations were given at the international conference* held in National Research Center for Maternal and Child Health, the negotiations with Heads of the National Medical Holding' clinics and Scientific Center of Pediatrics and Pediatric Surgery were held.
7. Primary immunodeficiency Center in the Republican Diagnostic Center of the National Medical Holding was established in November 2012.
8. International symposium "Diagnosis and treatment of primary immunodeficiency" was held in October 2013. Master-class of "Diagnosis and treatment of PID" with the invitation of the leading specialists from Kazakhstan.
9. The creation of the Registry for the patients with PID.
10. The development and publication of PID diagnostic protocols and guidelines in Kazakhstan in 2013.

Conclusion: The number of patients with PID significantly increased every year.

The J- project realization in the Republic of Kazakhstan allows to update the PID problem, to raise the availability of early diagnosis of PID, to improve the life quality of patients with PID by providing substitution therapy and as a result, the infant mortality and disability rate has been reduced.

MANAGEMENT OF PATIENTS WITH CVID – DATA FROM THE CZECH PID REGISTRY

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Common variable immunodeficiency (CVID) is the most common primary immunodeficiency (PID) characterised by impaired immunglobulin production and immune dysregulation. Chronic and recurrent infections and its results are typical manifestation of this disease. In addition there is a higher risk of autoimmune disorders, lymphoproliferative or granulomatous diseases and malignancies. Successful management of CVID patients is based on prevention and consistent therapy of infections with sufficient immunoglobulin replacement and/or antibiotics, prevention and active screening of CVID related complications.
In our study we analysed data of 41 patients gained from medical records. These data were also input into Czech PID Registry and PID Registry organized by ESID (European Organisation for Immunodeficiency). We aimed at the period before diagnosis- onset of the symptoms and their characters and the course of the disease- effect of therapy, occurence of the related complications. Finally, we compared our data with similar performed studies.
Chronic and recurrent upper and lower respiratory infections were the most frequent first manifestation of our CVID patients, but developed chronic lung disease or autoimmune disorder as well. In all patients the intravenous or subcutaneous imunoglobulin replacement therapy, eventually combined therapy with antibiotic prophylaxis, was initiated.
Beside chronic lung disease the most common complications were autoimmunity disorders, especially autoimmune thyroiditis, Evans syndrome, trombocytopenia (ITP), autoimmune hemolytic anemia (AIHA). On the contrary we revealed 2 patients with insuline dependent (type 1) diabetes mellitus and CVID. Only few case reports have been published with such association.
Successful management of CVID patients is based on a prevention and a consistent treatment of infections with sufficient immunoglobulin replcement and/or antibiotic therapy, a prevention and an active screening of CVID related complications. Such approach can significantly improve the prognosis of CVID patients and the quality of their life.

OVERVIEW OF PRIMARY IMMUNODEFICIENCY DISORDERS DIAGNOSED IN THE PRIMARY IMMUNODEFICIENCY CENTRE OF THE HOSPITAL OF LITHUANIAN UNIVERSITY OF HEALTH SCIENCES

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Background. Primary immunodeficiency (PID) is considered to be a rare disease. Despite that it is thought that six million people may be living with a PID worldwide. In the Hospital of Lithuanian University of Health Sciences (HLUHS) patients with suspected immune disorders have been diagnosed and treated since 1998. We aimed to review the structure of PID diagnosed and treated in HLUHS during the last five years.
Methods. Data about patients with PID consulted in the HLUHS was collected from the Department of Medical Statistics. Case histories of these patients were revised and patients' data was collected: onset of symptoms, type and duration of disorder, type of treatment. All patients with PID were divided into several groups according to the classification of International Union of Immunological Societies Primary Immunodeficiency Diseases Classification Committee (2011).
Results. There were 57 patients with PID diagnosed in the Centre. Antibody deficiency was diagnosed for 38 patients: 3 – Bruton's disease, 14 – common variable immunodeficiency (CVID) and 21 – selective immunoglobulin (Ig) A deficiency. Complement deficiencies were diagnosed for 13 patients: 11 – C1 esterase inhibitor deficiency and 2 – C4 deficiency. Another well-defined syndrome with immunodeficiency was found in six patients.
The most prevalent symptom in patients with predominant IgG deficiency was recurrent pneumonias which occurred at the age 11.9 ± 4.9 yrs. The mean time between the onset of symptoms and confirmation of the diagnosis was 14.6 ± 6.4 yrs. Thirteen patients are on the replacement therapy with intravenous immunoglobulin. These patients had 2-6 infections/year before the treatment initiation and only 0-1 infections/year during the treatment.
Conclusions. Most commonly diagnosed type of PID in the Centre of HLUHS is antibody deficiency, especially selective IgA deficiency and CVID. IVIG therapy is an effective treatment of patients with predominant IgG deficiency.

PID CENTER IN SAINT- PETERSBURG, RUSSIA

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St.Petersburg (SPb) PID center was established in Saint– Petersburg in December 2011 as a result of "St-Petersburg PID group activity" efforts. SPb PID center is based on St-Petersburg Pasteur institute and branches works also in Saint-Petersburg Pediatric Medical University Consultative Center and Russian Center of Emergency and Radiation Medicine.
SPb PID center includes clinical and laboratory divisions. Clinical division works as consultative and diagnostic polyclinics center. PID medical aid is free for patients and covered by St-Petersburg Government Health Insurance funding. Total number of PID patients observed in our center increase annually and now about 250. •PID center has successful side-project as Regional charitable public organization of invalids "Society of patients with primary immunodeficiency diseases in St. Petersburg" Solovushka (Nightingale) "". Web site for patients (www.opidspb.ru) was opened due to mutual efforts of PID center staff and patients.
PID Center laboratory is based on SPb Pasteur Institute Central Clinical Diagnostics Laboratory and Laboratory of Molecular immunology and seroepidemiology. Main groups of tests perform for PID patients are: general clinical assays; flow cytometry (6-color assay on FACS Canto II); humoral factors assays (Ig levels, IgG subclasses, post-vaccination IgG levels, etc.); burst-test on flow cytometer; genetic analysis of Btk, Rag1, Rag2,WAS, CYBB genes.
Despite of relatively short story of SPb PID Center it has a variety of completely diagnosted and successfully cured cases of PID including agammaglobulinemia with B-cell in Identical siblings, Wiskott-Aldrich syndrome, chronic granulomatous disease (CGD), etc.

Perspectivres of SPb includes program of further development of center activities: the introduction into screening (postnatal) TREC and KREC quantification; expanding the range of the analyzed genes; optimization lymphocytes subpopulations detection for the diagnosis of various nosological forms of PID's

SURVEY ON PRIMARY IMMUNODEFICIENCIES IN ALBANIA

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Introduction: The primary immunodeficiency diseases are a group of disorders caused by basic defects in immune function that are intrinsic to, or inherent in, the cells and proteins of the immune system. There are more than 200 primary immunodeficiency diseases.. Laboratory studies are necessary to determine the presence of a primary immunodeficiency diseases. The standard screening tests for antibody deficiency starts with measurement of immunoglobulin levels in the blood serum. These consist of IgG, IgA and IgM levels. The results must be compared to age-matched controls. Additional studies used to evaluate patients with antibody deficiencies include measuring the different types of lymphocytes in the blood by marking those cells with molecules that can identify the different types. A commonly used test is called flow cytometry that can identify B-cells and T Cells present in the circulation.
Methods: In 2008 in our laboratory of Immunology is created the sector of examination for the PID and we measure the immunoglobulin levels with a Beckman Coulter IMMAGE Immunochemistry System fully automated rate turbidometry and rate nephelometry method. We have determine the aged- matched levels of immunoglobulins in our laboratory. We have install also a new flow Cytometer of Beckman Coulter company and we can determine the B Cells by CD19 marker and T cell with CD3 , CD4 and CD8 marker. This examinations has been of great help in diagnosis of primary immunodeficiencies.
Results: In years 2010-2013 from the examination of children aged from 0-14 years old reported in our laboratory for immunological examination from the pediatric department of UHC Mother Teresa in Tirana we have selected 41 cases with disorders regarding the primary immune deficiencies. We have 5 cases (3 cases reported in 2008-2009 and 2 new cases) with nul B cell in Cytoflorometry (B Cd19 cell = 0 %). The level of immunoglobulins was indetectable for IgG , IgA and IgM in the moment of diagnosis. They were boys and the age at diagnosis was 3 and 4 years and actually they are 4 and 6 years treated with IVIG. We have classified them as Bruton (XLA). We have 12 case with low Cd19 B- cell in circulation but only in 4 of them we have done the immunoglobulin level. The low level of Cd19 B cell is accompanied with different kind of hypoglobulinemies: 1Common Variable Immunodeficiency CVID, 1 with isolated IgA deficiency, 1 with IgG deficiency and 1 with both IgG + IgM deficiency. The immunoglobulins disorders : we have classified them according the antibody deficiencies (tab1) and we noted that the most frequent one is the deficiency of IgA (12/19 or 63.2 % - from which 6 IgA isolated, 5 accompanied with low IgM and 1 with low IgG) with average age at diagnosis 5.09 years old. In children in the first years of live aged from 0.8 to 2 years old we found 8 case with transient hypogammaglobulinemia of infancy. According this survey we can report our 92 cases of primary immunodefiecies in UHC Mother Teresa of Tirana with different classification
Conclusion: The finding are to be completed with other cases in Albania and it is necessary to do the national register for PID in order to estimate exactly the prevalence of this disorders in our country.

Tab 1. 2010-2013 DATA REPORT OF SURVEY OF PRIMARY IMMUNODEFICIENCIES

CHU " MOTHER TERESA" TIRANA ALBANIA	Nr of cases in 2010	Nr of case in 2010-2013	TOTAL
COMBINED T AND B CELL IMMUDEFICIENCIES			
SCID	5	0	5
PREDOMINANTLY ANTIBODIES DEFICIENCIES			
Agammaglobulinemia (XLA)	3	2	5
Common variabel immunodeficiency	3	2	5
Hypogammaglobulinemia of infancy (Transient)	1	8	9
Hypogammaglobulinemia unspecified	28	2	30
IgA deficiency selective	15	6	21
IgA with IgG deficiency		1	1
IgA with IgM deficiency	0	5	6
IgG subclass deficiency isolated	1	2	3
Hyper IgM AR (AICDA,UNG, CD40)	3	0	3
OTHER WELL DEFINED IMMUNODEFICIENCIES SYNDROMES			
DiGeorges Syndromes (DGS)	1	0	1
Wiscott Aldrich Syndromes (WAS)	1	0	1
AUTOINFLAMATORY DISORDES			
Familial Mediterranean fever		1	1
Hyper IgD syndrome	1	1	2
PFAPA Syndrome	0	1	1
TOTAL NUMBER OF CASES WITH IMMUDEFICIENCIES IN 2013	62	32	94

CORRELATION BETWEEN PHENOTYPE AND GENOTYPE IN 27 CASES OF HYPER IGE SYNDROME EGYPTIAN INFANTS AND CHILDREN

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Background: HyperImmunoglobulin E Syndromes (HIES) are characterized by recurrent staphylococcal abscesses, pneumonia and high IgE levels. HIES may be transmitted in an autosomal dominant or recessive pattern.
Methodology: Cases presenting with HIES were included (n = 27) and molecular testing was conducted in 15 cases. The objectives were to diagnose genetic mutations and correlate mutations with clinical phenotypes.
Results: Based on their clinical phenotype, patients were divided into one of two groups. Fifteen patients belonged to the group having as main features: pneumonias, recurrent staphylococcal abscesses, skeletal abnormalities and no CD4 lymphopenia. Only one patient in this group was diagnosed with a STAT 3 mutation. The second group, associated with CD4 lymphopenia, included twelve patients who presented mainly with eczema, viral infections, gastrointestinal and hepatic involvement. Only one patient within this group was diagnosed with a DOCK8 mutation.
Conclusion: The autosomal recessive forms of HIES are as frequent as the autosomal dominant forms in the geographic areas of high consanguinity. The underlying genetic mutations remain undetected in more than eighty percent of HIES patients. More extensive studies including whole exome sequencing is required to understand the underlying defects in those patients.

AUTOSOMAL DOMINANT STAT3 MUTATION IN A HUNGARIAN HIES PATIENT

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The STAT3 mutation was confirmed in 2007 as the cause of autosomal dominant hyper-IgE syndrome (AD-HIES). The disease, which also mentioned in the literature as Job's syndrome, is a rare primary immunodeficiency.
This disease can be characterized by the following classic triad: recurrent purulent skin infections, cold abscessus which are formed in the ground of chronic ekcematoid dermatitis, pneumatocele, formation causing pneumonia and extremely high IgE level. Dental training interdependency as well as bone and connective tissue disorders frequently occur in the non-immunological symptoms as multi-systemic disease. The STAT 3 protein has an important role in the area of wound healing, immunity, tumor and neovascularization.
We would like to show this in case of 3-years old Kitti whom the perinatal medical history was eventless. There is a frequent hospitalization in Kitti's case history since her infancy.
Due to the age of three months because of serious exsiccotoxicosis, 5 months old bilateral bronchopneumonia and pleurisy required ICU care. Bronchoscopy was made because of recurrent pneumonia, which excluded the bronchial malformation. Lately rather otitis, mastoiditis and airway obstructive symptoms dominated the clinical picture. From serum immunoglobulins- IgG is very low, whereas high levels of IgE-was indicated. On this basis, the diagnosis of Job's syndrome was up, which is a negative STAT3 mutations as the molecular genetic test performed demonstrated.
The disease has a great clinical importance, since the risk of emergence of serious and often life-threatining complications are high. Because of the prevention of disseminated infections, the early detection and the appropriate treatment are essential. In default of causal therapy, the treatment primarily concern to prevention of infections, or their aggressive antibiotic therapy. Calcium and vitamin D and as well as histamine 1 on the case of itchy skin symptoms are reccurrended to use.

NOVEL AND RECURRENT STAT3 MUTATIONS IN HYPER-IGE SYNDROME PATIENTS FROM DIFFERENT ETHNIC GROUPS

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We performed clinical, immunological and genetic studies of 12 hyper-IgE syndrome (HIES) patients from 4 Hungarian, 2 Lebanese, one Russian, one Polish, and one Swedish families with autosomal dominant (AD) or sporadic forms of the disease to reveal cross-ethnicity of recurrent and novel mutations in the signal transducer and activator of transcription-3 gene (*STAT3*). Four patients from 3 Hungarian families, and one Russian, and one Swedish patient carried the heterozygous R382W germline mutation at the DNA-binding site of STAT3. The recurrent V637M mutation affecting the SRC homology 2 (SH2) domain was detected in one Lebanese and one Polish family, and the V463del deletion located in the DNA-binding domain was unveiled in another Lebanese family. A novel H332Y mutation affecting the DNA-binding site of STAT3 in three Hungarian patients from a Gypsy family was also found. The segregation of this mutation with HIES, restriction fragment length polymorphism analysis of *STAT3* from patients and controls and the negligible production upon IL-6 stimulation of monocyte chemotactic protein-1 by the patient's blood mononuclear cells suggested that the H332Y mutation was disease-causing. These data suggest, that dominant negative mutations of the DNA-binding and SH2 domains of STAT3 cause AD and sporadic cases of HIES in different ethnic groups with R382W as the predominant mutation found in 5 of the 9 families. Functional and genetic data support that the novel H332Y mutation may result in the loss of function of STAT3 and leads to the HIES phenotype.
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NEUROENDOCRINE CARCINOMA ASSOCIATED WITH X-LINKED HYPER-IGM SYNDROME

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X-linked hyper-immunoglobulin M syndrome (XHIGM) is a primary immunodeficiency disorder characterized by severe defects of both cellular and humoral immunity due to impaired expression of CD40 ligand on activated T lymphocytes. Patients with XHIGM usually present with a wide variety of infections caused by common and opportunistic pathogens including Pneumocystis jirovecii. In addition, subjects with XHIGM have an increased risk for hepatocellular and bile duct carcinomas, which are rarely observed in other primary immunodeficiencies. We present here clinical, immunological, and molecular findings of four patients with CD40 ligand deficiency associated with neuroendocrine carcinoma (NEC). NEC developed as a rapidly disseminated solid cancer leading to death in three patients. Data presented here and published previously suggest that CD40 ligand deficiency may predispose patients for the development of NEC. Histochemical findings suggested that CD56, in addition to cytokeratin and chromogranin A, may be a useful marker for early detection of NEC. We conclude that patients with XHIGM should be carefully followed to diagnose and treat NEC, a formidable neuroendocrine cancer.
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CHARACTERIZATION OF A NEW DISEASE-CAUSING MUTATION IN A FAMILY WITH X-LINKED LYMPHOPROLIFERATIVE DISEASE

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Males with an expressed mutation in the SAP (signaling lymphocyte activating molecule [SLAM]-associed protein) gene have an X-linked syndrome characterized by an increased vulnerability to infection with Epstein-Barr virus (EBV). We evaluated two related male patients with fatal infectious mononucleosis (FIM) and mutation in the SAP gene. Sequence analysis revealed hemizygous G to A transition at nucleotide position 47 in exon 1 in one of the patients, and heterozygosity for this mutation in the genomic DNA from his mother and maternal grandmother. This mutation resulted in asparagine instead of glycine in the sequence of the SAP protein at amino acid position 16. To analyse the effect of this missense mutation on protein function cDNA was generated by site-directed mutagenesis and cloned in pCMV-FLAG vector. We found that the mutant SAP (SAP/G16D) protein was defective in protein folding as manifested by the reduced half-life compared to that of wild type SAP. Furthermore, the SAP/G16D protein was defective in binding to its philological ligands SLAM and 2B4. These results suggest that defects in protein folding and ligand binding collectively contribute to the loss of function of the SAP protein in patients carrying G16D mutation.
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NEW DEDICATOR OF CYTOKINESIS 8 MUTATIONS IDENTIFIED BY MULTIPLE LIGATION-DEPENDENT PROBE AMPLIFICATION

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Dedicator of cytokinesis 8 (DOCK8) deficiency is an innate error of adaptive immunity characterized by recurrent viral, bacterial and fungal infections, very high serum IgE concentration and a progressive deterioration of T- and B cell-mediated immunity. Traditional Sanger sequencing may fail to identify mutations in *DOCK8,* due to overlapping large deletions in heterozygous patients. We studied the genetic and immunological features of two sisters (11 and 6 years of age) born to healthy Hungarian parents. Mutational analysis of genomic DNA and cDNA from the patients and parents by a combination of PCR and bidirectional targeted sequencing failed to identify the mutation. However, a multiple ligation-dependent probe amplification (MLPA) assay revealed two previously unknown large deletions, del1-14 exons and del8-18 exons, of *DOCK8* in both patients. The children's mother was heterozygous for the del1-14 exons mutation, whereas the father carried the del8-18 exons deletion. Immunoblot analysis showed an absence of DOCK8 protein from the peripheral blood lymphocytes of both patients. These data suggest that the new compound heterozygous del1-14 exons and del8-18 exons mutations result in a loss of DOCK8 protein function and a typical DOCK8 deficiency phenotype. Our findings suggest that traditional sequencing technology may give misleading results in such cases and that MLPA may be indispensible for the definition of the large deletions frequently observed in patients with DOCK8 deficiency.
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INVASIVE CRYPTOCOCCUS LAURENTII DISEASE IN A 9-YEAR-OLD BOY WITH X-LINKED HYPERIMMUNOGLOBULIN M SYNDROME

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We describe here a patient with invasive *Cryptococcus laurentii* infection and the X-linked form of hyper-IgM syndrome (X-HIGM). *C.laurentii* is an extremely rare human pathogen. This fungus was previously considered saprophytic and non-pathogenic to humans, but it has been isolated as the etiologic agent of skin infection, keratitis, endophthalmitis, lung abscess, peritonitis, meningitis, and fungemia. Most affected individuals had a compromised immune system because of leukemia, cancer, diabetes mellitus, AIDS, or prematurity. Repeated isolation of *C.laurentii* from

the oropharynx of an immunocompromised patient has also been documented. Invasive *C.laurentii* infection has not been reported in patients with any form of primary immunodeficiency disorder emphasizing the true rarity of disease due to this fungus.
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GENETIC CHARACTERISTICS OF EIGHTY-SEVEN PATIENTS WITH THE WISKOTT–ALDRICH SYNDROME

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The Wiskott–Aldrich syndrome (WAS) is an X-linked recessive immune deficiency disorder characterized by thrombocytopenia, small platelet size, eczema, recurrent infections, and increased risk of autoimmune disorders and malignancies. WAS is caused by mutations in the WASP gene which encodes WASP, a 502-amino acid protein. WASP plays a critical role in actin cytoskeleton organization and signalling, and functions of immune cells. We present here the results of genetic analysis of patients with WAS from eleven Eastern and Central European (ECE) countries and Turkey. Clinical and haematological information of 87 affected males and 48 carrier females from 77 WAS families were collected. The WASP gene was sequenced from genomic DNA of patients with WAS, as well as their family members to identify carriers. In this large cohort, we identified 62 unique mutations including 17 novel sequence variants. The mutations were scattered throughout the WASP gene and included single base pair changes (17 missense and 11 nonsense mutations), 7 small insertions, 18 deletions, and 9 splice site defects. Genetic counselling and prenatal diagnosis were applied in four affected families.

CLINICAL AND LABORATORY FEATURES OF PATIENTS WITH MHC-CLASS II DEFICIENCY

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Introduction: MHC-Class II deficiency is an autosomal recessively inherited combined immunodeficiency disorder characterized by less than 5% expression of HLA-DR on B cells or monocytes. It is caused by mutation of genes (CIITA, RFXANK, RFX5, RFXAP) regulating transcription factors which controls expression of MHC-Class-II molecules on cell surface. MHC-Class II molecules are expressed on thymic epithelial cells, antigen presenting cells (B lymphocytes, dendritic cells, monocytes and macrophages) and activated T cells. These molecules are of critical importance to immunity, CD4+ T cell development, antibody production, tolerance induction and inlammatory response. Consequently, patients present with clinical findings related to combined immunodeficiency during infancy.
Material and Methods: Medical records of thirteen patients with MHC-Class II deficiency, followed-up in Ankara University, Medical School, Division of Pediatric Immunology/Allergy from 1999 to 2013, were evaluated retrospectively.
Findings: During study period, 6 male and 7 female patients were diagnosed with MHC-Class II deficiency. Age of diagnosis were between 3 months and 4 years of age. Consanguinity were present in eleven out of thirteen patients. Most frequent clinical findings during initial diagnosis were failure to thrive, pneumonia and oral moniliasis. Lymphopenia was absent in all of the patients, however, low serum IgG level was present in all of them. Except for the 15 yo female patient with a positive family history and whose HLA-DR expression was 0,2%, HLA-DR expression was 0% in the rest of the patients. Eight patients underwent hematopoietic stem cell transplantation (HSCT). Two patients were lost soon after HSCT due to complications and three patients died of opportunistic infections. Four patients died of severe opportunistic infections without underwent HSCT.
Results: MHC-Class II deficiency is a combined immunodeficiency and not considered a rare disease in our country. To date, only known treatment is HSCT. Since it has poor prognosis, HSCT should be performed before development of chronic viral infections and sequelae related to infections in patients who have HLA-matched sibling.

LATE-ONSET PURINE NUCLEOSIDE PHOSPHORYLASE DEFICIENCY WITH SPASTIC PARAPLEGIA

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Purine nucleoside phosphorylase deficiency (PNP deficiency) is a rare autosomal recessively inherited type of immunodeficiency. PNP deficiency constitutes about 1 to 2 percent of all combined immunodeficiencies. It is characterized by progressive combined immunodeficiency and neurologic findings which includes ataxia, developmental delay, and spasticity. The immunodeficiency is progressive, with normal immune functions at birth, but severe T cell deficiency with variable B cell functions presented by the age of 2 years . The only curative treatment is the hematopoietic stem cell transplantation (HSCT). Here, we present a 14 year-old girl with recurrent respiratory tract infections, short stature and spastic paraplegia. Immunological, biochemically and genetics investigation revealed PNP deficiency with A117T mutation in PNP gene.

Case report: A 14 years-old girl was referred to our pediatric immunology clinic for recurrent sinopulmonary infections since 6 year of age. She was full term neonate and her parents were not consanguineous. She had a history of prolonged and resistant bronchopneumonia, and an attack of generalized chickenpox complicated with pneumonia. She had also severe zona infection resolved with ulceration in cornea, one year ago. She has been suffering from frequent infections like chronic sinusitis, oral moniliasis, recurrent pneumonia and sclerosing cholangitis. She has also nonprogressive cerebral palsy, spastic paraplegia, behavioral problems and limited motor and mental retardation. There was no family history of recurrent infections or immunological disorders. On her physical examination, there was failure to thrive, (her weight and height <3rdp) oral moniliasis, bilateral crepitus ralls, and splenomegaly. She has also marked spasticity with brisk reflexes in lower extremities.
Laboratory tests revealed lymphopenia: hemoglobin 11 g/dl and platelets 158000/mm^3 WBC 4000/mm^3, absolute lymphocyte 560/mm^3. The laboratory results are shown in the **table**. Lymphocyte proliferation is lower than normal limits in response to PHA stimulation (WST1 assay). PPD response and HIV was negative. AntiHbs, and antiHAV were negative despite vaccination. Uric acid level 1,8 mg/dl. Direct Coombs was negative, thyroid autoantibodies were within normal limits. Genetic analysis revealed homozygous **missense mutation (c.349G > A), which causes the A117T amino acid substitution in PNP gene, in exon 4, which has previously been reported.** Additionally, a homozygous G/A polymorphic site in IVS3 has been detected (c.285 + 10G (IVS3 + 10G)).
Discussion: PNP deficiency is caused by mutations in the PNP gene at 14q13.1. This gene encodes the protein purine nucleoside phosphorylase, one of the enzymes involved in the purine salvage pathway. Adenosine deaminase (ADA) deaminates adenosine to yield inosine, which is then converted to hypoxanthine by PNP. PNP also converts guanosine to guanine. A number of metabolites are elevated in the plasma and urine in PNP deficiency, including deoxyguanosine and deoxyinosine. There is an intracellular accumulation of their deoxy triphosphate compounds, particularly deoxyguanosine triphosphate (dGTP). The latter is toxic to T cells, a property similar to deoxyadenosine triphosphate in adenosine deaminase deficiency.
In this report, we demonstrate the clinical characteristic of the patient with late diagnosis of PNP deficiency. PNP mutations likely lead to an intense alteration of the enzyme activity which in turn, cause severe and early onset of the clinical findings. However, in our case, the clinical onset of the disease is quite late (after 6 years) which can be explained by the residual activity of the PNP. In conclusion patients with PNP deficiency can be late onset. Additionally, late diagnosis of this patient can cause severe comorbidity which limits the chance of bone marrow transplantation.
Table: Immunological and biochemical investigations of the patient

	14 yrs	*Normal Ranges*
Immunnoglobulin levels	183	43-207
IgM (mg/dL)	50	14-159
IgA (mg/dL)	9	0-230
IgE (IU/mL)	713	345-1236
IgG (mg/dL)		
absolute lymphocyte	560/mm^3	43-76
Lymphocyte subsets(%)	33	23-48
CD_3 (%)	14	14-33
CD_4 (%)	15	14-44
CD_8 (%)	16	4-23
CD_{19} (%)	33	
$CD_{16\text{-}56}$ (%)		
PNP activity (nmol/h/mg Hb)	18.4	1354 ± 561
ADA activity (nmol/h/mg Hb)	52	26.4 ± 10.0
Guanosine (μmol/g Hb)	2.6	<1.1
D-guanosine (μmol/g Hb)	0.17	0
Inosine (μmol/g Hb)	33.6	<16.83
D- Inosine (μmol/g Hb)	1.5	<0.08

SCREENING DI GEORGE SYNDROME WITHIN ONLY ONE TUBE IN CASES WITH CONGENITAL CARDIOPATHIES

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Di George syndrome, a disorder caused by a defect in chromosome 22 (22q11.2 deletion), results in the poor development of several body systems. Clinical features include congenital heart defects, hypoparathyroidism and thymic hypoplasia or aplasia leading to T-cell immunodeficiency. The aim of our study is to screen and determine the incidence of Di George syndrome within only one tube of blood in children with congenital heart anomalies in our population.
Children who were found to have a cardiac defect during routine visits in pediatric cardiology and neonatalogy departments were included into the study. Cases with known genetic syndromes and newborns younger than 32 gestational weeks of age and small for gestational age (birth weight <2500 gr) were excluded. A total of 136 patients were included. There were 79 (58%) males and 57 (42%) females. Age ranged between 0-80 months (10.2 ± 15.9 months). Parental consanguinity was 17% (n = 23) in the study group. The majority of patients diagnosed after murmur was heard during the routine physical examination (n = 62, 46%). Five patients (3%) diagnosed antenatally. Remaining clinical signs on admission were as follows; respiratory distress (n = 33, 24%), tachycardia (n = 20, 15%) and central cyanosis (n = 16, 12%). Echocardiagorafic examinations revealed ventricular septal defect (VSD) (n = 27), tetralogy of fallot (TOF) (n = 17), VSD-ASD (n = 13), aortic coarctation (n = 11), double outlet right venticle (DORV) (n = 10), transposition of the great arteries (n = 6), truncus arteriosus (n = 5) and pulmonary atresia (n = 6). Pulmonary stenosis, endocardial cushion defects, total pulmonary venous return anomaly and hypoplastic left heart were the other defects. 22q11.2 deletion was ascertained in 7 (5.1%) patients; these patients were diagnosed to have TOF (28.6%), truncus arteriosus (14.6%), DORV (14.3%), VSD (14.3%) and VSD-ASD (14.3%).
Preliminary results of the study showed that the frequency of 22q11.2 deletion is 5% in patients with known cardiac defects. Single tube of blood is enough for flow cytometric and genetic analyses. Further studies involving higher number of patients is mandatory to give sufficient information about the exact incidence of the disease.

DI GEORGE SYNDROME – WHERE DO WE STAND NOW?

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Di George syndrome (DGS) classically comprises T-cell deficiency (due to thymic hypoplasia), hypoparathyroidism, cardiac malformations,and facial abnormalities. Deletions of the long arm of chromosome 22 at position q.11 are most commonly associated with DGS. Syndrome is also found associated with other genetic abnormalities (10p deletions, CHAR GE), certain teratogenic influences (retinoid acid, foetal alcoholic syndrome, maternal diabetes). The DGS phenotype is very heterogenous with variable expression of the different features including the immunodeficiency. The initial treatment emphasis is to control the hypoparathyroidism. Correction of congenital heart defects (if present) is usually needed. The best treatment of the immune defects of DGS is still controversial. Both HSCT and transplant with fetal thymus are the option for complete DGS (cDGS). Long term survival after HSCT has been reported, though at a lower rate (41–48%) compared to survival after HSCT for SCID. Survival in the subgroup receiving matched sibling donor

transplants was better at over 60%. The use of post natal human thymus was pioneered by Markert at Duke University and has become established as the treatment of choice for cDGS, with the result of 43 out of 60 treated patients survived (72%). More recently this approach has also been used in London, at GOSH. . Under care of CMHI there are119 patients fulfilling ESID criteria, 59 girls (49.6%) and 60 boys (50.4%), age 2/12 - 23 y.o. In 70% of them 22q11 deletion in locus D22S75 was found. The vast majority children were diagnosed as partial DGS. None of them had significant hypogammaglobulinemia and no regular IVIG therapy or antibiotic prophylaxis were required.. The mean number and percentage of CD3, CD8 and CD4 lymphocytes as well as lymphoproliferative answer to PHA and CD3 in DGS patients were slightly diminished. In many improvement of cellular immunity was observed with age. About 86% presented with congenital heart disease, requiring surgery, while almost 50% had the symptoms of hypocalcemia and hypoparathyroidism, next 46% - speech and learning difficulties. One child was diagnosed as cDGS. The child underwent cardiac surgery (at age of 6 m.o.), followed by twice thymus transplantation (12 m.o. and 2 y.o. at GOSH, London, by Dr. G. Davies). Clinical course was complicated by B cell lymphoma (19 m.o.), inflammatory bowel disease (6 m.o., resolved spontaneously after TTX), local BCGitis, thyroiditis. Now the child is doing well, still treated due to hypoparathyroidism and thyroiditis. The prognosis of DGS is quite varied. Most patients undergo spontaneous T-cell improvement. No genotype/phenotype correlation was established among pDGS.

SEVERE COMBINED IMMUNODEFICIENCY (SCID): ANALYSIS OF 17 LATVIAN PATIENTS

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SCID is a rare, inherited condition, is caused by numerous molecular defects that lead to severe compromise in the number and function of T cells, B cells, and occasionally natural killer cells.
Seventeen patents with SCID were registered during the period from 1994 till 2013 in the Children's Clinical University Hospital. Medical charts of these patients have been reviewed. There were 9 boys and 8 girls. Positive family history was in 4 families. Mean age at the onset of symptoms and SCID diagnosis was 1.7 ± 1.23 and 4.03 ± 1.6 months, respectively. Pneumonia (65%), candidacies (65%), BCG infection (47%), diarrhea (35%) were the most important infections. Anemia and relative lymphopenia were in 76% cases , growth retardation, hypotrophy had 59% children . Pathogens such as *Candida albicans* (11), *Mycobacterium tuberculosis complex* (8), *CMV* (3) and others have been identified. Totally 15 patients died.Two girls are alive (29 and 17 months post-transplant). Autopsy was done in 8 patients. We saw different changes in thymus and lymphatic nodes. Artemis deficiency (n = 1), T-B- SCID (n = 4), T-B + SCID (n = 5), γc deficiency (n = 1 mutation R224W in γ-chain of receptor for IL-2), unspecified SCID (n = 6) were detected.
Conclusion: Generalized BCG infection had 47% of our SCID patients. (Incidence of TB is still high 36.2 / 100 000 population in Latvia and newborns obligatory are vaccinated on the second to fifth day of life). Due to possibility of absence for PID routine genetic identification in only few SCID forms were identified precisely.

CLINICAL HETEROGENEITY OF IMMUNODYSREGULATION, POLYENDOCRINOPATHY, ENTEROPATHY, X-LINKED: PULMONARY INVOLVEMENT AS A NON-CLASSICAL DISEASE MANIFESTATION

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Purpose: IPEX (Immunodysregulation, Polyendocrinopathy, Enteropathy, X-linked) is a rare X-linked recessive life-threatening disorder characterized by autoimmunity and early death. Pulmonary complication related with IPEX has not elucidated exactly. Here, we report 4 I.E. patients, 3 of which died from severe pulmonary disease.
Methods: Clinical data and laboratory findings included autoantibodies, immunoglobulin levels as well as number of T, B and NK cells were evaluated. FOXP3 expression was performed by flow cytometry. Genomic DNA was isolated and all exons and exon-intron boundaries of the *FOXP3* gene were sequenced by Sanger sequencing.
Results: Patient I (PI) presented with nephrotic syndrome at 3 years of age and then developed autoimmune hepatitis without eczema, enteropathy or high IgE and died at 9 years of age due to acute respiratory distress syndrome (ARDS). Two cousins of PI had the same hypomorphic splice site mutation leading to normal FOXP3 protein expression and suppressive capacity. However, they exhibited typical symptoms such as eczema, diabetes and enteropathy with eosinophilia at early age (PII, PIII) and were transplanted in infancy. One of them had severe respiratory distress right after birth (PIII). Patient IV from another family presented with chronic diarrhea without autoimmune manifestations and died due to ARDS.
Conclusion: Lung disease related to IPEX syndrome has not been reported before and this entity could be a critical factor in disease outcome.
Key words: IPEX, FOXP3, clinical heterogeneity, lung involvement.

OUR EXPERIENCE IN SCREENING FOR SCID IN EGYPTIAN CHILDREN USING TRECS

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Severe combined immunodeficiencies (SCIDs) are a group of primary immunodeficiencies that comprise a number of monogenic disorders characterized by a block in T cell differentiation with or without impairment of B cell and natural killer (NK) cells. Without early diagnosis and treatment most children die in the first year of life. A lack or very low number of T-cell receptor excision circle (TREC) detected by realtime quantitative polymerase chain reaction assay (qPCR) is consistent with T-cell lymphopenia and has repeatedly demonstrated clinical validity in population based newborn screening for SCID. However, the impact of population screening will be less in communities with high consanguinity and family history of SCID, in

which targeted screening may be more appropriate. Here, we screened 100 high risk neonates and infants (with one or more of the following: clinical presentation and/or family history suggestive of PID, failure to thrive otherwise unexplained, lymphopenia) at Cairo University Hospitals. Their full history and clinical examination were recorded. Immunoglobulin profile and immunophenotyping of peripheral lymphocytes were performed as confirmatory tests. Sixteen classical SCID cases were detected, as well as another 2 SCID variants (Omenn syndrome and Major Histocompatibility Complex class II deficiency) (totally 18.4% of all subjects screened). The rate of consanguinity in this group was 77.8%. Secondary causes of Low TRECs, other than SCID, in our series included: bacterial septicemia (4 preterm, 1full-term), prematurity (2 cases), one preterm with omphalocele and facial dysmorphism, one preterm with Congenital Adrenal Hyperplasia, one full term with Microvillus Inclusion Disease, and one full term with Idiopathic T-cell lymphopenia. This demonstrates that in populations with high consanguinity rates, as in Egypt, targeted (non-population based) TRECs assay may provide a more efficient screening strategy.

FACE THE MONSTER IN DEVELOPING COUNTRIES HLH: TWO CASES WITH UNUSUAL PRESENTATIONS

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CASE 1: A is a 4 years old Female, 1st kid of non consanguineous marriage presented with fever for 5 months. One week after the onset of the fever red patches appeared on the face, hands, abdomen, LL. Mother sought medical advice and received antibiotics, antipyretics and oral steroids for about one month with no signs of improvements regarding fever. One week later the mother noticed pallor and sought medical advice and the baby was admitted to local hospital and received one bag of blood. And then she was referred to our hospital **(Zagazig University Hospital)** where she developed acute pallor again which needed recurrent Blood transfusions. Dark colored urine occurred in frequent attacks with abdominal enlargement and pain, and interestingly upto this time, no improvement regarding fever, bone pain or pallor. On examination she was Underbuilt (all parameters are under 3rd centile), pallor, tinge of jaundice, generalized skin pigmentation, **generalized lymphadenopathy**, 2nd degree clubbing and **HSM**
Investigations: CBC (pancytopenia with reticulocytopenia) - LFT (increased AST with indirect hyperbilirubinemia)- KFT (normal)- LDH (Highly elevated 7238 U/L)- ESR (105) - **Fibrinogen (0.336 gm/ L)- serum triglycerides (315.7 mg/dl)- EBV-VCM IgM positive and IgG negative** - C3 (1.3 normal) – RF and ANA(-ve) – **Serum ferritin (32436 ng/ml) – CD 56 is low** – Bone marrow biobsy revealed dysplastic changes – L.N. biopsy revealed non specific inflammatory changes.
Treatment: HLH protocol 94 with no SCT
Prognosis: patient passed initial phase with complete resolution and waiting for BMT
CASE 2: M is 4 months old boy, 2nd kid of non consanguineous marriage (the 1st is healthy 3 years old female) presented with fever and difficult breathing since the age of 2 months. The fever was of gradual onset stationary course and not responding to treatment with antipyretics and antibiotics. One week later the mother noticed abdominal enlargement with red rash over the abdomen that was associated with pallor but there was no evidence of bleeding from any site, no change in the color of urine, no jaundice, no ecchymosis, no joint swelling then he is referred to our hospital **(Zagazig University Hospital).** This boy is delivered by NVD at term with no evidence of any problem either during pregnancy or delivery, he is exclusively breast fed and vaccinated as scheduled. **Examination:** his weight was 6 kg, length 53 cm, and head circumference 35 cm all are average for age, he was pale with no jaundice or cyanosis he had HSM and other systemic examination was quite well.

Investigations:

- CBC: HB 8 gm/dl , PLT 24000 and WBC 5.1 with normal differential count
- LFT: normal apart from mild elevation of AST (45 u/l the high level is 40 u/l) and mild hypoalbuminemia 2.6 gm/dl.
- KFT: normal
- LDH : highly elevated 1052 u/l (normal upto 387)
- ESR : elevated 25
- PT and PTT : both were prolonged more than one minute
- Fibrinogen: 0.1 g /l
- Serum triglycerides : elevated (171.6 mg/dl N.upto 160)
- Ferritin : 1942 ng / ml highly elevated
- BM biopsy: hypercellular with macrophages engulfing RBC's , platelets and neutrophils **(shown in figure 2)**

Treatment: HLH 2004 with no SCT
Prognosis: Patient died at week 7 from fulminant infection

ECONOMIC EFFICIENCY OF SCREENING OF NEWBORNS IN THE URAL REGION

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Children with PID usually are admitting to the hospitals and intensive care units of infants' pathology Regional Children Clinical Hospital №1, but at a later date, in serious condition, after the development of clinical manifestations in the form of severe generalized infectious disease, or various complications including hematological.
The screening technology approves children to be diagnosed in newborn period and to be observing by immunologist and hematologist for the next preventative therapy and bone marrow transplantation or hematopoietic stem cell transplantation.
Costs for the differential diagnosis and verification of the diagnosis before the manifestation and complications development of PID – 51 245 USD.
Costs for the differential diagnosis and verification of diagnosis after manifestation and complications development of PID would be 115 208 USD in 2 months.
Economic loss prevention in PID – 63 872 USD. Economic loss prevention in T - lymphopenia – 105 884 USD. We also should include into account the contribution to the state's economy, which will later be obtained, due to the presence of a healthy member of society.

HYPER IGM SYNDROME AS A PRESENTING SIGN OF ATAXIA TELANGIECTASIA AND A.T LIKE DISEASES(REPORT OF THREE CASES)

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AT is an autosomal recessive multisystem disorder characterized by progressive cerebellar ataxia, telangiectasia and increased susceptibility to infections and malignancies, particularly lymphomas and leukemia. *Laboratory immune investigations typically show decreased peripheral T cells, particularly of naïve T cells, with abnormal in vitro response to mitogens.* Most AT patients have decreased serum IgA and IgG subclass concentrations.

While about 10% of patients with AT show raised serum IgM concentrations during the course of the disease, it is unusual to find a high level of IgM at onset.

As cerebellar ataxia and oculocutaneous telangiectasia are not present at very young age, these patients are often erroneously diagnosed as hyper IgM syndrome (HIGM). To prevent mistaking A-T patients for HIGM it is proposed to add DNA repair disorders as a possible cause of HIGM. . Diagnosis of AT, suggested by elevated alfa-feto-protein and increased sensitivity of patients' cells to irradiation, can be confirmed by identifying a mutation in the ATM gene.We report 3 female case of AT that with diagnosis of hyper IGM received IVIG but later they had manifestation of ataxia in the course of their disease and then had telangiectasia of conjunctiva.

First case was a 3 yrs girl that was suffered from ITP and granulomatosis lesion of skin associated with Hyper IgM before AT diagnosis.

Second case was a 6 years old girl with microcephaly, sever FTT , neurodevelopmental delay , abnormal faces and hypo and hyperpigmentation lesions and anemia. With respect to these manifestation and increased AFP ,Nijmegan breakage syndrome was suggested. Third case was suffered from HyperIgM before A T diagnosis for 2 years.

DOCK8 DEFICIENCY: A SINGLE UNIQUE CASE

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We present a patient with a DOCK8 deficiency. Mutations in the dedicator of cytokinesis 8 gene (*DOCK8*) cause a combined primary immunodeficiency syndrome that is characterized by elevated serum IgE levels, depressed IgM levels, eosinophilia, sinopulmonary infections, cutaneous viral infections, and lymphopenia.

Onset of the disease was observed at 1-month of age with severe eczema and recurrent respiratory infections (pneumonia, bronchitis, otitis). At 5 years of age neuroblastoma was diagnosed. From the age of 6 years he started with severe skin infection , subsequently recurrent mucocutaneous aspergillosis was established based on skin biopsy and bacteriological studies. Immunological investigations revealed persistent leukocytosis, hypereosinophilia, low level of IgM and increased IgE up to 5 000 IU/ml. So Hyper IgE syndrome was diagnosed and genetically confirmed when a large deletion of the DOCK8-gene was identified. Stem cell transplantation was performed in 2012 when the patient was 11 y.o. One year later progressive multifocal leukoencephalopathy secondary to infection by Polyomavirus JC was diagnosed. But after immunosuppressive therapy with Cyclosporine A was suspended our patient's condition improved: the load of Polyomavirus JC on plasma showed a decrease; MRI brain was essentially stable ; immunological tests showed an initial improvement of subpopulations and proliferative response to mitogens; donor chimerism 100% stable.

RECURRENT WHEEZING AND HYPOGAMMAGLOBULINEMIA DURING INFANCY

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Background: Bronchiolitis and infantile asthma are the most frequent causes for typical wheezing signs in infants. However, when a physician comes across patients with recurrent wheezing are resistant to β2-agonist and anti-cholinergic therapy, known as atypical wheezing cases; he should investigate for hypogammaglobulinemia in these patients.

Aim: Here, three cases are reported to make pediatricians aware of hypogammaglobulinemia, which is one of the reasons causing recurrent and persistent wheezing attacks during infancy and beyond.

Case presentations: Case 1: 24 month-old girl presented to us with complaining of coughing and persistent wheezing. She has been having wheezing and breathing difficulty for the last 2 months after she got upper respiratory tract infection. Her symptoms persisted even though she was using religiously nebulized salbutamol + budesonid therapy. Before this episode, she had had 9 other wheezing attacks in her past medical history beginning from 2 months of age. In her family history, her father has asthma. Physical examination revealed her breathing difficulty. Ronchi as well as rales were heard on the auscultation of her lungs. At the fourth day of admission, she was given IVIG 500mg/kg/dose. Later, her symptoms did improve and not recur for the last 5 months. Laboratory findings showed normal routine biochemistry, complete blood count and sedimentation rate. Chest X-ray showed normal findings. Echography was normal. pH-metry for reflux investigation was normal. Sweat test was normal. In the serological evaluation: low IgG level for his age (358 mg/dl) was detected at two different times. IgG subgroups, IgM (156 mg/dl), IgA (34 mg/dl) and IgE (68) levels were within normal.

Case 2: 8-month-old girl came to our outpatient clinic with complaints of coughing and wheezing. At 2 months of age, she had urinary and upper respiratory tract infections. Despite antibiotic therapy, wheezing persisted for 2 months and wheezing severity increased and it did not respond to β2-agonist therapy. Thereafter, she was admitted to the hospital for 7 days and symptoms resolved. However, she came back to hospital due to recurrence of her symptoms in 10 days. In her family history, grandmother and her cousins have asthma. Physical examination showed breathing difficulty. Ronchi as well as rales were heard on her lungs. Although salbutamol, ipratropium, antibiotherapy (clarithromycin) and anti-reflux therapies were given, her symptoms did not improve for 2 weeks. At the 15th day of admission, she was given IVIG 500mg/kg/dose. Later, her respiratory system symptoms did not recur for the last several months. Once she was evaluated for persistent wheezing attacks during admission, biochemistry, CBC, ESR were normal. Chest X-ray and echography were normal. In serological evaluation: low IgG level for his age (304 mg/dl) was detected at two different times. IgG subgroups, IgM (106 mg/dl), IgA (34 mg/dl) and IgE (<5) levels were normal.

Case 3: 20 month-old boy was brought to us complaints of having frequent lower respiratory tract infections (bronchiolitis). He was experiencing recurrent wheezing attacks almost every other week for the last 6 months. In past medical history, he was diagnosed with trisomy 21 and hypothyroidism at the 3 months of age. He went thru an operation for atrio-venticular septal defect. Physical exam revealed dyspnea, tachypnea and wheezing. Crackles were heard on the chest auscultation. Abdominal, cardio-vascular and the rest of the examination were normal. When he was evaluated for frequent wheezing attacks in our outpatient clinic, routine biochemistry, CBC and ESR were normal. Chest X-ray showed normal findings. In serological evaluation: low IgG level for his age (300mg/dl) was detected twice. IgG subgroups, IgM, IgA and IgE levels were within normal. He was given IVIG 400mg/kg/dose. For the last three months, he did not have any lower respiratory tract infection.

Conclusion: The awareness of immunodeficiency among pediatricians has been greatly improved. Recurrent respiratory tract infections are major infections in these patients. THI is a relatively common condition associated with infant hypogammaglobulinemia. In patients with recurrent and/or persistent wheezing symptoms during infancy and beyond, especially resistant to therapy, hypogammaglobulinemia should be excluded from possible diagnoses.

FOOD ALLERGY IN PATIENTS AFTER SOLID ORGAN TRANSPLANTATION

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Background: The acquisition of new food allergy after transplantation or transplant-acquired food allergy (TAFA) is usually reported in adults and rarely in children. TAFA is described mainly after liver, but also after small bowel/intestinal, lung and heart transplantations. In different studies, the male/female ratio is equal. Literature data suggest that children with TAFA typically present within the first year after surgery and they are typically allergic to multiple foods.
Aim: TAFA is generally characterized with allergy to multiple foods and increased level of total and/or spesific IgE. Here, a patient although who had normal total. IgE and specific IgE test results, he developed reaction to skin prick test for cow's milk is presented and his clinical presentation will be discussed.
Case presentation: 15 month-old- boy came to our allergy clinic with complaints of vomiting after drinking cow's milk and skin rush on the area where contact ed with chocolate. In his past medical histroy, left lateral segment of liver (donor was his mother) was transplanted to him when he was at 5 months. The liver donor was not recorded as having a history of allergic disease. Methylprednisolone and tacrolimus immunosuppression were used after the transplantation, and tacrolimus therapy was continued for prophylaxis of chronic rejection. When he was at 7 months, family fed the patient with cow's milk but 3 hours later he began to vomit. He vomited five times in two hours. Then, he developed constipation. Rectal irrigation was used. Then oral intake stopped for two days. He was thought to be having food protein induced enterocolitis. His vomiting complaints repeated after intake of formula and baby food which include grain. So he fed with special formula including short-chain peptides and free aminoacids and his symptoms improved. Past medical history: Extrahepatic biliary atresia was diagnosed at 3 weeks age with conjugated hyperbilirubinemia (according to scintigraphy and biopsy results). Family history: His father has penicillin allergy and his aunt has asthma. At our outpatient clinic: Height and weight were within normal percentiles. Physical examination reevaled normal examination findings. Laboratory findings: WBC was 4.420/mm3, with 21% neutrophils, 6% eosinophils and 69% lymphocytes. His hemoglobin was 8.2 g/dL , platelet count was 280.000/mm3. Total IgE : <5 and ImmunoCAP specific IgE against milk, grain and other classsic foods was <0.35. Skin prick test results: saline: 0x0mm, histamine 4x4mm, fresh cow's milk:2x2mm, other food allergens (peanut, egg, fish, soybean, wheat): 0x0mm.
Conclusion: Our patient seemed to have cow's milk allergy related to liver transplantation. Laboratory investigations and clinical presentation of the patient did not look like typical IgE–mediated food allergy, which is expected in TAFA.

AN ADULT PATIENT PRESENTED WITH EXTREMELY ELEVATED SERUM IGM, MASSIVE SPLENOMEGALY AND RECURRENT LOWER RESPIRATORY TRACT INFECTIONS

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Patient History: 33 years old male patient, The first pneumonia at the age of 18 followed by 3 times pneumonia attacks/year, otitis media and sinusitis. Hospitalization due to respiratory insufficiency caused by bronchiolitis obliterans and diagnosed with hypogammaglobulinemia at the age of 27. No consanguinity.
Patient findings at diagnosis (02/2008) had hepatospenomegaly, bilaterally cervical, supraclavicular axillar LAP, osteoporosis, bronchiolitis obliterans organizing pneumonia, hyper IgM, lower IgG, IgA, IgE, low B-cell. No response to tetanus toxoid. İsohemagglutinin AntiB was ¼. CD40,CD40L, AID, TACI, BAFFR, ICOS gene mutation were negative. Protein electrophoresis revealed polyclonal IgM increase, immunofixation was no clonality. lymph node biopsy result was available paracortical expantion . CD3(+) T and CD20 were positive. B lymphocyte distribution were normal. Malignancy ruled out. No giant germinal centers. Evaluation of bone marrow aspiration/ biopsy were abnormal localization of megakaryocytes, dismegakaryopoiesis, blasts in normal range. Lymphocyte ratio 10% mostly consisting of CD3+ cells, CD20+ cells were rare, Plasma cell ratio was 2%, amyloid negative. Progression of patient, IgM level and spnenomegaly were increased and patient had respiratory failure. Splenectomy could not be done due to respiratory failure. Than patient was treated with Rituximab (375mg/kg/week). After Rituximab therapy, lymph nodes and splenomegaly were (5 cm), regressed and IgM level decreased (from 4390 mg/dl to 2040 mg/dl), increased effort capacity. After 7 month after rituximab therapy splenomegaly and IgM level were progressed. Splenoctomy was performed. Pathological evaluation of the spleen malignancy ruled out. Current IgM level is 6300 mg/dl.
Conclusion: The most convinient scenerio for this patient would be a CSR defect of unknown etiology presented as CVID. The recent litarature revealed genetic defects of some molecules operating in DNA repair pathways such as MSH2, MSH4, MSH5, MSH6, MLH1, RAD50, RAD 52, NBS1 leading to CSR abnormality and impaired antibody maturation.

RHEUMATOID ARTHRITIS, SCLEROSING CHOLANGITIS AND RECURRENT THYMOMA IN AN ADULT CVID PATIENT

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CVID is characterized by hypogammaglobulinemia, recurrent respiratory and gastrointestinal bacterial infections. Good's Syndrome(GS) is a thymoma-related immunodeficiency and characterized by hypogammaglobulinemia, decreased B cell and variable deficiencies in cell-mediated immunity.
Case: A 47-year old male patient presented with a palpable anterior chest wall mass. In 2005, he was diagnosed with rheumatoid arthritis. Laboratory showed hypogammaglobulinemia and all autoantibodies were negative. $CD19^+$, $CD20^+$, $CD22^+$ cells were <1%. Bone marrow(BM) examination demonstrated low $CD20^+$ B-lymphocyte and increase in $CD3^+$ T cells. Tuberculin skin test was positive. T-cell proliferative response was normal. Immunizations with *H.influenzae type-b* and tetanus toxoid revealed no response. Anti-B titer was low. TACI, Btk and ICOS mutattions were negative. Ultrasonography showed hepatosplenomegaly. Mild edema, mononuclear cell infiltration (suggested the early stages of extrahepatic biliary obstruction) were detected on liver biopsy. In the medical history, he had reported chronic sinusitis, otitis and bronchitis dating back to 3rd decade of life. At age 38, he underwent surgery for thymoma.

In follow-up, the computed tomography showed soft tissue mass on the anterior chest wall and pathology was thymoma.
Discussion: Frequent respiratory infections with encapsulated pathogens beginning at the age of 30, lack of opportunistic pathogen infections, presence of hepatosplenomegaly and rheumatoid arthritis, BM examination findings and successful management of infections with IVIG therapy all indicated a diagnosis of CVID.
The coexistence of CVID and thymoma has been reported in the literature.

A CASE OF COMMON VARIABLE IMMUNODEFICIENCY ASSOCIATED WITH HEMOLYTIC ANEMIA

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Introduction: Common variable immunodeficiency (CVID) is a primary immunodeficiency disorder characterized by impaired B cell differentiation with defective immunoglobulin production. It has heterogeneous clinical manifestations including recurrent infections, chronic lung disease, autoimmune disorders, gastrointestinal disease, and susceptibility to lymphoma. Patients with this disorder have evidence of immune dysregulation leading to autoimmunity. Autoimmune cytopenias are a more common presenting disorder in children and may be the initial manifestation of the disease. We want to present a patient presenting with autoimmunue hemolytic anemia and finally diagnosed as CVID.
Case: A 15 years old, previously healthy female patient applied to emergency clinic with complaint of paleness, light headedness and yellow discoloration of her scleras. Her history was not compatible with blood loss. She denied having melena, hemotochezia or hematuria. Her mensturation history was also normal. Her hemoglobin level was 7.2 gr/dl, reticulocyte count was % 4.17, complete blood count was otherwise normal. Direct coombs was (+++). For the differential diagnosis of immune hemolytic anemia, viral serology, ANA and anti-dsDNA were studied, but the results were normal. IgG, IgM and IgA levels were lower than normal normal for her age. Other causes of hypogammaglobulinemia were excluded. Blood group was ARh (+), blood isohemagglutinin were Anti A(-) and Anti B (-/1+). Lymphocyte subsets were also studided. As the patient has reduced immunoglobulin levels with normal lymphocyte subset analysis, she presented after puberty and other defined immunodeficiency states were excluded, she was diagnosed as CVID and monthly immunoglobulin replacement therapy was planned. She had aseptic meningitis after her first IVIG transfusion. The IVIG preparation was changed with another trade and she did not have any problem during the following treatments. It has been one year since she was diagnosed and she did not have any other medical problems.
Conclusion: The diagnosis of CVID requires decreased IgG, IgM and IgA levels are also reduced but are less valuable for diagnosis. IgE level is checked to exclude other disorders. IgG subclass determinations are indicated if antibody titers are decreased but immunoglobulin levels are near normal. Hypogammaglobulinemia secondary to other disorders should be excluded. Autoimmune conditions can be the presenting signs/symptoms in CVID. Autoimmune hematologic disorders may precede, present at the time of diagnosis or develope during the course of CVID in approximately one-half of the patients with autoimmune problems.

SELECTIVE IMMUNOGLOBULINE M DEFICIENCY ASSOCIATED WITH ANGIOEDEMA

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Selective immunoglobuline deficiency is an uncommon dysgamaglobulinemia, in which immunoglobuline levels except IgM level are normal. It can be primary or secondary to cancer, autoimmune diseases, gastrointestinal system diseases and immunosuppressive therapy. Patients can be asymptomatic or have recurrent infections, asthma, angioedema, autoimmune diseases, celiac disease and bronchiectasis. Allergic diatheses are the second commonest presentation of selective IgM deficiency. In this presentation, we report a case with asthma and angioedema who has selective immunoglobuline M deficiency. A 16 year old male patient who has been diagnosed with asthma for 12 years with a well controlled asthma for 2 years presented with labial angioedema. He had labial angioedema daily without antihistamines. He did not have any suspected food or drug allergy. He did not have family history of angioedema. Physical examination was normal under antihistamine therapy. Laboratory evaluation revealed a 4.3% percentage of eosinophils. Absolute lymphocyte count was 2700, absolute neutrophil count was 7000 cells/mm^3. Immunoglobuline E value was 260 ng/ml, levels of immunoglobuline G and A were within normal limits for age. Immunoglobulin M value was 28.7 mg/dl (73-448). Anti A was 1/8, anti B was ½ positive, antiHbs was above 1000 mlu/mL. Lymphocyte subsets were normal. Because of the continuous usage of antihistamines, prick tests could not be done. Levels of D1 was17.8, D2 was12.4 kU_A/l. Thyroid functions, antiTPO, C3, C4 and C1 esterase inhibitor values were normal. Antinuclear antibodies and antitransglutaminase lgA was negative. Immunoglobuline M value of his father was normal, immunoglobulin M value of his brother was 53.50 mg/dl (88-322). Selective immunoglobuline deficiency is a rarely seen dysgamaglobulinemia. It was reported in children with asthma, but it was not reported in children with angioedema. It can have value in the clinical evaluation of patients with angioedema.

AUTOİMMUNE HEPATİTİS AND SCLERODERMA IN A PATİENT WİTH X-LİNKED AGAMMAGLOBULİNAEMİA

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A patient who is at age of 11 years at present and who has been followed up at the our clinic with XLA diagnosis presented with pain in his ankles and wrists and swelling of his right knee. He also was suffering from skin tightening of the lower extremities. His physical examination revealed arthitis of the right knee and sclerotic changes were detected in the skin.
Skin biopsy was performed and it revealed morphea (localized scleroderma). After the diagnosis of morphea and arthritis, IVIG 2 gm/kg and NSAID were applied. Following the treatment skin findings and arthritis resolved, however approximately two months later liver enzymes were detected to be high in his routine control. Liver biopsy performed to clarify the aetiology of elevated liver enzymes was reported as autoimmune hepatitis. In addition to IVIG 2 gm/kg, budenofalk 6mg/day was started. After 3 months of treatment, his liver enzymes normalized. Currently he is being treated with IVIG monthly and ursofalk daily.
Patients with XLA typically present with recurrent bacterial infections and it might be associated with some autoimmune diseases. There are not any reports indicating an associaton of autoimmune hepatitis and scleroderma with XLA.

BRUTON DISEASE DIAGNOSED WITH CERVICAL ABSCESS IN EARLY INFANCY

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Bruton agammaglobulinemia is an inherited immunodeficiency disease caused by mutations in the gene coding for Bruton tyrosine kinase (BTK). The median age at the diagnosis of the antibody deficiency is about 4.6 years in Turkey. Here, we report a case of Bruton Disease presenting with recurrent cervical abscess at two months old infant.
A 2-months-old boy was firstly hospitalized for the treatment of the right cervical abscess at 25 days old. After the recurrence of swelling on the cervical area, the patient was referred to the admitted to hospital secondly. There was no consanguinity between parents and, his family history was unremarkable except four of the mother's cousins, died because of unknown etiology in infancy.
On his physical examination, his weight, height andhead circumference were normal range by age. There were no visible tonsils. There was a palpable, mobile 1x1 cm mass on right upper cervical area. The Molecular analysis of the causal gene for Bruton's tyrosine kinase (BTK gene) revealed the mutation in exon 19. This mutation g.67662delG (c.1750 + 57del) leads to the changes of amino acid order in the protein with the subsequent changes in activity of BTK (at the level of DNA: substitution of glutamic acid (p.Glu507*) causes non-sense mutation leading to the formation of stop codon with premature end of DNA transcription to cause STOP codon. After initiating the intravenous immunoglobulin with antibiotics, the cervical mass was getting smaller in a short period, and had not observed again. Neutropenia was improved within the 3 months.
This case is an important example to diagnose Bruton Disease in early life. It demonstrates that maintaining a high level of clinical suspicion is essential for the diagnosis of Bruton Disease in a child with recurrent cervical masses.

THE EFFECT OF IVIG THERAPY ON SPECIFIC ANTIBODY RESPONSES IN CHILDREN WITH TRANSIENT HYPOGAMMAGLOBULINEMIA OF INFANCY

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Transient hypogammaglobulinemia of infancy (THI) is characterized by recurrent infections and reduced serum immunoglobulin levels. Typically, THI patients recover spontaneously, mostly within 30-40 months of age, but sometimes recovery may be delayed until 5-6 years. The use of intravenous immunoglobulin (IVIg) as an alternative to antibiotic prophylaxis remains contraversial also in symptomatic patients. Some authors believe that IVIg therapy may cause a delay in the maturation of the humoral immune system because of the interference from passively transfered antibodies. The aim of this study was to investigate the effect of IVIg replacement on recovery from immunodeficiency in these patients. 43 patients (65%) received IVIg therapy while 23 patients (34.8%) showed spontaneous normalization without IVIg. The percentages of patients who had more than six times the number of febrile infections in a year decreased from 91% to 21% in the group receiving IVIg treatment. At admission, before being recruited to IVIg therapy, serum immunoglobulin G (IgG) levels and anti-hemophilus B (Hib) antibody titers were found to be significantly low in cases who were selected for replacement. The percentages of patients who did not have protective levels of anti-Hib, anti-rubella or anti-rubeola-IgG were also significantly high in IVIg cases. There was no statistically significant difference in the age at which IgG levels normalized between both groups. Patients in the IVIg group and non-IVIg group reached normal IgG levels at the age of 42.9 ± 22.0 and 40.7 ± 19.8 months, respectively. In conclusion, IVIg infusions do not cause a delay in the maturation of the immune system in THI patients. The very low and non-protective specific antibody responses against previously applied vaccines are important factors to consider when selecting patients for IVIg therapy.

CHRONIC INFLAMMATORY DISEASES IN PATIENTS WITH sIgAD

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Objective: To study the amplitude of the chronic inflammatory phenomena: atopic and autoimmune diseases, as well as their associations in pediatric sIgAD patients and to study the sIgAD patients' family history (1st degree relatives) for PIDs (primary immunodeficiencies).
Methods: Retrospective analysis of the clinical and laboratory records of pediatric sIgAD patients diagnosed between 1998 and 2013 at the departments for Pediatric Immunology of the Medical Universities of Debrecen (Hungary), Oradea and Timișoara (Romania).
Results: Out of 148 patients, we found out 74 (50%) with atopic diseases, mostly with respiratory localizations (asthma and allergic rhinitis), 16 (10,81%) patients with autoimmune diseases (JIA, psoriasis, celiac disease, thyroiditis etc.) and other 15 patients without clinical symptoms of autoimmunity but constantly elevated autoantibody levels. There were 7 patients with coexistent atopic and autoimmune diseases. Regarding the family history, we identified 8 families with multiple cases of PIDs : 6 with multiple sIgAD, 1 with sIgAD and CVID, 1 with sIgAD and HIgMS (hyper IgM syndrome).
Conclusions: The chronic inflammatory phenomena are present in the majority of the studied sIgAD patients: symptomatic atopic diseases in 50%, symptomatic autoimmune diseases in 10,8%, that means a cumulative 61%. There are comorbid associations within the atopic and autoimmune disease groups and also between the two groups.

SELECTIVE IMMUNOGLOBULINE A DEFICIENCY IN LATVIA

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SIgAD is the most common primary immunodeficiency. It's prevalence is 1/400-1/800.
Aim was to assess the prevalence of co-morbidity in patients with SIgAD in Latvian pediatric population and the analysis of some immunological abnormalities in these patients. The study included 120 patients 4 – 18 years old. Medical charts have been reviewed. Into account were taken the data, which were made at time of diagnosis. Patients were divided into 4 groups: 1st - patients with allergic disease, 2nd - patients with autoimmune diseases, 3rd - patients with infectious diseases, 4th - asymptomatic patients or patients with SIgAD unrelated diseases. Patients with multiple co-morbidities of various disease groups were not placed in any of these groups. Each patient group was divided by age: 4 – 6 years, 7 – 13 years 14 – 18 years.
Results.58.4% were boys and 41.6% girls. SIgAD in 53.9% of the cases were diagnosed before 7 years of age (inclusive). 85% of the patients had co-morbidities: allergic (30%), autoimmune (37.5%) or infectious

diseases (17.5%). **Patients 4 – 6 years old:** children with infectious and autoimmune diseases have 1.3 times greater IgG than healthy children or children with allergic diseases ($p < 0,05$); children with autoimmune diseases has 1.9 times more CD8 cells than children with allergic diseases ($p < 0,05$).; children with infectious diseases have 2.1 times lower absolute number of CD25 cells than children with autoimmune diseases ($p < 0,05$); **Patients 7 – 13 years old:** children with infectious diseases have 1.5 times more absolute number CD25 cells than children with allergic diseases ($p < 0,05$).
Patients 14 – 18 years old: children with autoimmune disease have 1.6 times higher CD4/CD8 index than children with infectious diseases ($p < 0,05$)

COMMON MANIFESTATION OF PID

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We present clinical manifestations of different PID for gaining experience and knowledge systematization. We identify the following common manifestation in our register patients: clinical manifestations of infection, proliferative syndrome, autoimmune syndrome, allergy syndrome, disembriogenetic stigmas and congenital defects development, faillure to thrive.

A CASE WITH ABSENCE OF B LYMPHOCYTES

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Introduction: Antiepileptic drugs are known to cause immunosupression in some cases. Levetiracetam is an anticonvulsant medication used to treat epilepsy in the posttraumatic seizures. We report a rare case of hypogammaglobulinemia and B cell aplasia associated with levetiracetam treatment.
Case Report: A 45-year-old female was operated for pituitary tumor with transnasal surgery and required second operation for postoperative rhinorrhea. After operation, menengitis developed and antibiotic treatment was administrated. However, there was a poor response to this treatment after one month and craniotomy was performed due to the diagnosis of "shimic menengitis". Her seizures occurred as a postoperative complication and levetiracetam was initiated. After the 9-month follow-up, the findings of menengitis could not be controlled with antibiotherapy. She was referred to our immunology department for chronic menengitis with fever, headache and high cerebrospinal white blood cell count.
Results: In her clinical evaluation, it was learned that she had previously healthy. Laboratory examination showed that decreased levels of IgG 778 mg/dl (normal: 913-1884) and IgA 97 mg/dL (n: 139-378). Peripheral blood flow cytometric analysis revealed the absence of B cells (CD19+ B cells; <1%). T cell subsets and natural killer cell numbers were normal. Neutrophil function, chemotaxis, phagocytosis and oxidative burst activity were found to be normal. Isohemaglutinin titer, levels of pneumococal and tetanus specific IgG antibodies were also normal. Antiepileptic drug was discontinued after epileptic seizure was controlled. B cells gradually increased three weeks later and returned to normal within two months (CD19+ B cells: 9.8%).
Conclusion: Patients requiring levetiracetam should have serum immunoglobulins measured and lymphocyte subsets analysis performed if they experience recurrent or persistent infections.

BRONCHIECTASIS AND IMMUNODEFICIENCY

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Introduction: Common Variable Immune Deficiency (CVID) may present with several clinical manifestations involved in different organs and tissues in adults. We present a case with a history of chronic cough for more than twenty years and further diagnosed as CVID.
Case: A 49-year-old male who works in a chemistry lab admitted to our clinic with a history of frequent upper respiratory tract infections for more than 20 years. He also had intermittent diarrhea symptoms and his respiratory symptoms have been worsened since 2009. He had been hospitalized due to pneumonia and empyema several times. He had undergone left lower lobectomy due to bronchiectasis in 2012. He had been admitted to intensive care unit due to worsening of his medical condition. He was further diagnosed with CVID and IVIG treatment was initiated. He is currently under remission with monthly IVIG treatment and without any respiratory or gastrointestinal symptoms.
Discussion and Conclusion: CVID is a clinical disorder in which the humoral part of the immune system is affected. Most frequent presenting symptoms belong to respiratory, gastrointestinal systems and skin. However, due to the organ specific physical examination and lack of awareness, the diagnosis is frequently overlooked. In our case, frequent upper respiratory infection, loss of weight, diarrhea, bronchiectasis and empyema with unknown etiology are the most informative clinical signs. Medical history is the most important part of patient evaluation.

SCIG REPLACEMENT IN 7 HUNGARIAN PATIENTS: A SINGLE CENTER OBSERVATION

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Immunoglobulin replacement therapy is a basic treatment in primary immunoglobulin deficiency disorders. Immunoglobulin substitution can be given intravenously (IVIG) or subcutaneously (SCIG) for patients with antibody deficiency. Both of these treatments are effective in prevention and cure of infections, although differences in advers events profile and patients' quality of life can be seen. The authors describe here their experiences in switching patients from IVIG treatment to SCIG and a few years observation of SCIG therapy of patients with antibody deficiencies.

AUTOIMMUNE DISEASES IN PATIENTS WITH PRIMARY ANTIBODY DEFICIENCIES

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Antibody deficiencies are the most common group of primary immunodeficiencies. The main hallmark of antibody deficiencies are recurrent infections but the patients have also higher risk of autoimmune and allergic diseases. We analysed retrospectively the frequency and character of autoimmune diseases in 159 patients (98 children and 61 adult patients) with primary antibody deficiencies. There were ana-lysed 2 patients with XLA, 24 patients with CVID, 65 patients with selective IgA deficiency, 26 pa-tients with IgA/IgG subclass deficiency and 42 patients with isolated IgG subclass deficiency. Autoimmune diseases were found in 39 patients (24,5%) besides in 17 children (17%) and in 22 adult patients (36%). In two boys with XLA there was not found autoimmune diseases but in patients with other forms of antibody deficiencies in 12-57% of cases. Autoiimmune diseases were found more often in IgA/IgG subclass defi-ciency (57%) than in other forms of antibody deficiencies (0-25%). The spectrum of auto-immune diseases differed in adults and child-ren and in different forms of antibody de-ficiencies. Immune thrombocytopenia was found in adult patients with CVID or IgG subclass deficien-cy, autoimmune connective tissue disorders in IgA and IgA/IgG subclass deficiency. In children there was found mainly thyroiditis, diabetes I type and juvenile arthritis.

EFFECT OF REPLACEMENT THERAPY ON THE T-CELL FUNCTION IN PATIENTS WITH PRIMARY AGAMMAGLOBULINEMIA

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Primary Immunodeficiency (PI) is currently one of most important genetically determined immunological clinical pathology which is hard to manage . Among different types of PIs almost 60 % of cases occurs due to a deficiency in antibodies production. Injections of immunoglobulin are current standard in the management of PI. However this treatment is expensive, often is hard for patients, and frequently has limited effectiveness. Substitution of immune proteins frequently is inefficient for treatment of severe infectious conditions in PI patients. We investigated maturation, activation and differentiation of immune T-cells in the dynamics of IVIG replacement therapy. We observed patients with with CVID (7) and XLA (5 people) over a year of regular replacement therapy. We have found that recovery of the humoral component does not affect the maturation and the differentiation of T-cells, but can reestablish activation and regulatory properties. These changes are more evident among patients with CVID, which immuneregulatory and functional potential reestablish faster. Obviously, the effects T-lymphocytes increase the effectiveness of replacement therapy in patients with XLA, CVID

LYMPHOCYTE SUBGROUPS IN PATIENTS WITH COMMON VARIABLE IMMUNODEFICIENCY

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Common variable immunodeficiency (CVID) is one of the most frequent symptomatic primary immunodeficiencies. The diagnosis is based on significantly decreased levels of immunoglobulins, with poor or absent response to vaccines and by excluding other defined causes of hypogammaglobulinaemia. As suboptimal antibody production is mainly due to B cell defects, therefore, we aimed to study lymphocyte subgroups of CVID patients and to compare the patterns with the clinical presentation in these patients. Six adult patients with CVID diagnosis were studied. Lymphocyte subpopulations were determined by flow cytometry. For B-cells subgroups CD3, CD27, IgM and IgD reagents were used. All lymphocytes were gated for finding $CD19^+CD27^+$memory B cells and from this population switched ($CD19^+CD27^+IgD^-IgM^-$) and non-switched ($CD19^+CD27^+IgD^+IgM^+$) memory B cells were counted. All patients had normal levels of total lymphocyte count and absolute counts of $CD4^+$, $CD8^+$and $CD16^+/CD56^+$ cells were also normal in all patients. Only one patient showed low levels of $CD19^+$ cells levels. According to Paris classification scheme the patients could divided into two subgroups: MB0 and MB1. Although almost all our CVID patients had normal number of total B cells, most of them showed reduced number of memory B cells and/or switched memory B cells. All of our patients had very low or absent level of class-switched memory B cells, therefore can be possible associated with a higher risk of granulomatous disease and splenomegaly. Detailed investigation of B-cell phenotypes can better characterise CVID patients and can provide more information about possible clinical outcome.

C-HEPATITIS IN COMMON VARIABLE IMMUNODEFICIENCY

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Background: Common variable immunodeficiency (CVID) is one of the most frequent symptomatic primary immunodeficiencies, often related to spectrum of infectious and autoimmune diseases. In CVID patients wide spectrum of gastrointestinal disorders, including infections, are frequently seen. Inflammatory bowel disease, Helicobacter pylori infection, Giardia lamblia infection, Campylobacter or Salmonella infection have been reported. However, abnormal liver function test and liver disease are found in approximately 10% of CVID patients.
Case history: A 47-year old female patient was admitted to infectious disease department due to recurrent pneumonia and purulent rhinosinusitis. Blood analysis confirmed panhypogammaglobulinaemia with impaired responses to vaccinations, elevated liver function tests and anti-HCV positivity, interpreted as old and passed infection. Due to CVID intravenous immunoglobulin substitution was started. However, liver function tests remained elevated and with HCV-RNA analysis high hepatitis C viral load was detected. Chronic hepatitis C virus infection was diagnosed and treatment with peginterferon α-2a and ribavirin was started.
Conclusion: Our case emphasizes the need for HCV-RNA and HBV-DNA analysis in patients with hypogammaglobulinaemia, as the serological detection is impaired and prognosis for chronic hepatitis in immunodeficiency patients is poor.

PULMONARY CHANGES IN PRIMARY ANTIBODY DEFICIENCIES

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Background: Primary antibody deficiencies are the most frequent primary immunodeficiencies. Recurrent respiratory tract infections may

result in permanent lung damage in 20-40% of patients, most commonly presenting with the development of bronchiectasis. We aimed to evaluate the lung function and radiographic pulmonary changes in our patients with primary antibody deficiency.
Material and methods: We reviewed the records of adult patients with a confirmed diagnosis of primary antibody deficiency at our clinic. 10 patients were included in this analysis in whom CT scan was performed during the last 24 months, comprising 8 patients with CVID and two with IgG subclass deficiency (median age 33 years; range 19-68 years; 60% females). All patients were on regular immunoglobulin replacement and one of the patients was on prophylactic antibiotic at the time of analysis. Mean trough levels of IgG were calculated based on the results measured during the last 12 months prior to CT scan. The spirometry was performed according to published protocols.
Results: All patients demonstrated normal spirometry data based on FEV1 and FVC. Two patients had slightly lower MMEF rates, however, the changes were not associated with higher rate of infection nor changes in CT scan.
None of our patients had bronchiectasis or atelectasis. Among parenchymal changes fibrotic lines were most frequently detected. In two patients ground glass due to fibrosis was noted. Mean immunoglobulin trough levels in our patients were between 4.9–8.6g/L, with the median of mean trough levels of all our patients 6.9g/L. When comparing the trough levels to lung function and CT scan results, no significant associations were seen.
Conclusion: No remarkable changes in lung function or chest CT scan in our patients with primary antibody deficiency were noted. As regular immunoglobulin replacement therapy could have prevented the development of permanent lung damage.

EFFICACY, SAFETY AND TOLERABILITY OF RECOMBINANT HUMAN HYALURONIDASE-FACILITATED SUBCUTANEOUS INFUSION OF IMMUNOGLOBULIN G IN ADULT PATIENTS WITH PRIMARY IMMUNODEFICIENCIES: PHASE 3 STUDY RESULTS

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Rationale: Patients with primary immunodeficiencies (PI) (N = 83) were treated subcutaneously (SC) with immunoglobulin G (IG) preceded by recombinant human hyaluronidase (IGHy) at 3 or 4 week intervals based on their previous intravenous IG (IGIV) dose. We report data for a subset of 59 patients aged ≥18 years from the final efficacy, safety and tolerability data of a pivotal phase 3 trial of IGHy.
Methods: Patients received IGIV for 3 months at prestudy doses and frequencies. Subsequently, IG 10% was administered SC, at 108% of the weekly equivalent of the IV dose, following rHuPH20 infused through the same SC needle at a dose of 75 U/g IgG. After a ramp up from a 1- to a 3- or 4-week dose interval, 59 patients received IGHy every 3 4 weeks for 12 months. The primary efficacy endpoint was the mean rate of validated acute serious bacterial infections (SBIs) per patient-year during the efficacy period.
Results: Fifty-nine patients received 985 IGHy infusions; 97.8% were completed without administration changes due to tolerability concerns or adverse events (AEs). Median infusion sites/month was 1.13. The temporally associated systemic AE rate was 0.20/infusion (IGHy) vs. 0.33/infusion (IGIV). The local adverse drug reaction rate was 0.286/infusion. The annual SBI rate was 0.00 and 3.10/patient-year for all infections.
Conclusion: In adults with PI, IGHy was effective in preventing infections. The majority of patients received full 3- to 4-weekly doses of IG using a single SC site with good local and systemic tolerability.

LONG-TERM TOLERABILITY AND SAFETY OF FACILITATED-SUBCUTANEOUS INFUSION OF HUMAN IMMUNOGLOBULIN G, 10%, AND RECOMBINANT HUMAN HYALURONIDASE: A PHASE 3 EXTENSION STUDY IN PATIENTS WITH PRIMARY IMMUNODEFICIENCIES

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Rationale: In a pivotal phase 3 trial of facilitated-subcutaneous (SC) infusion of human immunoglobulin G (IgG), 10%, and recombinant human hyaluronidase (rHuPH20) (IGHy) in patients with PI, rHuPH20 permitted most patients to have a single-site infusion (every 3-4-week IgG dosing) with bioavailability and infusion rates comparable to intravenously administered IgG (IGIV). We report the final analysis of the long-term extension of the initial phase 3 study, with a duration of up to 3 years of treatment with IGHy plus additional follow-up.
Methods: Sixty-six patients who completed the initial phase 3 study enrolled in the Extension study. Patients continued their pre-study IGHy dose/frequency every 3-4 weeks. After 3 months, some patients switched to 2-week dosing to evaluate effects of shorter IGHy interval on trough IgG levels. From the final analysis, tolerability and safety after up to 3 years of treatment were evaluated. The IGHy part of the Extension study was followed by a 24–48 week observation period during which patients received IgG 10% administered IV, or SC weekly without rHuPH20.
Results: In the Extension study, 66 patients were treated with IGHy and 14 discontinued prior to safety follow-up. Following discontinuation of rHuPH20, 48 patients switched to follow-up. No patients withdrew due to IGHy-related reactions (ADRs). No serious ADRs related to IGHy were reported. The maximum IGHy exposure for the initial and Extension studies combined was 3 years (total exposure = 187.69 patient-years; N = 2959 IGHy infusions); during this time, there were no clinically observable long-term changes in the skin or SC tissue. The rate of temporally related systemic adverse events (AEs), excluding infections, was 0.159/infusion. The rate of all local AEs was 0.103/infusion. Of the 1600 IGHy infusions administered in the Extension study, 97.9% had no administration changes (rate reduction, interruption or discontinuation) due to tolerability concerns or adverse events. The annual rate of all infections under IGHy treatment was 2.86/patient-year. Reducing the dosing interval from 4 to 2 weeks (same monthly dose) resulted in a 13% increase in trough IgG levels. Thirteen patients had at least 1 non-neutralizing anti-rHuPH20 antibody titer of ≥1:160 with no associated AEs; no patients had neutralizing anti-rHuPH20 antibodies.

Conclusions: In the Extension study, IGHy was well tolerated and effective, with no serious ADRs for treatment periods up to 2 years. Over a maximum 3-year IGHy exposure (for an individual patient) in the initial phase 3 and Extension studies combined, no long-term changes in skin or SC tissue were observed. The rates of infections and adverse reactions were stable or decreased over the course of the two studies, suggesting no increased risk with continued exposure to IGHy.

SAFETY, TOLERABILITY AND PHARMACOKINETICS OF HUMAN IMMUNE GLOBULIN SUBCUTANEOUS, 20%: INTERIM ANALYSIS OF A PHASE 2/3 STUDY IN PATIENTS WITH PRIMARY IMMUNODEFICIENCIES

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Rationale: We report interim analysis of safety, tolerability and pharmacokinetics (PK) of IGSC 20% in patients with primary immunodeficiencies (PI) aged ≥2 years in Europe.
Methods: Epoch 1: IGSC 16% or intravenous IG 10% (IGIV) administered at pre-study doses every 3 months. Epoch 2: IGSC 20% administered 1 time per week for 12 months at Epoch 1 doses. Serum IgG trough levels are maintained at >5 g/L. The primary endpoint is validated acute serious bacterial infection (SBI) rate.
Results: At the interim analysis in October 2013, 49 patients started the study. During IGSC 20% treatment (n = 48), 1 acute SBI episode (pneumonia, moderate in severity) was reported. The infection rate per patient-year was 4.3 (IGSC 20%). There were no serious adverse events considered related to any treatment. The rate of local adverse drug reactions (ADRs) was 0.055/infusion and all were mild in severity; no severe systemic ADRs were reported with IGSC 20%. Of 1812 IGSC 20% infusions, only 0.4% required slowing or interrupting the administration rate. Mean serum IgG trough levels were 9.2 g/L (IGSC 20%, n = 46), 9.1 g/L (IGIV 3-week interval, n = 4) and 7.7 g/L (IVIG 4-week interval, n = 25).
Conclusion: IGSC 20% provided an effective and well-tolerated therapy, with no dose adjustments needed from pre-study IG dose. This study is ongoing to confirm results over 12 months.

PHARMACOECONOMICS OF IVIG TREATMENT IN ANTIBODY IMMUNODEFICIENCIES

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It is well known, that intravenous immunoglobulin (IVIG) is the main therapeutic modality in B-cell primary immunodeficiencies (PID), it decreases mortality and morbidity in these patients dramatically. Yet, it is also well known that all IVIG products are very expensive, especially considering life-time use and almost normal life expectancy in these patients, if treated correctly. Irregular treatment and problems with insurance/state coverage of IVIG in some countries stems from this.
GOAL: The goal of our study was to compare medical and other costs, related to the disease in patients with humoral PIDs with or without IVIG treatment.
Patients: 21 patient with B-cell deficiencies (73% X-linked agammaglobulinemia, all genetically confirmed, 27% common variable immunodeficiency). The age of patients varied from 2 to 16 years.
Methods: We analyzed medical and other disease-related costs during 2 years preceding the diagnosis (without IVIG therapy) retrospectively and during 2 years on regular IVIG therapy.
The costs included those incurred by the state (hospitalization, home visits, emergency calls) and by the parents (costs of drugs, private consults, etc). The state costs caused by parents missing work were also considered. For standardization purpose for calculation we used the prices for the end of 2013.
Results:
The patients analyzed fell into 3 different categories:
1. The 1st group –(76% of patients studied) - patients with several severe infections before therapy, some chronic conditions as a result of those. Age of diagnosis varied from 2 years to 16 years (with average time to diagnosis 5 years).
In this group costs of IVIG treatment were 2,5 times higher than before the diagnosis (Fig. 1).
2nd group(10% of all). Patients with late diagnosis (average time to diagnosis 7 years), who had multiple severe infections before the IVIG treatment and acquired serious chronic lung complications due to it. In this group the costs before the treatment were higher, than on IVIG treatment.
3. Very early diagnosis –within the first year of life (mostly because of preceding family history) (14%). The comparative analysis was not possible, but it was noted that these patients had no history of serious infections before of while on IVIG therapy. The only additional costs, besides IVIG, were related to bad venous access, requiring occasionally 1 day in-patient hospitalization for IVIG infusion.
As expected, in all 3 groups, the number of infectious episodes, the number of hospitalizations (Fig. 2) and doctor visits (Fig. 3) after beginning of regular IVIG treatment dropped dramatically.
We also followed 2 patients with XLA, who did not receive IVIG therapy because of social aspects. Both patients died from severe infections. We evaluated this fact in economical prospective: in Russia one worker, who works continuously and retires at 60 years of age brings about 130 mln roubles into the state budget (when costs for schooling and routine medical care are subtracted). If one supposes that an XLA patient have been diagnosed very early in life, did not form complications prior to therapy and was on regular IVIG therapy for life, this sum equals to 160 years on IVIG.
Conclusions: Regular IVIG therapy not only leads to reduction of infectious episodes, hospitalizations, and as a result improved quality of life. In some cases it even brings down the disease-related costs, incurred by the medical system and the family, and is economically advantageous for the state.

SUBCUTANEOUS IMMUNOGLOBULIN REPLACEMENT THERAPY IN AN ADULT WITH REPEATED SYSTEMIC REACTIONS TO INTRAVENOUS APPLICATIONS

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Introduction: Replacement of immunoglobulins is a standard therapy for patients with primary immunodeficiency disease (PIDD) characterized by

primary antibody deficiency (PAD). This poster represents our clinical experiences of initiation of home-based treatment with subcutaneous immunoglobulin (SCIG) with the patients diagnosed with primary variable immunodeficiency (CVID).
Case report: The patient (age 30) has been treated at our immuno-allergy outpatient clinic since 2005 with the diagnosis of hypogammaglobulinemia (IgG, IgA, IgM) with normal B cell count, with – susp. CVID. With the repeated administration of intramuscular and intravenous immunoglobulins (IVIG, IMIG) repeatedly occurred serious adverse reactions, which resulted in discontinuation of the replacement therapy. In February 2012 the health condition of the patient worsened due to recurrent bacterial respiratory infections. There was a progressive decrease of serum concentrations of immunoglobulins (IgG 2,1 g/l, IgM 0,25 g/l, IgA 0,23 g/l). The patient was admitted to the intensive care unit of the 1st Internal Department, University Hospital Bratislava, for a subcutaneous immunoglobulin replacement trial. Despite serious adverse reactions with previous administration of several types of immunoglobulins, there have not occurred any clinically relevant side effects.
Conclusion: Compared with IM or IV formulations and administration, for selected patients, SCIG is better tolerated, clinically efficacious, safe, and appreciated by the patients.

„PER ASPERA AD ASTRA“ : DIAGNOSING COMMON VARIABLE IMMUNODEFICIENCY AND ALLERGIC ASTHMA IN ADOLESCENT

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Background: Common variable immunodeficiency (CVID) is primary immunodeficiency (PID) classically viewed as antibody deficit. Although, CVID is considerd to be a humoral immunodeficiency, approximately 40% of CVID patients have low T-cell counts or abnormal T-cell function. Despite adequate immunoglobulin replacement patient morbidity and mortality is variable and a number of complications are not those typically seen in pure antibody PID e.g. XLA. So, T-cell rather than B-cell phenotype could determine outcome in patients with CVID. Many patients with CVID have clinical history suggestive of allergic respiratory disease, but prevalence of asthma and role of atopy have not been well established. Apart from recurrent infections and their sequelae, CVID patients suffer from other disease-related complications in up to 45% of the cases. About 25% have onset before the age of 15 years.
Aims: 1) to present one more case of tadolescent with CVID and allergic asthma, 2) emphasise ultimate need of collaborative network of primary immunodeficiency centers.
Case report: Parents of 12,5 y boy were sure that “something was wrong” with their son and were seaking for problem solution for many years. Since age 3, child had frequent respiratory infections. Adenoidectomy and tonsillectomy were performed at age 6. Sinuitis was diagnosed several times. Boy was complaining of fatique for a long time. Last several years, his main problems were fever (max 41 C) usually lasting 5 days till 2 weeks, accompanying running nose, coughing, conjunctival problems; intermittently headache (lasting for a few hours till all day). Oral aphtae were present almost every two weeks. He was incompletely vaccinated (BCG, and once DiTePer). Morbilli and varicellae infections passed without complications. In Jan 2012 he was diagnosed as allergic asthma in Sarajevo (allergy to pollen, soya, nuts and antibiotics (“Ceclor” and “Pancef”). In February 2012 was admitted at Children’s Hospital Sarajevo for suspected primary mmunodeficiency. He had slightly lower levels of IgG and IgA (twice measured), normal IgE and decreased number of T helper Ly. Due to suspected PID, boy was checked up in two nearest regional PID centers : hypogammaglobulinemia was confirmed (IgG 4,7, IgA 0,24, IgM 0,46, as well as deficiency of IgG1, IgG2 and IgG3). Flow cytometry showed slightly raised concentration of lymphocites B (CD8), slightly raised number of nondifferentiated B cells. CVID was suspected but not proved. In July 2012 child visited center for primary immunodeficiencies in Munchen, Germany, were he was diagnosed ad probable CVID on the basis of hypogammaglobulinemia, lower levels od switch memory B cells, normal number of T-cells, positive antibodies to vaccinations and overcome infection (morbilli, varicellae). Allergic asthma was additionaly confirmed in specialised pediatric pulmology hospital in Germany (abnormal spirometry, normal IgE, positive skin prick test, abnormal fractional exaled nitric oxid test, incipient brochiectasies due to asthma confirmed by high -resolution lung CT scan). Low human immunoglobulin replacement was started (200 mg/kgBW) as well as antiasthmatic therapy (inhalatory steroids, antihistaminics). Excellent therapeutical response were achieved : after one 1,5 y follow up, we can confirm patient has excellent general condition, no subjective symptoms, no tiredness, no severe infections.
Conclusion: Diagnosing CVID is challenging task and quite often could be “per aspera ad astra”. There is ultimate need of collaborative work of primary immunodeficiency network aimed of diagnosing patients on time. CVID patients with history suggestive of allergic asthma, are negativne on traditional tests, additional test designed to identify allergic asthma might be conducted.

MALIGNANCIES IN 47 CVID PATIENTS REGISTERED AT ALLERGY AND IMMUNOLOGY DEPARTMENT OF RASOOL E AKRAM HOSPITAL IN TEHRAN

Rasol Molatefi; Saba Arshi; Mohammad Nabavi; Mohammad H. Bemanian; Morteza Fallahpour; Hosein Esmailzadeh; Mahsa Rekabi; Javad Ahmadian; Narges Eslami; Sima Shokri

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Common variable immune deficiency (CVID) is a heterogeneous syndrome characterized by hypogammaglobulinemia, recurrent infections, immune disregularity (autoimmunity, autoinflamation) and propensity to malignancies. In the US report, 8.2% of CVID patients had a lymphoid malignancy, and cancers of other sorts developed in 7% of patients. It is not clear why CVID patients have higher risk of malignancy but chronic antigenic stimulation, chronic inflammation and increased chromosomal radiosensitivity may be the cause. CVID patients with higher IgM level, reduced or absent B cell numbers, CD4 T cells lower than 200 and PLI phenotype have higher prevalence of malignancy.
Allergy and clinical immunology department of Rasool E Akram hospital has registered 47 CVID patients. Mean age of the onset of CVID symptoms was 11.2 years. Mean diagnosis age was 20.2 years with mean diagnostic delay of 9 years. Mean follow up time was 7 years (minimum 0.5-maximum 23 y). Malignancy occurred in the follow up of 6 patients (13%). One patient had two different malignancies (breast cancer and GI adenocarcinoma). Malignancy risk per case was 15%. Hodgkin’s lymphoma was the most common type (43% of cancers).Other cancers include: Breast cancer, gastrointestinal cancer, Leukemia and CNS cancer. Malignancy is one of the main complications of CVID. It is necessary to monitor and follow early signs and symptoms of malignancies.

AUTO IMMUNE MANIFESTATIONS OF 47 CVID PATIENTS REGISTERED AT THE ALLERGY AND IMMUNOLOGY DEPARTMENT OF RASOOL E AKRAM HOSPITAL IN TEHRAN

Mohammad Nabavi; Saba Arshi; Mohammad H. Bemanian; Rasol Molatefi; Morteza Fallahpour; Hosein Esmailzadeh; Mahsa Rekabi; Javad Ahmadian; Narges Eslami; Sima Shokri

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Common variable immune deficiency is a heterogeneous syndrome characterized by hypogammaglobulinemia , recurrent infections , auto immunity and auto-inflammation . More than 25 % of CVID patients have auto immune complications and among them, auto immune cytopenia is the most common. CVID patients with higher IgM level – higher 21 low B Cells – lower T reg levels – lower CD4/CD8 ratio and lower class switched memory B cells have higher prevalence of autoimmunity.
Allergy and clinical immunology department of this hospital has registered 47 CVID patients.
Mean age of onset of CVID symptoms was 11.2 years. Mean diagnosis age was 20.2 years with mean diagnostic delay of 9 years. Mean follow up time was 7 years (minimum 0.5 maximum 23 y). Autoimmunity was detected in 23 cases (49 %) and 12 cases (26 %) had more than one autoimmunity. Autoimmunity was the first symptom of CVID in 15 percent of cases.
Autoimmune disorders should be considered in the follow up of CVID patients.

table 1: Auto immune disorders in 47 CVID patients

Autoimmune disorder	Number (percent)
ITP	12 (26%)
autoimmune hemolytic anemia	7 (15%)
hypothyroidism	7 (15%)
vitiligo	5 (11%)
JRA	3 (6%)
aphthous	3 (6%)
psoriasis	2 (4%)
pernicious anemia	2 (4%)
SLE	1 (2%)
alopecia	1 (2%)
lichenplanus	1 (2%)
Diabetes Melitus type 1	1 (2%)
Multiple autoimmunity	12 (26%)
Any autoimmunity	23 (49%)

CLINICAL ASSOCIATION OF IGG G1 SUBCLASS DEFICIENCY AND CHRONIC EOSINOPHILIC PNEUMONIA: ONE CASE

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IgG is major immunoglobulin and classified subgroups as IgG1, IgG2, IgG3 and IgG4. IgG1 and IgG3 subclasses are rich in antibodies aganist proteins such as the toxins produced by the diphtheria and tetanus, as well as antibodies aganist viral proteins. Recurrent ear infections, sinusitis, bronchitis and pneumonia are common in Ig g subclass deficiency. Ig G1 is the major subclass of Ig G. IgG1 subclass deficiency is very rare.
Chronic eosinophilic pneumonia is one of the eosinophilic lung disease and is seen rarely. In the presence of peripheral eosinophilia and radiological pulmonary infiltrates diseases suspected. When increase in the number of eosinophils in bronchoalveolar lavage fluids and/or presence of eosinophils in lung tissue diagnosis is confirmed. According to different recording systems chronic eosinophilic pneumonia is %0-2 of the interstitial lung disase. There is not any criteria for diagnosis but also diagnoses is confirmed with suspected findings. Symptoms inludes that: 1)In the presence of respiratory symptoms for two weeks long 2)Eosinophilia at alveolar lavage and\or peripheral blood (BAL fluid cytological examination > %25, blood >1500/mm^3) 3)Radiological imaging of the lung peripheral infiltration 4)Exclusion of the other causes of eosinophlic lung disease
There is eosinophilia over 1000/mm^3 nearly all patients. One of third or half of patients have diagnosed as asthma. Disease begin with systemic symptoms such as night sweats, weight loss, anorexia and pulmoner symptoms such as cough, shortness of breath, wheezing. Patients have restrictive or obstructive findings in PFT. One of third patients, especially with history of asthma, have obstruction in PFT. İn the pathologic biopsy findings include; thickening of alveolar walls and accumolation of eosinophils and lymphocytes. Long time used corticosteroids treatment is recomended. Relaps is common when treatment is discontinued.
We present the patient who has Ig G1 deficiency, chronic eosinophlia and %42 eosinophils in bronchoalveolar lavage fluid. The patient improved long time used oral steroid then inhaled steroids. This was presented in terms of clinical association.
Case: A 12 years old female patient who were followed due to asthma in the other center for two years, although use of combination inhaled fluticasone and salmeterol, patient was admitted with cough and sputum production. In thorax CT there were, bronchiectasis at right lower lobe, pneumonic consolidation in the right lower lobe and ground glass opacities. We detected as IgG 924 mg/dl (835-2094mg/dl), IgA 157 mg/dl (67-433 mg/dl), IgM180 mg/dl (47-484 mg/dl), IgE 108. 6 mg/dl, IgG1 4896 mg/dl (5990-15600 mg/dl), IgG2 2354 mg/dl (1110-5150mg/dl), IgG3 1024 mg/dl(290-2000mg/dl), IgG4 616 mg/dl (40-1600 mg/dl). Because eosinophilia (717 cells) and symptoms continued, bronchoscopy was performed. Left main bronchus was normal, right bronchus were seen dilated. Purulent secretion was aspirated on rigt bronchus with flexible bronchoscopy ..In cytological examination % 42 eosinophils was detected in BAL. Bronchoalveolar lavage cultures was negative. The patient was diagnosed chronic eosinophilic pneumonia and 1 mg/kg oral steroid was began. IVIG was given up to patient; because of frequently recurrent sinopulmonary infection and patient had IgG1 subclass deficiency. In the third month of oral steroid therapy physical examination findings and PFT were improved and started inhaled steroid.
Conclusion: Immunodeficiencies often can be seen alone. Although, the pathogenesis of immundeficiencies with lung disease is not well understood and associated with interstitial lung disease. Therefore, investigations must be include bronchoscopy and bronchoalveolar lavage.

IG	Patient (mg/dl)	Normal (mg/dl)
Ig A*	157	67-433
Ig ^{M*}	180	47-488
Ig G*	924	835-2094
Ig G1*	**489**	**599-1560**
Ig ^{G2*}	235	111-515
Ig G3*	102	29-200
Ig G4*	61	4-160
Ig E	108.6	IU/dL

HEMATOPOIETIC STEM CELL TRANSPLANTATION IN PATIENTS WITH SEVERE COMBINED IMMUNODEFICIENCY: A SINGLE CENTER EXPERIENCE

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SCID is a congenital heterogeneous group of diseases characterized by severe impairment of T,B, NK cell development and function. The hematopoietic stem cell transplanted 93 patients with SCID in the time period from 1994 to 2014 were evaluated. Male/female ratio is 59/34. Median follow-up time is 5 years (6 months-20 years). Parental consanguinity ratio was 81,7%. Mean age of onset of the symptoms was 3 ± 2,7 months. Most common clinical findings on admission were; pneumonia (75,3%), moniliasis (62,4%), diarrhea (39,8%), dermatitis (19.4%). Classification according to T, B, and NK cell counts; (Figure 1). Molecular genetic defects were determined in 60 patients (Figure 2) are given.
There is no difference between age groups according to occurrence of acute and chronic gvhd. Death ratio increases with the increasing age. Acute and chronic gvhd and number of deaths were significantly higher in peripheral stem cell transplanted patients.
There is no statistically significant difference in occurrence of acute/chronic GVHD between B- and B + SCID, who had been HLA idantically transplanted from family donor. Both groups have similar ratios of IVIG treatment need after HSCT. There is no statistically significant difference in occurrence of acute/chronic GVHD between NK- and NK + SCID, who had been HLA idantically transplanted from family donor. Both groups have similar ratios of IVIG treatment need after HSCT. Death ratio was similar in groups. BCG dissemination in BCG vaccinated patients is significantly higher in the NK + group.
The rate of complications due to severe infections is high and increases with age in patients with SCID. HSCT is curative, should be considered as early as possible. TREC analysis for neonatal screening will give chance for early diagnosis and treatment of the patients.

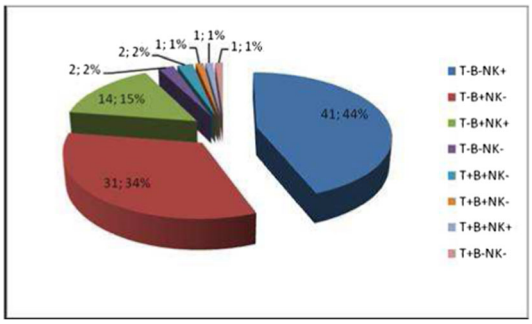

Figure 1. SCID phenotypes of the patients with SCID

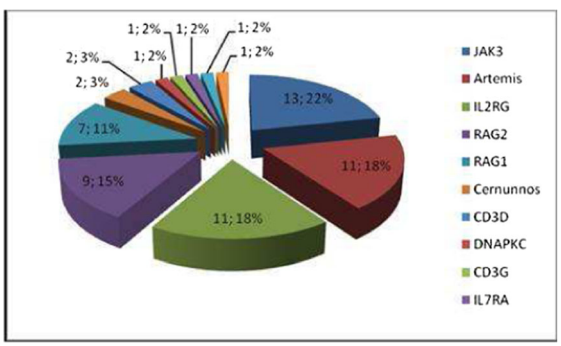

Figure 2. Molecular defecs determined in patients with SCID

STK-4 DEFICIENCY AMONG PATIENTS WITH AUTOSOMAL RECESSIVE HIES PHENOTYPE

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The hyper-IgE syndromes are rare PIDs and are characterized by atopic dermatitis, skin abscesses recurrent pneumonias, elevated serum IgE levels and sometimes mucocutaneous candidiasis. We have been evaluating and following up a group of patients with features suggestive for autosomal recessive Hyper IgE Syndrome (AR-HIES). Homozygous Dock8 mutations were identified in several of these patients. However, two siblings from a consanguineous family in this group of patients showed homozygous block in chromosome 20p1.2 in homozygosity mapping which includes STK4 gene. Sanger sequencing was performed for STK4 deficiency and showed a novel c.57-60delGATA mutation in STK4 gene causing a premature stop codon. Clinical manifestations of STK4 deficiency, also known as a Macrophage Stimulating 1 (MST1) deficiency, STK4 deficiency comprise recurrent and severe viral skin infections including molluscum contagiosum and warts, fungal and bacterial infections and autoimmunity which are also the features of AR-HIES. Our patients's main features include autoimmune cytopenias (AIHA and ITP), cutaneous viral (molluscum contagiosum and mild perioral herpetic lesion), mild atopic dermatitis, seborrheic dermatitis, lymphopenia (particularly CD4 lymphopenia), and intermittent mild neutropenia. Serum IgE level was mildly high in these patients. Our results indicates that patients that show clinical phenotype of AR-HIES needs to be also evaluated for STK4 deficiency. Determination of the underlying defect and reporting the patients are required for the description of the phenotypic spectrum of PIDs and the frequency of these diseases as well as for genetic counselling.

PRESENTATION OF INTERLEUKIN-12/23 RECEPTOR BETA1 DEFICIENCY WITH VARYING CLINICAL SYMPTOMS

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Mendelian susceptibility to mycobacterial disease (MSMD) is a rare entity. Patients with MSMD have susceptibility to Salmonella and some other intracellular microorganisms in addition to weakly pathogenic mycobacterial species. IL-12Rβ1 deficiency, most common form of MSMD, is caused by mutations in the *IL12RB* gene.
37 patients who have symptoms suggestive for MSMD or history of sibling death due to BCGosis were evaluated. The expression of the IL-12RB1 was detected in patients and family members by monoclonal antibodies on the lymphocyte surface by flow cytometry after the lymphocytes were stimulated in vitro with PHA. Mutation analyses was done by Sanger sequencing. All index cases were presented either with BCG or salmonella infection. Two patients, though they were BCG vaccinated had no clinical

symptom, six presented with the symptoms of Salmonella infections, two developed leukocytoclastic vasculitis, candidiasis was the accompanying feature in seven. Recurrent Leishmaniasis that necessitated subcutaneous interferon-γ and prophylactic Amphotericine B therapy was present in a patient. In all patients the percentage of lymphocytes with IL12Rβ1 expression was found to be less than %1.
Prophylactic antimycrobial treatment and in severe and resistant infectious episodes IF-γ therapy, should be given. Many patients have associated mucocutaneous candidiasis. The prognosis is good unless the patient admits at the later stages of BCG infection. The results of our patients showed that the analysis of the surface expression of IL12Rβ1 on activated lymphocytes is an effective diagnostic method which can also be used in screening of the patients with probable MSMD.

UNUSUAL CLINICAL PRESENTATION AND HEMOPHAGOCYTOSIS OF ATAXIA-TELANGIECTASIA IN TWO SIBLINGS WITH A RARE MUTATION

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Ataxia-telangiectasia (A-T) results from the loss of ataxia-telangiectasia mutated gene (*ATM*) function and is a heterogeneous, multisystemic disease and characterized by accelerated telomere loss, genomic instability, progressive neurological degeneration, immunodeficiency, premature ageing and increased neoplasia incidence. Even in classic A-T with ataxia and telangiectasia, the onset of clinical symptoms and the rate of progression are variable.
Here, we report two siblings was diagnosed as A-T with severe and early hypogamaglobulinemia, decreased CD19, increased CD45RO, no ataxia and telangiectasia, purulent otitis and hemophagocytosis that harbor a rare frameshift mutation of ATM gene.

FOOD ALLERGY IN PATIENTS AFTER SOLID ORGAN TRANSPLANTATION

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Background: The acquisition of new food allergy after transplantation or transplant-acquired food allergy (TAFA) is usually reported in adults and rarely in children. TAFA is described mainly after liver, but also after small bowel/intestinal, lung and heart transplantations. In different studies, the male/female ratio is equal. Literature data suggest that children with TAFA typically present within the first year after surgery and they are typically allergic to multiple foods.
Aim: TAFA is generally characterized with allergy to multiple foods and increased level of total and/or spesific IgE. Here, a patient although who had normal total. IgE and specific IgE test results, he developed reaction to skin prick test for cow's milk is presented and his clinical presentation will be discussed.
Case presentation: 15 month-old- boy came to our allergy clinic with complaints of vomiting after drinking cow's milk and skin rush on the area where contact ed with chocolate. In his past medical histroy, left lateral segment of liver (donor was his mother) was transplanted to him when he was at 5 months. The liver donor was not recorded as having a history of allergic disease. Methylprednisolone and tacrolimus immunosuppression were used after the transplantation, and tacrolimus therapy was continued for prophylaxis of chronic rejection. When he was at 7 months, family fed the patient with cow's milk but 3 hours later he began to vomit. He vomited five times in two hours. Then, he developed constipation. Rectal irrigation was used. Then oral intake stopped for two days. He was thought to be having food protein induced enterocolitis. His vomiting complaints repeated after intake of formula and baby food which include grain. So he fed with special formula including short-chain peptides and free aminoacids and his symptoms improved. Past medical history: Extrahepatic biliary atresia was diagnosed at 3 weeks age with conjugated hyperbilirubinemia (according to scintigraphy and biopsy results). Family history: His father has penicillin allergy and his aunt has asthma. At our outpatient clinic: Height and weight were within normal percentiles. Physical examination reevaled normal examination findings. Laboratory findings: WBC was 4.420/mm^3, with 21% neutrophils, 6% eosinophils and 69% lymphocytes. His hemoglobin was 8.2 g/ dL, platelet count was 280.000/mm^3. Total IgE : <5 and ImmunoCAP specific IgE against milk, grain and other classsic foods was <0.35. Skin prick test results: saline: 0x0mm, histamine 4x4mm, fresh cow's milk:2x2mm, other food allergens (peanut, egg, fish, soybean, wheat): 0x0mm.
Conclusion: Our patient seemed to have cow's milk allergy related to liver transplantation. Laboratory investigations and clinical presentation of the patient did not look like typical IgE–mediated food allergy, which is expected in TAFA.

A SINGLE CENTER EXPERIENCE OF HSCT IN ANKARA

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Background: Except for antibody deficiency and complement defects, hematopoietic stem cell transplantation (HSCT) is the single best curative treatment defined for Primary immunodeficiency (PID) so far. In the current study, we aimed to assess the role of PID type, donor type and clinical status on HSCT success rates.
Materials and Methods: We retrospectively reviewed the records of a total of 91 HSCTs procedures performed in 68 patients diagnosed with PID between 1997 and 2013, in Ankara University Pediatric Allergy and Immunology Department.
Results: Of the 68 patients, 40 had severe combined immunodeficiency (SCID) and 28 had non-SCID. The survival rates following HSCT, in both SCID and non-SCID patients were 75%. When classified according to the source of donor, patients who had a HLA-matched sibling donor (MSD) in the SCID group had 90.9% survival rate post transplantation, those who had a matched related donor (MRD) had 85.7% and those who received a haploidentical donor had 63.6% survival rates. In the non-SCID group there were 3 patients with haploidentical transplants (2 Omenn syndrome and 1 MHC Class II deficiency) and all patients died. We assessed several potential risk factors associated with survival in SCID patients. Patients diagnosed over 6 months of age with a pre-existing pulmonary infection, requiring intensive care and/or mechanical ventilation had significantly lower survival rates.
Conclusion: HSCT is the best curative treatment for PID. Our results demonstrated that HSCT performed from matched family donors or even haploidentical parents is a lifesaving treatment in various types of PID's, especially in SCID.

ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION FOR PRIMARY IMMUNODEFICIENCY DISEASES IN BUDAPEST

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Introduction: In case of donor availability allogeneic hematopoietic stem cell transplantation (HSCT) can be regarded as a definitive therapy for a variety of primary immunodeficiency syndromes (PIDs), including severe combined immunodeficiency (SCID) and non-SCID PIDs.
Study Period: We retrospectively reviewed the hospital records of 32 consecutive children with PID, who had 41 allogeneic HSCT in the last 22 years, between January 1991 and January 2014. Our median follow-up time is 2,1 years (2 months - 22,1 years)
Patients and Methods:
The median age of children at HSCT was 10,5 months (3,5 months- 18 years). 23 boys/9 girls
Diagnoses were based on anamnestic data, clinical findings, and immunological and genetic analysis.
Conditioning regimens included busulphan + cyclophosphamide, busulphan + cyclophosphamide + ATG, fludarabine + melphalan or fludarabine + anti-CD52
In B-, T-, NK- SCID cases conditioning was not used.
Indications for transplantation: Patients' diagnoses were severe combined immunodeficiency (N = 16), Wiskott-Aldrich syndrome (WAS, N = 6), chronic granulomatous disease (CGD, N = 3), X-linked lymphoproliferative disease (XLP, N = 3), Whim-syndrome (N = 1), hyper IgM syndrome (CD40 ligand deficiency, N = 1), leukocyte adhesion deficiency (LAD, N = 1), DOCK8 mutation (N = 1)
Transplantations:
41 HSCTs for 32 children were performed.
6 patients were retransplanted (4 pt once, 1 pt twice, 1 pt 3 times), because of rejections.
At the first HSCTs in 5/32 cases sibling bone marrow, 1/32 sibling peripheral blood, 1/32 sibling cord blood, 4/32 unrelated cord blood, 9/32 unrelated bone marrow, 2/32 unrelated peripheral blood, 7/32 haploidentical donors were used
Median CD34 count was $2,52x10^6$/kg ($0,13x10^6$-$26,95x10^6$/kg)
Patients engrafted on median 27 ± 8 day (ANC > 0,5 G/l)
Acute GVHD occured in 17/32 cases (Grade 3-4 in 8/17)
Results:

- Overall survival is 62,5%.
- Overall survival improved after the year 2008, 83% (10/12) vs. 50% (10/20); p = 0,05
- 12/32 patients died. Caues of death were infections in 9 cases (4 bacterial sepsis, 1 systemic BCG disease, 2 CMV-pneumonitis, 1 EBV-reactivation, PTLD, 1 Aspergillosis) acute GVHD in 2 cases and chronic GVHD (pulmonary fibrosis) in 1 case. 7/12 patients had GVHD, 5/7 was severe, Grade 3-4 GVHD.
- Cumulative survival is lower in SCID (50%, 8/16), than in non-SCID PID (74%, 12/16), p = 0,15
- Children with SCID had more severe infections at the time of transplantation.
- 14/16 SCID patients recieved BCG-vaccination after birth, 5 patient had systemic BCG disease at the time of transplantation, out of which 4 children have died.

Conclusion: For non-SCID PID patients HSCT is a feasible therapeutic option with a relatively good outcome. Infections and GVHD were the main causes of death. The early onset systemic BCG disease and other severe infections can influence the outcome of HSCT in SCID pts. The awareness of the early diagnosis for children with PID could improve the outcome of HSCT in these patients.

HISTOLOGICAL FINDINGS IN ALPS PATIENTS

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Objective: Autoimmune lymphoproliferative syndrome (ALPS) is a human genetic disorder of lymphocyte apoptosis resulting in an accumulation of lymphocytes and chronic non-malignant lymphoproliferation, autoimmune disorders, mainly hematological (immune neutropenia, hemolytic anemia, ITP), and peripheral expansion of double negative (DN), CD3 + CD4-CD8-TCRα/β cells. Majority of patients with ALPS harbor heterozygous germline mutations in the gene for the TNF receptor-family member Fas (CD 95, Apo-1). The aim of these study - to examine pathomorphological features in ALPS children.
Design and method: Biopsy of lymph nodes was performed in 19 ALPS patients and biopsy of spleen - in 5 cases. Immunohistochemistry with CD3, CD4, CD8, CD7, CD5, CD19, CD22, HLA-DR, CD10, CD15, CD37, CD68 monoclonal antibodies was performed in 6 ALPS patients.
Pathomorphological findes: distortion of the structure of lymph nodes due to enlargement of paracortical zones and follicules was found in all patients. Presumed atypical cells (makrolymphoblastes and Berezovsky-Sternberg-Reed cells), were detected in 2 patients overwise during follow-up for 2-5 years in these patients revealed no specific infectious and malignansy. Accumulation of proliferating DN cells (a lot of mitoses) was characteristic fiture in lymph nodes and spleen of ALPS patients. Setting of plasma cells in follicular zones in the lymph nodes was reveald in 5 cases, and eosinophiles – in 2, pronounced immunoblast proliferation – in 2, sinus histiocytosis – in 3. Multiple hyperplastic follicles, extended sinuses with many phagocytizing macrophages, lymphocytic infiltration was revealed by histological examination of the spleen in all cases.
Immunohistochemistry findes: T- and B-cells proliferation (Ki-67 expression), atypical location of lymphocyte populations, settings of plasma cells in all lymph node zones.
In paracortical zones was found CD5+, CD7+, CD3 + CD4-, CD3 + CD8- cells in 5 patients, CD38+, CD68+ cells in 1 patient; and in restricted follicular zones - CD19+, CD22+, HLA-DR + cells in 4 patients, CD3+, CD15+ and CD68+ in 2 patients.

KIMURA DISEASE IN A PATIENT WITH THE WISCOTT-ALDRICH SYNDROME

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The presentation of a case of Kimura disease in a patient with WAS. The WAS was diagnosed In 1 year 2months, based on infectious syndrome, atopic dermatitis, hematological syndrome - skin hemorrhages and thrombocytopenia - $25*10^9$/L. After he performed often SARS. Regularly received IVIG at 400mg/kg, antibiotic therapy with a positive effect - infectious syndrome stopped, controlled hemorrhagic syndrome.

Since 2010 there was a herpes virus infection with frequent exacerbations on the face. Patient received acyclovir, valacyclovir, Famvir with a temporary effect.
In 08.2011 on the left side of the face - periorbital region, eyelids, malar region appeared the site of soft tissue hyperproliferation 10 - 12 cm in diameter with a thickness of 3-4 cm, with moderate moist, painful on palpation, the left eye was closed, the lid margin ciliated dramatically thickened, deformed. In October-November 2011 was admitted in Diagnostic department, massive antibiotic, antimycotic, antiviral therapy, IVIG therapy.
The histological study showed the angiolimphoid hyperplasia with eosinophilia without Immunomorphological signs of malignant tumor growth. Based on histological, immunohistochemical studies of the skin, these clinical and laboratory findings, diagnosis: mass lesion of the left face - Kimura disease. Patient helded 6 courses of chemotherapy with positive dynamics: mass lesion decreased, erosive surfaces disappeared and now receives Romiplostimum, Acyclovir, Biseptolum, IVIG 0.5 g/kg 1 time per month.

UNUSUAL PRESENTATION OF PID: FAMILY CASE OF DI GEORGE ANOMALY

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Under the observation there is a family K., which is unique in the deletion variants of the same region 22q.11.2 and the presence of an adult patient with the Di George syndrome. Clinical manifestations of the syndrome in family members is differ.
Methods: clinical, laboratory, instrumental and genetic (DNA was isolated using a kit «QIAamp DNA Mini Kit» and DNA from dried blood spots was isolated using a commercial kit "DNA-sorb-B». MLPA-analysis set SALSA MLPA probemix P250-B2 DiGeorge, Genetic Analyzer Applied Biosystems 3500).
Mother (34 years), had few incidents of pneumonia before 10 years. She was diagnosed Ullrich–Turner syndrome at age 10 years. All childbirths by Caesarean section. She has not any laboratory and instrumental findings of immunodeficiency, endocrinopathy, cardiac and thyroid abnormalities. She has deletion in the starting area of the Di George region (LCR22-A), including genes CLTCL1, HIRA, CDC45, CLDN5, GP1BB, TBX1, TXNRD2, DGCR8.
Father (36 years), healthy, current smoker. The DNA microstructural violations in Di George region haven't been identified.
Son was from I pregnancy, heart defect was set prenatally, marked growth retardation. Childbirth at 38 weeks. He had unstable reduced cell parameters and hypogammaglobulinemia, the size reduction of the thymus and congenital heart disease: truncus arteriosus, DC 2b stage by Lang. After 42 days of life operated for congenital heart disease. During the surgical intervention the thymus wasn't found in a typical place. The postoperative period was complicated by sepsis, heart and respiratory failure. Received IVIG, antibiotic and antifungal therapy. He suffered from SARS, severe course, the degree of respiratory failure 2 (8 months) - death. In MLPA-DNA defined microdeletion disorders starting region Di George (LCR22-A) - from the 4-year-old dry blood sample (postmortem study).
Dother (1,5 years) is from II pregnancy occurring against the backdrop of severe gestosis, premature birth in 34 weeks, a cesarean section. Breastfeeding up to 3 months. Thymus U.S. - a reduction of the thymus weight - 1.4 g. Congenital heart disease: atrial septal aneurysm, tricuspid regurgitation III, not operated. She had normal cell parameters and hypogammaglobulinemia. She has deletion in the starting area of the Di George region (LCR22-A), including genes CLTCL1, HIRA, CDC45, CLDN5, GP1BB, TBX1, TXNRD2, DGCR8.

WISKOTT–ALDRICH SYNDROME: A CASE REPORT

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Introduction: Wiskott – Aldrich syndrome (WAS) is an X-linked immunodeficiency characterized by thrombocytopenia with small size platelets, eczema, recurrent infections and autoimmune disorders. WAS is transmitted recessively, thus closely relative marriage is a predisposing cause. Azerbaijan has its own national features, particularly high rates of closely relative marriages. Due to this peculiarity, our society faces genetic diseases more frequently than in other countries.
Objective and Methods: In the reported case presented the clinical, immunological and genetic features of two brothers with WAS syndrome in Azerbaijan Republic. Leukocyte subset in peripheral blood were identified on Flow cytometer (USA) and levels of IgM, IgG, IgA, IgE antibodies in serum were measured by ELISA method . Phagocytic activity of neutrophils was studied by NBT method. Circulated Immune Complexes (CIC) were examined by photometric method. Genetic analysis for both patients were done in University of Debrecen Medical and Health Science Centre (Hungary).
Results: Both sons were born from closely relative married parents (first line cousins). During pregnancy mother had severe anemia (Hb 48-50 g\l). Both boys were borne normal. One of the children is 3 years old and the other is 8 months old. Both of these patients were examined in indicators CD3+, CD4+, CD8+, CD19+, CD16/56+ and serum IgA, IgM, IgG, IgE levels. Genetic analysis in the patients revealed a c.12_13insGG hemizygous mutation in exon 1 of the WAS gene. The insertion resulted: G4fsX41. Afterwards, according to age and weight IVIG therapy (Intratect and Octagam) used monthly.
First case: From the first month of life child had periodic bleeding from the tooth and skin hemorrhage. Later general weakness, anemia, splenomegaly and decrease in height and weight are observed. The amount of thrombocytes was very low level 12-20/ml (norm is 180000-350000/ml). Repeated respiratory infections are 4-6 times/year. **Second case:** Thrombocytes are revealed in the blood around 70/ml of the second child. Since the first month multiple boils appear on the neck and bottom area as well as petechias and skin hemorrhages in the child.
Conclusion: The diagnosis of WAS should be based on the results of immunological and gene examination. It was found out that following indicators of cellular immunity: CD3+, CD4+ and IRI are decrease, but CD8+ cytotoxic cells and CD16/56+ killer cells are increase. Although the number of antibodies are within the norm (due to IVIG), B-lymphocytes are on the lower limits. Both patients are getting ready for BMT.

CASE REPORT: TWO BROTHERS WITH WISKOTT-ALDRICH SYNDROME

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Introduction: Wiskott-Aldrich Syndrome (WAS) X-linked recessive microthrombocytopenia, eczema, secondary pyogenic infections, autoimmune diseases and increased risk of lymphoreticular neoplasia well defined immunodeficiency syndrome. WAS and X-linked recessive mutations in the gene responsible for thrombocytopenia is showing. WASP mutations weight varies according to the type of disease.

Case: A 3 year old boy with bleeding, eczema and recurrent pyogenic infection was admitted to our department. The child who received treatment in hematology accidentally a few times, but has not had the effect of treatment . Laboratory parameters - CD3-cells- 59% (5550), CD4- cells - 22% (1221), CD8- cells - 37% (2053), CD19- cells - 29% (2728), CD16 / 56- cells - 15% (1411), CD4 / CD8- 0.59, HLA-DR- 22, NBT- 73. IgG- 14.6 q /l, IgA- 3.3 q / l, IgM -4.3 q / l, IgE- 328 U / ml. HB- 40 g / l, erythrocytes- 1.75x 10^{12} / l, leukosytes – 15.6x10^{9}/ l, neutrophils-31%, lymphocytes -56% (9408), eosinophils-2%, monocytes- 2%, metamielosytes:-9%, platelets – rare was observed.Normal bone marrow cells, the separation of platelets from meqakariosyt has become weak. The advantage of erythroid unordered have been observed. Bone marrow puncture the mielokariosytes - 87.0 x10^{9} / l, meqakariosytes - 0.01x10^{9} / l, blasts- 1.2%, myelosytes - 7.4%, metamyelosytes -9.2%, seqments - 14.2% neutrophils-% 51.6, eosinophils-1.4%, lymphocytes- 5.8%, monocytes- 0.4% erythroblasts-2.0%, pronormoblasts- 2.8%, normoblasts-40.0% meqakariosytes - 0.4%, plasmatic cells- 0.2%.His younger brother with eczema, pyogenic infections (furunculosis) was admitted to our department. CD3- 38% (1761), CD4- 39% (686), CD8- 56% (986), CD19- 19% (880) CD16 / 56- 36% (1668), CD4 / CD8- 0.7, HLA-DR- 185, NBT- 34 IgG- 6.8 q / l IgA- 1.1 q / l, IgM- 0.9 q / l, IgA- 217 U / ml.HB- 40 g / l,erythrocytes- 3.1x 10^{12} / l, leukosytes – 12.2x10^{9}/ l, neutrophils-65%, lymphosytes -24% ,eosinophils-3%, monosytes- 8%, platelets-180 .0.Both brothers genes were positive WASP . Genetic analysis in the patients revealed a c.12- 13insGG hemizygous mutation in exon 1 of the WAS gene. The insertion resulted: G4fsX41. The patient's parents are relatives. Children from birth often get sick with viral and bacterial diseases. DESA + PAGID essentially diagnostic criteria, children were diagnosed with Wiskott-Aldrich syndrome.
Conclusion: Bleeding, eczema and recurrent infections in children with Wiskott-Aldrich syndrome must be considered.

COMPARISON OF PERİPHERAL BLOOD LYMPHOCYTE SUBPOPULATIONS AND RECENT THYMIC EMIGRANTS IN PATIENTS WITH ATAXIA TELANGIECTASIA AND AGE-MATCHED HEALTHY CHILDREN

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Ataxia telangiectasia (A-T), is a genetic disorder caused by the homozygous mutation of the ATM gene and, frequently associates with variable degrees of cellular and humoral immunodeficiency. However, the immune defects in patients with A-T are not well characterized. To our knowledge, there is no work on major lymphocyte subpopulations and recent thymic emigrants of A-T patients comparing to age-matched healthy controls.
According to ESID criteria, 17 patients diagnosed as A-T and 12 age-matched healthy children were assigned to the study. Both patients and healthy controls were grouped as 0-5, 6-10, 7-15 years and older than 16 years. Using flow cytometer, major lymphocyte subpopulations and CD4 + CD45RA + CD31+ recent thymic emigrants (RTE) were determined as per cent and absolute cell numbers and compared.
No significant differences regarding all lymphocyte subpopulations were observed between age groups of A-T. Comparing to the healthy controls, there were a **decrease** (in T cells, effector memory T4 cells, B cells, naïve B cells, switched B cells and RTE) and there were an **increase** (in active T8 cells, naïve T4 cells and nonswitched B cells) in the absolute number and percent of some cell populations in the A-T group.
Findings of this study showed effector functions in some cell lymphocyte populations were decreased and could be thought that bone marrow of patients should be tried to increase the cells numbers. However, the study has an important limitation about patient and healthy population.

UNUSUAL CLINICAL PRESENTATION AND HEMOPHAGOCYTOSIS OF ATAXIA-TELANGIECTASIA IN TWO SIBLINGS WITH A RARE MUTATION

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Ataxia-telangiectasia (A-T) results from the loss of ataxia-telangiectasia mutated gene (*ATM*) function and is a heterogeneous, multisystemic disease and characterized by accelerated telomere loss, genomic instability, progressive neurological degeneration, immunodeficiency, premature ageing and increased neoplasia incidence. Even in classic A-T with ataxia and telangiectasia, the onset of clinical symptoms and the rate of progression are variable.
Here, we report two siblings was diagnosed as A-T with severe and early hypogamaglobulinemia, decreased CD19, increased CD45RO, no ataxia and telangiectasia, purulent otitis and hemophagocytosis that harbor a rare frameshift mutation of ATM gene.

OCULAR FINDINGS IN 22Q11.2 DELETION SYNDROME

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Many syndromes named as Di George, velo-cardiofacial, Shprintzen, CHARGE, conotruncal anomaly face and Opitz GBBB syndrome were gathered in the name of 22q11.2 deletion syndrome. Characteristic features include cleft palate, conotruncal heart malformations, thymus hypoplasia, hypoparathyroidism, a characteristic facial phenotype and learning difficulties. This syndrome is the most common microdeletion syndrome (1/4000) with a wide range of facial and ocular abnormalities. The purpose of our study was to identify the most common ocular features associated with this syndrome and to provide ophthalmic screening recommendations for such patients. In our study, 15 patients (7 females, 8 males) who admitted to Division of Pediatric Allergy and Immunology in Necmettin Erbakan University Meram Medical Faculty between April 2007-February 2012 and had the diagnosis of 22q11.2 deletion syndrome were referred to ophthalmology department. They underwent a detailed ophthalmological examination including evaluation of the eyelids and extraocular muscle functions, assessment of refractive error and visual acuity, biomicroscopic examination, refraction and fundus examination. All patients were evaluated by the same ophthalmologist who was experienced in syndromic children. 22q11.2 deletion was shown by using standard probe (DiGeorge/VCFS TUPLE 1 or DiGeorge/VCFS N25). Median age at diagnosis was 38.5 months (1 month-35 years), median follow-up period was 14 (4-59) months. The ophthalmological abnormalities detected were telecanthus/hypertelorism (67%), eyelid hooding (47%), narrow palpebral fissure (47%), refraction errors (33%), tortuous retinal vessels (33%), posterior embryotoxon (27%), marked conjunctival vasculature (27%), strabismus (20%), blepharitis (13%), hyperemic optic disc (13%), iris pathology (iris remnant, iris nevus) (13%), bilateral cataract (7%) and distichiasis (7%).

As conclusion, appropriate genetic referral may be indicated for the patients with telechanthus/hypertelorizm, eyelid hooding, narrow palpebral fissure, posterior embryotoxon and tortuous retinal vasculature to exclude 22q11.2 deletion if other suggestive systemic features are also present. A comprehensive ophthalmological examination is recommended for children upon the initial diagnosis of chromosome 22q11.2 deletion syndrome.

DELAYED DIAGNOSIS OF NIJMEGEN BREAKAGE SYNDROME IN AN ADULT PATIENT PRESENTING WITH RECURRENT INFECTIONS

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Nijmegen breakage syndrome(NBS) is a rare autosomal recessive disease usually presenting at birth with microcephaly. Here we present a case of NBS diagnosed at the age of twenty seven who admitted to our outpatient clinic with malaise, loss of appetite, weight loss and dyspnea on effort . She was hospitalized in another centre 2 years before because of pneumonia, pancytopenia, generalized lymphadenopathy, hepatosplenomegaly and hypogammaglobulinemia (very low IgG and IgA) where she couldn't have any definite diagnosis. Her past medical history was remarkable for primary amenorrhea and basal cell carcinoma excision from preaericular region when she was 23. She had no severe infection history before 25 except frequent upper respiratory tract infections. Her parents were consanginous and she had a brother died at 6 months of age. Microcephaly together with short stature, multiple palpable lymphadenopathies , splenomegaly and absent secondary sexual characteristics were prominent features in physical examination. Direct fluorescence sequencing of the NBN gene showed a homozygous mutation in exon 6 (c.657_661delACAAA) which confirmed the diagnosis of NBS in our patient. NBS is mostly diagnosed in childhood. The delay in diagnosis was partly due to the lack of severe infections in her past medical history until she was 25. Another factor that lead to the delay is that it is an unknown disease among physicians in Turkey. The longest known survival is 53 years in a patient who had no clinical features of NBS other than primary amenorrhea. As a result, our patient is one of the oldest patients reported in the literature presenting nearly all of the classical features of the disease and carrying the most common pathologic mutation.

STK-4 DEFICIENCY AMONG PATIENTS WITH AUTOSOMAL RECESSIVE HIES PHENOTYPE

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The hyper-IgE syndromes are rare PIDs and are characterized by atopic dermatitis, skin abscesses recurrent pneumonias, elevated serum IgE levels and sometimes mucocutaneous candidiasis. We have been evaluating and following up a group of patients with features suggestive for autosomal recessive Hyper IgE Syndrome (AR-HIES). Homozygous Dock8 mutations were identified in several of these patients. However, two siblings from a consanguineous family in this group of patients showed homozygous block in chromosome 20p1.2 in homozygosity mapping which includes STK4 gene. Sanger sequencing was performed for STK4 deficiency and showed a novel c.57-60delGATA mutation in STK4 gene causing a premature stop codon. Clinical manifestations of STK4 deficiency, also known as a Macrophage Stimulating 1 (MST1) deficiency, STK4 deficiency comprise recurrent and severe viral skin infections including molluscum contagiosum and warts, fungal and bacterial infections and autoimmunity which are also the features of AR-HIES. Our patients's main features include autoimmune cytopenias (AIHA and ITP), cutaneous viral (molluscum contagiosum and mild perioral herpetic lesion), mild atopic dermatitis, seborrheic dermatitis, lymphopenia (particularly CD4 lymphopenia), and intermittent mild neutropenia. Serum IgE level was mildly high in these patients. Our results indicates that patients that show clinical phenotype of AR-HIES needs to be also evaluated for STK4 deficiency. Determination of the underlying defect and reporting the patients are required for the description of the phenotypic spectrum of PIDs and the frequency of these diseases as well as for genetic counselling.

IVS10 + 1 G > A VE IVS9 + 1G > C SPLICING MUTATIONS IN *WAS* GENE

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Wiscott-Aldrich syndrome (WAS) is a rare X-linked recessive immunodeficiency disorder characterized by thrombocytopenia, small platelets, eczama, recurrent infections and an increased risk of autoimunity and malignancy. The gene responsible for WAS is located in chromosome Xp11.22-p11-23, which consists of 12 exons, and encodes a 502-amino acid protein. In this study, we aimed to screen *WAS* gene mutations and analyze the effects of determined mutations in 2 boys with non-classical WAS phenotype. IVS10 + 1G > A gene alteration in intron 10 of *WAS* gene was identified in Case 1, previously. So, RNA isolation and then cDNA synthesized was carried out. In Case 2, after amplification of 12 exons of *WAS* gene by PCR, the amplicons were sequenced. In this patient, G > C alteration was detected in the first base of intron 9. Afterwards, cDNA synthesized for detecting the splicing effect. Based on the gel image results, cDNA found to be 400 base pairs smaller than the normal in Case 1. In Case 2, G > C alteration was detected in the first base of intron 9 and then we determined multiple splicing products. Two different splicing mutations (IVS10 + 1G > A and IVS9 + 1G > C) were detected in two cases with non-classical phenotype. IVS9 + 1G > A splicing mutation was stated in the literature, previously, but IVS9 + 1G > C mutation was first time identified in this study.
(This study was supported by JMF Ankara Center.)

WHIM SYNDROME WITHOUT HYPOGAMMAGLOBULINAEMIA AND WITHOUT WARTS

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WHIM is rare (<1 / 1 000 000), heterozygous, autosomal dominantly inherited PID, caused by mutations in the gene encoding for the chemokine receptor CXCR4, mapped on 2q21 locus. The altered CXCR4/CXCL12 interaction impairs cellular homeostasis and trafficking,

resulting in immunological dysfunctions with abnormal retention of mature neutrophils in the bone marrow (myelokathexis) and consecutive severe neutropenia, variable degree of lymphopenia and hypogammaglobulinemia. WHIM patients suffer from recurrent bacterial infections since early childhood and later on manifest a specific susceptibility to HPV infections with developing widespread warts. Because of rarity of the disease, heterogeneity in clinical presentation and usually incomplete phenotype, the diagnosis is often delayed and WHIM syndrome is not suspected.
A 13 year old boy who is suffering from recurrent bacterial infections, often complicated with bronchopneumonia, with severe neutropenia, but also, with lower level of lymphocytes and still, normal serum immunoglobulin level is presented. He has no developed warts; neither his parents nor relatives have warts. At the age of 10 years was unveiled the disease-causing mutation in the CXCR4 gene (c.1000C > T; p.R334X; heterozygote).
Severe congenital neutropenia accompanied with lymphopenia and findings of mature neutrophils in bone marrow, might be an easy approach for getting closer to the clinical diagnosis of WHIM syndrome. Early identification is important for clinical and therapeutic management, allowing a more comprehensive follow-up and administration of appropriate therapy.

FAMILIAL MEDITERRANEAN FEVER – CASE REPORT OF FIVE PATIENTS IN MACEDONIA

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Familial Mediterranean Fever (FMF) is autosomal recessive disorder due to MEFV gene mutation. It is primary dysfunction of the innate immune system with recurrent self resolving attacks of systematic inflammatory reactions which usually accompanied by associated symptoms and signs. We retrospectively analyzed the medical records of patients with FMF and present clinical and genetic characteristics of 5 patients with FMF. 3 of patients are boys and 2 females, with age of onset between 3 and 10 years. The recurrent febrile attacks are between 12 hours and 3 days, with recurrent abdominal attacks and arthritis. All of them present diffuse erysipelas like eruthema on skin. All are heterozygote for MEFV gene: 3 (60%) for M694V mutation, one (20%) E148Q and one (20%) R761Hmutation. Although 16% of Macedonian healthy population is heterozygote for FMF genes, M694V is most frequent in our patients and correlate with severe clinical form. R761H and E148Q are rare, has good answer to Cochicine and do not develop amyloidosis. Laboratory markers show inflammation with increased erythrocyte sedimentation, CRP and granulocytosis. In all patients treatment with Cochicine was started, and the frequency of febrile attacks was decreased. The patients are followed every 6 months and till now no one develop amyloidosis. In a country with high incidence of FMF mutations in healthy population early diagnosis is important because of specific therapy with colchicines.

THE VALUE OF MEAN PLATELET VOLUME/PLATELET COUNT RATIO TO PREDICT 22q11.2 DELETION SYNDROME

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Diagnosis of 22q11.2 deletion syndrome depends on a time-consuming and expensive method, fluorescence in situ hybridisation (FISH). We aimed to determine new parameters which can aid for diagnosis of 22q11.2 deletion syndrome. In our study, 14 patients who admitted to Pediatric Allergy and Immunology department of Necmettin Erbakan University Meram Medical Faculty between April 2007-February 2012 and had the diagnosis of DGS due to 22q11.2 or 10p13 deletion were evaluated retrospectively. Facial-dysmorphism and mental-motor retardation were detected in 100% of patients. Mean platelet (PLT) counts were lower (224.980 versus 354.000, $p = 0.001$), mean PLT volume (MPV) (9.95 versus 7.07, $p = 0.002$), and MPV/PLTx10^5 ratios (5.36 versus 2.08, $p < 0.001$) were higher in patients with 22q11.2 deletion when compared with control group. When MPV was 8.6, area under the receiver-operator characteristic (ROC) curve was 0.864, sensitivity 84.6%, specificity 90.9%, positive predictive value (PPV) 91.7%, and negative predictive value (NPV) 83.3%. When PLT was 265.500, area under ROC curve was 0.864, sensitivity 76.9%, specificity 90.1%, PPV 90.1%, and NPV 76.3%. When MPV/PLTx10^5 was 3.3, area under ROC curve was 0.906, sensitivity 84.6%, specificity 100%%, PPV 100%, NPV 84.6%. Expression of PLT surface markers which were not in GPIb-V-IX receptor complex (CD61, CD41a) increased as the surface area increases, but markers which were in complex (CD42a, CD42b) could not increase or decreased.
As conclusion, high MPV/PLT value can be a good predictor for diagnosis of 22q11.2 deletion syndrome. We suggest that if MPV $\geq$ 8.6fl, MPV/PLTx10^5 ratio $\geq$ 3.3 and PLT count $\leq$ 265500/mm^3, the patient should be tested by FISH analysis to confirm 22q11.2 deletion. If there is not macrothrombocytes in a patient with manifestations of DiGeorge syndrome, 10p13 deletion should be tested in suspected cases.

AUTOSOMAL RECESSİVE HIPERIGE SYNDROME: SİNGLE CENTRE EXPERİENCE

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Hyper IgE syndrome (HIES) is a rare primary immunologic disorder affecting multisystem. Eczema, sinopulmonary infections, and markedly elevated serum IgE are characteristic features in all patients with HIES. Autosomal-recessive hyper-IgE syndrome (AR-HIES) is a combined immunodeficiency recently found to be associated with mutations of DOCK8. Here we report 11 cases of AR-HIES syndrome mainly presenting with atopic eczema. Eleven patients, 6 born to consanguineous parents, were evaluate. Mean age at diagnosis was 6 years. Eczematous dermatitis, mainly on face, scalp and repeated bacterial skin and respiratory system infections were present in all patients. Cutaneous viral infections and chronic candidiasis of the nails were seen in 3 patients. All but except one had high serum IgE levels and hypereosinophilia. CD3 and CD3 + CD4+ lymphopenia were present in 8 patient. IgM levels were decreased in 9 patients. DOCK8 mutations were identified in 7 patients. Therapeutic measures included antibacterial and antifungal prophylaxis, immunoglobulin replacement therapy in all

patients. Bone marrow transplantation has been attempted in one case and this patient is healthy in 9. month follow.

CLINICAL SPECTRUM AND MOLECULAR DIAGNOSIS OF SHWACHMAN-DIAMOND SYNDROME IN THREE CROATIAN FAMILIES

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Introduction: Shwachman-Diamond syndrome (SDS) is an autosomal recessive disease that affects different parts of human organism, especially bone marrow, pancreas and skeletal system. Mutations in SBDS gene are determined in 90% of patients with SDS.
First case: female, 10 years old, from neonatal age presented with failure to thrive, recurrent infections, thoracic dysplasia. Diagnosis of SDS was confirmed by genetic analysis: compound heterozygote for c.[297_300delAAGA];[258 + 2T > C].
Second case: male, 4 years old, at infant age shows signs of thoracic dysplasia and elevated liver enzymes and later failure to thrive and various infections. SDS diagnosis was confirmed by genetic analysis: compound heterozygote for c.[183_184delinsCT];[258 + 2T > C].
Third case: female, 7 years old, at neonatal age manifested with thoracic dysplasia and failure to thrive. Diagnosis of SDS was confirmed by genetic analysis: compound heterozygote for c.[41A > G];[258 + 2T > C]. Mutation c.41A > G (p.Asn14Ser) was not found in any SBDS mutation database, but since nucleotide substitution causes change of aminoacid in protein chain, it is very likely that mutation is pathogenic.
Conclusion: Shwachman-Diamond syndrome often remains unrecognized, considering the incidence of the disease. The variability of the clinical picture in different patients as well as the dynamics of the disease in individual patients represents a major challenge in the diagnosis.

CONGENITAL HEART DEFECTS IN DIGEORGE SYNDROME – OUR EXPERIENCE

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DiGeorge syndrome (DGS) is caused by a submicroscopic chromosome deletion of band 22q11. The common thread among all the organs involved in DiGeorge anomaly is that their development depends on migration of neural crest cells to the region of pharyngeal pouches.
Approximately 75–80% of patients with DGS have congenital heart disease (CHD) with conotruncal and ventricular septal defects. Various cardial malformations are seen, particularly affecting the outflow tract. We report two cases of congenital heart disease (Tetralogia Fallot and Interruption aortic arch) with confirmed microdeletion chromosome 22q11.2 by karyotype and Fluorescence In Situ Hybridization analysis (FISH). Children underwent surgical correction of congenital heart defects with good postoperative outcome, although were complex. The phenotype of these patients can be extremely variable, frequently leading to clinical confusion, diagnostic delay, excess morbidity, early mortality. Identification of these patients is essential for their adequate management and genetic counseling. A multidisciplinary approach is fundamental to ensure that the patient will be able to attain his or her maximal potential.

Key words: DiGeorge syndrome, congenital heart disease, microdeletion chromosome 22q11.2.

PAPILLON – LEFEVRE SYNDROME IN A 10 YEARS OLD GIRL

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Background: Papillion and Lefebvre envisioned PLS being a variant of mal de Meleda. Both conditions belong to a heterogeneous group of skin disorders called palmoplantar keratodermas or kurtosis (PPKs).The PPKS are characterized by hyperkeratotic lesions primarily affecting the palms of the hands and soles of the feet.
The biological mechanism of PPK appears to be genetically as well as clinically heterogenous (Stevens et al. 1996). Historically PPK classifications have been based on pattern of inheritance, clinical expression, histology and co occurrence with associated clinical features.
PLS differs from other PPKs by the presence of early-onset and aggressive periodontitis. Haneke (1979) used the following criteria to classify a case as PLS:
(i) Presence of palmoplantar hyperkeratosis,
(ii) Loss of primary and permanent teeth, and
(iii) Autosomal recessive inheritance.
The underlying cause of the juvenile periodentitis is not well understood but is now thought to be related to an abnormal immune system and to invading bacteria in the cementum of the teeth. Instead painful fissures and recurrent pyogenic infections of the skin seem to be the most common medical complications. However, a number of PLS patients with abscesses or pseudotumors of the liver have been described.
There have been reports of PLS patients with other stigmata such as growth retardation, non-symptomatic intracranial calcifications and mental retardation Furthermore, coinheritance of PLS and albinism type 1 has been reported.
Case Presentation: A 13 yr old girl admitted to our hospital with chief compliant of skin lesions since early months of birth. In the past medical history; she had skin abscess and failure to thrive. On admission she had erythematous, shiny skin with generalized dry scaly predominantly palmoplantar hyperkeratosis and loss of teeth except four or five molar teeth. She informed that she had malformed teeth since childhood which fell off one by one. She had also poor oral hygiene non-pitting edema on lower extremities. No hepatosplenomegaly detected. Family history was negative. She investigated for probable immune-deficiency with regard to skin lesions, history of skin abscess and FTT the lab finding are as following:
CBC diff = Normal ,CRP = Neg, ESR = 6, AST = 31, AlT = 15, Alph = 1656, Alb = 3.8, Total Pr = 6.2 , Urea = 16, Cr = 0.4
IgG = 1620, IgM = 230, IgA = 43, IgE = 10.8, CD19 = 17%, CD_8 = 20%, CD3 = 55%, CD4 = 34%, CD8 = 20%, CD_{56} = 15%
Conclusion: According to nearly normal lab values and presenting signs such as: Generalized pyogenic periodentitis, palmoplantar hyper keratosis and negative family history were attributed to a very rare autosomal recessive disorder with ectodermal dysplasia known as papillon-lefevre-syndrome manifesting with palmoplantar hyperkeratosis and severe early onset of destructive periodontal leading to pre-mature loss of both primary and permanent dentitions.
Key words: Papillon-lefevre syndrome, Periodentitis, Palmoplantar hyperkeratosis

CLINICAL AND IMMUNOLOGICAL FEATURES OF TWO PATIENTS WITH NIJMEGEN BREAKAGE SYNDROME

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Nijmegen breakage syndrome (NBS) is a rare autosomal recessive syndrome of chromosomal instability mainly characterized by microcephaly at birth, combined immunodeficiency and predisposition to malignancies. The disease is caused by mutations in the NBS1 gene, which encodes nibrin, a component of the hMre11-Rad50-p95 complex involved in cellular response to DNA double-strand breaks.
The aim of the present case report was to discuss two siblings with immunologically and clinically different phenotypes of disease presentation and to make an attempt to explain possible genotype-phenotype relation.
The two patients and their non-consanguineous parents were clinically, laboratory and genetically investigated. For mother and father we observed no clinical presentation and no immunological abnormalities. Sibling no.1 (6 years old boy) had no history of recurrent infections and no deviation in immunological tests. Sibling no.2. (6 month old girl) had recurrent infections since birth and IgA, IgG2 and IgG4 deficiency as well as T- and B-cells deficiency. Cytogenetic analysis revealed variable percent of spontaneous chromosomal instability which was more severe (in 50% of chromosomes analyzed) in sibling no.2.
Additionally we sequenced bi-directionally (26 amplicons) the DNA samples from all family members to survey the germline genetic variation in the *NBS1*gene. The 657del5 (exon 6) was detected in both siblings in homozygous and in both parents in heterozygous feature. In order to explain different clinical and immunological presentation of two siblings the rest of the NBS exones were analyzed for genetic heterogeneity. No additional changes were observed. In conclusion patients with the same *NBS1* genotype may show different phenotypes. Other gene/epigenetic factors seem to play a role in phenotype modulation.

MOLECULAR CHARACTERISTICS, CLINICAL AND IMMUNOLOGICAL MANIFESTATION OF OMENN SYNDROME IN EASTERN SLAVS (RUSSIA, BELARUS, UKRAINE)

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Omenn syndrome [Mendelian Inheritance (OMIM 603554)] is an autosomal recessive form characterized by the presence of fatal generalized severe erythroderma, lymphoadenopathy, eosinophilia and profound immunodeficiency.

Objective: We studied clinical and immunological presentation of the disease manifestation and frequency c.368-369delAA (p.K86Vfs118) in *RAG1* gene among Eastern Slavs population.
Results: We collected clinical and immunological data of 9 patients (1 from Belarus, 5 – Ukraine, 3 – Russia) 6 females, 3 males. Age of Omenn syndrome manifestation varied from 1st day of life to 1 yr 1 month. Age of diagnosis – 20 days to 1 year 10 months. 8 in 9 patients had classical immunological phenotype T(+/-)B-NK+, 1 pt had TlowB + NK + with CD3 + TCRgd + expansion. 6 in 9 pts had mutation in *RAG1* gene, 4 in 6 had c.368-369delAA (p.K86Vfs118) in one or two alleles. At present moment 4 in 9 pts are alive, 3 were transplanted, 1 pt is prepared to BMT.
Conclusion: This study demonstrates that the most popular genetic abnormalities in Eastern Slavs children with Omenn syndrome is c.368-369delAA (p.K86Vfs118) in *RAG1* gene. This information may be useful for rapid diagnostic of Omenn syndrome in laboratories used SSCP (single strand conformation polymorphism) before sequencing.

PRIMARY IMMUNE DEFICIENCIES IN CHILDREN IN BELARUS: FIRST COUNTRY REPORT (2006-2013)

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Belarus is a country in Eastern Europe, with its population of 9, 464 million peoples. The first immunological division was established in 2002 at the Belarusian Research Center for Pediatric Oncology and Hematology, Minsk region. National registry for children with PID was established in November 2006 after 1st J-Meeting in Belarus under the patronage of Professor László Maródi.
At present moment Belarusian Research Center for Pediatric Oncology, Hematology and Immunology collects all clinical information and provides immunological and genetics investigation (27 genes) for all children with PID suspicion in Belarus.
As of February 2014 208 children (131 males, 77 females), 163 alive (78,4%) were registered.
Consanguineous marriages are not typical in Belarus, 20% of PID is X-linked, among autosomal recessive forms Nijmegen syndrome is the most popular (16 patients).
The percentage of some of the major immunodeficiency groups and individual disease Belarusian register differ in comparison with others European countries, f.e. domination Other well-defined PID (32,7% n = 68), but not humoral immunodeficiencies (25%, n = 52).

CLINICAL POLYMORPHISM IN PATIENTS WITH THE SYNDROME OF NIJMEGEN

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There are two case histories we have observed in the children's hospital in Chelyabinsk (Russia), patients with the syndrome of Nijmegen

characterizing polymorphism of clinical manifestations in this form of primary immunodeficiencies.

Evgeny L.	***Dmitry K.***
In the history:	*In the history:*
Mucosal candidiasis of the mouth, enterocolitis, then recurrent bronchitis, including obstructive were marked from the first months of life.	At the 1st year of life the boy suffered from obstructive bronchitis twice. In 1 year 3 months he suffered from pneumonia. In later years he endured bronchitis no more than 4 times a year. Recurrent perianal condylomas are marked since 4 years old.
The boy has suffered from 4 pneumonias, bronchitis and recurrent otitis since 5 years old in a short period of time.	

Under examination the patient particularly bright phenotype attracted attention: microcephaly, "birdlike" facial features (sloping forehead, nape, hypoplasia of brow ridges, broad nasal bridge and protruding midface, hypoplasia of the mandible). In addition, besides specific anomaly of the facial bones we noted: big ears, sparse hair and clinodactyly of the fifth fingers.
Clinical and immunological characteristics:

The feature of the case is pancytopenia syndrome we have diagnosed at the early stages of observation and which is continued throughout the period of observation.	The results of clinical laboratory and immunological examination without significant features:
***Erc* - 2.9-3.6 x 10^{12}/l**	***Erc* - 4,0-5,4 x 10^{12} /l**
***Hb* - 71-105 g/l**	***Hb* - 121-133 g/l**
***Leuk* - 0.5-3.0 x 10^{9}/l**	***Leuk* - 11,5-6,2 x 10^{9}/l**
***Neu* - 10-26 % (300-780 cells/mcl)**	***Neu* - 40-70% (2640-11680 cells/ mcl)**
***PLT* - 40-60 x 10^{9}/l**	***PLT* - 512 x 10^{9}/l**
Data of immunological examination:	***IgA* - 0,85 g/l - 1.45 g / l**
***IgA* - 0,06 g / l**	***IgM* - 1,33 g/l - 0.66 g / l**
***IgM* - 0,6 g / l**	***IgG* - 11,3 g/l - 11.8 g / l**
***IgG* - 0,75 g / l**	(Other results of immunological examination are without features)
(Other results of immunological examination are without features)	
The deep insufficiency of antibody production in our patient was the cause of serious, recurrent, and subsequently chronic bacterial sinopulmonary infections after 3 years old.	

Molecular genetic examination:
657del5 mutation in the NBS1 gene in the homozygous state
Diagnosis: ***Primary immunodeficiency: syndrome of Nijmegen.***
Prospective observation:

T-cell lymphoma has developed.	There is no severe life-threatening complications development.

INVASIVE PNEUMOCOCCAL DISEASE IN A 6-YEAR-OLD CHILD WITH IRAK4 DEFICIENCY AND ANTI-POLYSACCHARIDE

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We describe here a patient with invasive *Cryptococcus laurentii* infection and the X-linked form of hyper-IgM syndrome (X-HIGM). *C.laurentii* is an extremely rare human pathogen. This fungus was previously considered saprophytic and non-pathogenic to humans, but it has been isolated as the etiologic agent of skin infection, keratitis, endophthalmitis, lung abscess, peritonitis, meningitis, and fungemia. Most affected individuals had a compromised immune system because of leukemia, cancer, diabetes mellitus, AIDS, or prematurity. Repeated isolation of *C.laurentii* from the oropharynx of an immunocompromised patient has also been documented. Invasive *C.laurentii* infection has not been reported in patients with any form of primary immunodeficiency disorder emphasizing the true rarity of disease due to this fungus.
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DECTIN-1-MEDIATED IMMUNITY IS REDUNDANT FOR HOST DEFENSE AGAINST MUCOCUTANEOUS CANDIDIASIS

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Two groups have recently reported that dectin-1 deficiency due to the mutation of *CLEC7A* or premature termination of the dectin-1 signal transduction molecule CARD9 may predispose patients to chronic mucocutaneous candidiasis (CMC). We studied the frequency of *CLEC7A* mutation in 76 healthy individuals, 10 patients with the hyper-IgE syndrome (HIES), and 8 patients with autoimmune polyendocrine syndrome type 1 (APS-1), all aged between 2 to 60 years. Genomic DNA was isolated from peripheral blood. Monocytes and monocyte-derived dendritic cells (MDDCs) were used to study the phenotypic expression of dectin-1. *CLEC7A* gene was sequenced with the Big Dye Terminator cycle sequencing kit. Mononuclear cells (MCs) were isolated from heparin-treated venous blood. MDCCs were obtained by culturing monocytes isolated by immunomagnetic cell separation assay. Receptor expression was assessed by flow cytometry. Secretion of IL-17A by MCs stimulated with killed *C. albicans* blastoconidia was assessed by ELISA. We report here on healthy individuals with homozygous (one 38-year-old man) or heterozygous (32 men and 44 women) Tyr238X mutation in the dectin-1 gene but no signs of CMC. Dectin-1 levels on monocytes and MDDCs were negligible in the homozygous man and the heterozygous individuals displayed intermediate levels of dectin-1, between those of the homozygous man and the wild-type controls. Markedly lower levels of IL-17A production were observed in the cells of the man with the homozygous mutation than in the control cells. Levels of production of this cytokine were intermediate in heterozygotes. The frequency of Tyr238X heterozygous individuals was 21% among healthy donors and 10 % in patients with HIES and 20 % in patients with APS1. Importantly, the 10 year-old HIES girl with heterozygous Tyr238X mutations has never had mucocutaneous candidiasis. We suggest that dectin-1 receptor-mediated immunity is redundant for host defense against CMC, possibly due to the involvement of multiple lectin receptors in the recognition and uptake of *Candida*.

HEPATIC VARIANT OF CHRONIC GRANULOMATOUS DISEASE

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The X-linked chronic granulomatous disease (CGD) is a primary phagocytic cell deficiency characterized by severe bacterial and fungal infections of various organs. We report of a 19 years of a male patient with X-linked CGD who presented with recurrent hepatic abscesses as the sole manifestation of the disease. Phagocytic and bactericidal activities of granulocytes were studied by using microbiological assays. Generation of superoxide anion by blood granulocytes was measured by the ferricytochrome c reduction test. Mutational analysis of the CYBB gene was performed by genomic DNA sequencing. Ultrasound, CT and MRI imaging techniques were used to define and follow up liver pathology. Killing of viable S.aureus, and generation of superoxide by the patient's granulocytes were negligible compared to that of control cells. Analysis of genomic DNA revealed a c.1169C > T missense mutation in exon 10 of the CYBB gene resulting in a p.P390L amino acid replacement in the gp91-phox protein structure. Despite the severe functional and biochemical defect of granulocyte functions the patient developed only recurrent hepatic abscesses without involvement of any other organ. Association of CGD with recurrent hepatic abscesses as the sole manifestation of the disease is exceptional. We propose that a hepatic variant of CGD may exist in patients with gp91-phox deficiency.
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TYPE 1 C2 DEFICIENCY IN A BOY WITH RECURRENT BACTERIAL INFECTIONS

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We report here 8 year-old boy, who presented with severe, recurrent, upper respiratory tract infections, purulent otitis media, several episodes of pneumonia and asthma. One of his maternal cousins was diagnosed with selective IgA deficiency. Laboratory investigations revealed normal levels of immunoglobulin isotypes, and normal percentages of lymphocyte subpopulations in the patient. He demonstrated good antibody responses to tetanus and diphtheria toxoids, and H. influenza type b conjugate vaccine. Vaccination with pneumococcus and meningococcus plain polysaccharide vaccines triggered normal antibody responses.

THE DEMOGRAPHIC DATAS OF CHRONIC GRANULOMATOUS DISEASE PATIENTS AND THE COMPARATION OF THE CLINICAL DATAS BEFORE AND AFTER INTERFERON-GAMMA TREATMENT IN TURKEY

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Introduction: Chronic granulomatous disease (CGD) is a genetically heterogeneous primary immunodeficiency that is characterised by bacteria and fungal infections with defective phagocytosis. Interferon-gamma (INF-γ) has diverse roles in the innate and adaptive responses. Despite several decades of work on INF-γ treatment in CGD, contraversy remains about its use. Here we investigated the demographic datas of CGD patients and the comparation of the clinical datas before and after interferon-gamma treatment in our country.
Materials and Methods: Fifty seven patients with CGD from 14 immunology centers were enrolled to our multi-center study. A questionnaire including patients demographic datas and clinical manifestations such as infectious and granulomatous complications up to enrolment was obtained before and after INF-γ therapy**.**
Results: Fifty seven patients 14 (25%) girls and 34 (75%) boys aged from 2-35 years (mean age:10.9 ± 7.4) were enrolled. The mean age of diagnosis were 4.9 ± 4.8 (0.1-19). 56% of the patient's family had consanguineous marriage and 60% had a primary immunodeficiency (PID) history. Ninety five of the patients were treated with trimethoprim-sulfamethoxazole (TMP-SMX) and 89.5% of them with itraconazol while 60% of them were received INF-γ treatment. The patients receiving INF-γ therapy tend to have lower infectious complications like severe infections, pneumonia, soft tissue infections and lymphadenitis. Aspergillus infection, tissue abcesses and granulomatous complications were also lower in this group. The annual infectious complications according to CGD subtypes, were also lower in gp91phox subtype with receiving INF-γ therapy.
Conclusion: The demographic and clinical data of CGD patients in our study indicate that INF-γ prophylaxis treatment decreases the infectious and granulomatous complications in some majority of CGD patients especially in gp91phox.

AN INFECTOLOGICAL CHALLENGE: BRAIN ABSCESS IN CGD

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CGD is an immunodeficiency caused by mutations in genes encoding subunits of the NADPH oxidase complex. Normally, assembly of the NADPH oxidase complex in phagosomes of phagocytic cells leads to a "respiratory burst" essential for the clearance of microorganisms. CGD patients lack this mechanism, which results in life-threatening infections and granuloma formations. The leading cause of death are pneumonia and pulmonary abscess, septicemia and brain abscess. In neurogical manifestations various pathogens have been involved including *Aspergillus spp., S. prolificans, A. infectoria, Salmonella and Staphylococcus spp.* There are only some several reports on fungal brain and spinal cord infection, Aspergillus abscess resembling brain tumor, meningitis due to *Streptococcus* and *Candida spp.* In the past 20 years we treated 7 children with CGD. We present the infectological challenge of an X-linked CGD patient with brain abscess. In spite of our effort we were unable to identify its causative pathogen. Empiric therapy sometimes resembles polypragmasia in CGD. To decrease mortality and morbidity from fungal infections in CGD the prophylactic use of itraconazole or voriconazole is widely recommended. A relatively new azole, posaconazole is active in pulmonary and cerebral fungal manifestations , indeed may be effective against fungi with inherent resistance to AmpB or voriconazole. There was no etiological diagnosis in our case that did not respond to conventional antifungal and antibacterial treatment. Based upon the findings and literature data we presume the causative agent might be some kind of moulds. We suppose the use of echinocandin and posaconazole as salvage ("prophylactic") therapy has resulted significant regression of the brain abscess.

EARLY DIAGNOSIS OF CHRONICGRANULOMATOUS DISEASE

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The diagnosis of chronic granulomatous disease (CGD) was verified in 7 children during the past few years in the Department of Clinical Immunology of Regional Children's Hospital of Chelyabinsk (Russia). In our opinionin 3 casesthe diagnosis was establishedearly enough.

Case history №1

Michael W.

Transferred to the neonatal pathology unit of our clinic at the age of 5 days with vesiculopustules. Take into consideration our own experience of observing children with this form of primary immunodeficiency in previous years, the child was conducted immunological examination, in particular, the test of restoration Nitroblue tetrazolium by superoxide anionformed when oxygen explodes in leukocyte (nitro blau tetrasolium – NBT-test). This decision is caused by the fact that previously observed children with chronic granulomatous disease, had vesiculopustules in 90 % at birth. The survey has revealed a complete lack of production of reactive oxygen species by neutrophils in the evaluation of NBT- test, which allowed us to suggest the diagnosis of CGD.
The baby was banned vaccination against tuberculosis, and after reliever vesiculopustules the boy was discharged home.
However, at the age of 1 month the baby suffered from glandular abscess and right-segmental pneumonia. In CBC there is expressed anemia (Hb 60 g/l, erythrocytes – 1.98 x 10^{12}/l), leukocytosis (22x 10^{9}/l), accelerated ESR (36-55 mm/h).
At the age of 3 months in the University of Debrecen, Medical and Health Science Center Debrecen, Hungary, molecular genetic studywas conducted by prof. Dr. Laszlo Marodi. It was revealed a mutation in c. 374 G > A in exon of 6 gene CYBB (encoding subunit gp91-phox), after that the diagnosis of CGD was finally verified.
It was assigned a basic preventive antimicrobial therapy by trimethoprim-sulfamethoxazole, and itraconazoleto prevent fungal infections.
Despite this since 6 months the child has repeatedly and consistently suffered from bilateral groin lymphadenitis during the year, acute hematogenous osteomyelitis of the left ulna, 2 pneumonias, purulent mesadenitis, endoperitonitis. The fact that the child aged 8 months was diagnosed sepsisis evidence of the severity of infectious complications. Clinical and biochemical blood tests were distinguished by consistently high levels of ESR and the presence of leukocytosis, and also severe anemia.
Now the child is 2 years 11 months, he is undergoing treatment at the Department of Clinical Immunology, Russian Children's Clinical Hospital (Moscow) after bone marrow transplantation.

Case history № 2, 3

Christina N.

From the early history we know that the girl's newborn period was uneventful. She was vaccinated against tuberculosis in the nursing home (no reaction). It was noted the formation of abscesses after vaccination against whooping cough, diphtheria and tetanus in 3 and 4.5 months. In 2 years 8 months she suffered from mezootit.
For the first time the girl came under our observation in the children's hospital in Chelyabinsk (Russia) at the age of 3 years with right segmental pneumonia, complicated by the destruction. After further examination it was diagnosed tuberculosis of intrathoracic lymph nodes to the right with upper lobe bronchopulmonary defeat.
To take into consideration given above, it was conducted immunological test that revealed a complete lack of production of reactive oxygen species by neutrophils in the evaluation of NBT-test. On the basis of the history, clinical manifestations and results of immunological examination chronic granulomatous disease was diagnosed. After four – month period treatment a recovery came from tuberculosis and child was transferred to outpatient monitoring.
In 2 years in this family a second daughter was born - *Arina N.*
Taking into account revealed immunodeficiency of her sister, the child was not vaccinated against tuberculosis on our recommendations. A six–month-old child was conducted immunological examination, which, like her older sister, also shows a complete lack of production of reactive oxygen species by neutrophils in the evaluation of NBT- test.
During the molecular genetic studies of both sisters it was identified identical mutation c. 73-74 del GT gene NCF1 (encoding subunit p47-phox).
Now the older girl is 8 and her sister is 3 years old. Observing them in the dynamics neither of them do not show any life-threatening infections.
Thus, the recovery test of nitrobluetetrazolium by superoxide anion formed when oxygen explodes in leukocyte (nitro blau tetrasolium - NBT- test) is a fairly reliable method of early diagnosis of chronic granulomatous disease.

EYE FİNDİNGS OF CHRONİC GRANULOMATOUS DİSEASE: CASE REPORT

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Chronic granolomatous disease (CGD) is due to defective phagocyte superoxide production leading to impaired microbial killing. It is comprised of a group of five genotypes with a common phenotype, chracterized by recurrent severe bacterial and fungal infections and tissue granuloma formation. Patients with CGD often present with pneumonia, liver abscess, skin infections, lymphadenitis, osteomyelitis.
A five month old boy was referred to pediatric infection unit by lymphadenitis. On the medical history, he had taken antibiotic therapy for lymphadenopathy when he was 2 months old. The abnormal eye movement was noticed by the family and on the eye examination peripheric chorioretinal hypopigmented lesions were determined when he was 4 months old. İn his labratory examination, viral serology were negative. His parents were not consanguineous. His mother's brother had died at 3 years old. He had history of skin infections and osteomyelitis. His grandmother had been diagnosed as having tuberculosis lymphadenitis one year ago.
On his physical examination, his growth was normal, patological findings were horizontal nistagmus, 2/6 degree systolic murmur, fistulized lymph tissue on the left submandibuler region. On the laboratory findings; he had anemia and neutropenia. Immunglobulin levels and lymphocyte subtypes were normal. His respiratory burst activity was very low. Chronic granulamatous disease was thougth in the patient by the clinical and laboratory findings. İt was detected gp91phox mutation in the genetical analysis.
He was diagnosed as having X-linked CGD. Antibiotic prophylaxis (tmp-smx, flucanazol) and interferon gamma were started. He is 14 months old

now and he is on the list of match unrelated donor screening. Patiens who has history of lympadenitis, skin infections and chorioretinal findings should be evaulated for the X-CGD.

EARLY DİAGNOSİS OF LEUCOCYTE ADHESİON MOLECULE DEFİCİENCY TYPE 1

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Leucocyte adhesion deficiencies (LADs) are rare autosomal recessive inherited disorders. Three different forms of LADs have been described so far. In LAD-I, the most common leucocyte adhesion deficiency, the function of β2 integrin CD18 is lost. . While one of the first signs of the disease consist in delayed separation of the umblical cord, severe infections already start early during infancy. Another feature of LAD-I includes impaired wound healing. Therefore, mortality during infancy is high.
A fifty day old boy was referred to the hospital due to diarrhea and leukocytosis. The patient was delivered following an uncomplicated full term pregnancy. The parents were first degree cousins. Father's brother and mother's uncle had died during infancy period. His umblical cord had separated on the 19th day. Patient had applied because of diarrhea by starting in the first days of life and leukocytosis was detected (61.000/mm^3). On the physical examination, his body weight was 5200 gr (10th to 25th percentile) and his height was 56cm (10th percentile). There was a granuloma on the umbliculus. Other systems were normal.
In the laboratory examination, leukocyte count was high, Immunoglobulins, respiratory burst activity, gaita analysing and culture were normal. In the lymphocyte subtype analysing, CD19+ B cells ratio was mildly low. CD18, CD11a, CD11b, CD11c levels were found to be very low. In the genetic analysing, it was detected two deleterious mutations in the ITGB2 gene.
Patient had been diagnosed as LAD-1. He treated by antibiotics and then started prophylactic antibiotherapy. Family screened for tissue match. His older sister was found full matched. He was referred to transplantation unit. It was applied bone marrow transplantation when he was 3 months old.
Presence of delayed umblical cord separation and leucocytosis should be considered in the diagnosis of LAD but these patients might have different symptoms such as diarrea.

PRESENTATION OF INTERLEUKIN-12/23 RECEPTOR BETA1 DEFICIENCY WITH VARYING CLINICAL SYMPTOMS

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Mendelian susceptibility to mycobacterial disease (MSMD) is a rare entity. Patients with MSMD have susceptibility to Salmonella and some other intracellular microorganisms in addition to weakly pathogenic mycobacterial species. IL-12Rβ1 deficiency, most common form of MSMD, is caused by mutations in the *IL12RB* gene.
37 patients who have symptoms suggestive for MSMD or history of sibling death due to BCGosis were evaluated. The expression of the IL-12RB1 was detected in patients and family members by monoclonal antibodies on the lymphocyte surface by flow cytometry after the lymphocytes were stimulated in vitro with PHA. Mutation analyses was done by Sanger sequencing. All index cases were presented either with BCG or salmonella infection. Two patients, though they were BCG vaccinated had no clinical symptom, six presented with the symptoms of Salmonella infections, two developed leukocytoclastic vasculitis, candidiasis was the accompanying feature in seven. Recurrent Leishmaniasis that necessitated subcutaneous interferon-γ and prophylactic Amphotericine B therapy was present in a patient. In all patients the percentage of lymphocytes with IL12Rβ1 expression was found to be less than %1.
Prophylactic antimycrobial treatment and in severe and resistant infectious episodes IF-γ therapy, should be given. Many patients have associated mucocutaneous candidiasis. The prognosis is good unless the patient admits at the later stages of BCG infection. The results of our patients showed that the analysis of the surface expression of IL12Rβ1 on activated lymphocytes is an effective diagnostic method which can also be used in screening of the patients with probable MSMD.

CUTANEOUS LEUKOCYTOCLASTIC VASCULITIS DUE TO SALMONELLA ENTERITIDIS IN A CHILD WITH INTERLEUİN-12 RECEPTOR BETA-1 DEFICIENCY

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Introduction: Mendelian susceptibility to mycobacterial disease (MSMD, Online Mendelian Inheritance inMan 209950) is a rare immunodeficiency characterized by predisposition to infections caused by weakly virulent mycobacteria, such as Mycobacterium bovis bacille Calmette-Gue´rin (BCG), environmental nontuberculous mycobacteria (NTM), and Salmonella strains in otherwise healthy individuals. IL-12Rb1 deficiency is the most common form of MSMD and is characterized by childhood-onset mycobacteriosis with frequent recurrence. It has been found that patients with IL-12Rb1 deficiencies are also prone to developing infections with nontyphoidal salmonella species with bacteremia and lymphadenopathy. Here we present a girl with recurrent cutaneous leukocytoclastic vasculitis (CLV) with Salmonella enteritidis due to IL-12Rb1 deficiency.
Case report: A four year old girl that had been diagnosed serologically with recurrent *Salmonella* infections, associated with lymphadenopathy and skin eruption was admitted as having Henoch-Schönlein purpura. She had been vaccinated with BCG and developed left axillary lymphadenitis which spontaneously drained and had recurrent oral monilia plaque. Edema and purpuric eruptions were present on the upper and lower extremities and the abdomen.Multiple mobile, painful,enlarged submandibular lymph nodes of about 2x2 cm in diameter were palpable. Skin biopsy showed a dense

inflammatory site with eosinophils, neutrophils and fibrin in the upper dermis and dermal vessel wall,compatible with leukocytoclastic vasculitis. Serological studies to assess diagnostic markers for vasculitis and infectious agents were all negative. Immune work-up were unremarkable other than hypergammaglobulinemia. *Salmonella enteritidis* was identified in blood culture. She responded dramatically to ceftriaxone treatment within a few days and lesions cleared completely. Extended immunological and molecular genetic examination of the patient was carried out for IL-12/IFN-γ pathway defects. On the FACS analysis of T cells for cell surface expression of the cytokine receptor chains, she did not express any IL-12Rβ1.

Discussion: In thepresent report, we describe a child with CLV with Salmonella enteritidis due to IL-12Rb1 defi-ciency.In a large cohort of patients with IL-12Rb1 deficiency, NTM, M. tuberculosis, disseminated BCG infection after inoculation with the vaccine, and salmonella infection have been described. Sporadic cases with other infectious agents have also been reported. Salmonella infections reported in these patients were due to extraintestinal, or septicemic, recurring infections caused by nontyphoidal Salmonella species.

Only two IL-12Rb1-deficient patients have been identified with vasculitis due to salmonella strains; both came from Turkey, where consanguineous marriages are common. Kutukculer and colleagues reported the first case of S. enteritidis–associated CLV. Sanal and colleagues reported a CLV case associated with group D Salmonella infection. Leukocytoclastic vasculitis is an immune complex mediated disease predominantly involving small vessels of the skin and can be associated with drugs or can be found as a component of other disease, such as infections, connective tissue disorders, and malignancies. Infectious agents can cause vasculitis directly or clinically mimic primary vasculitis .Multiple infectious agents have been suspected as triggering or contributory factors in the vasculitic process . Several factors contribute to the primary vasculitis related to infections: a type 3 or immune-complex reaction, cell-mediated hypersensitivity, abnormal immune regulation, and direct endothelial cell invasion by infectious agents. In our case, extensive evaluation was performed to determine the underlying vasculitis process. Clinical and laboratory examinations revealed no association between vasculitis and other infections or an underlying connective tissue disease or medication. She responded well to ceftriaxone treatment, and clinical manifestations gradually resolved within a few days, providing strong evidence that improvement of the vasculitic lesions was due to elimination of the salmonella with antibiotics

Conclusion: Our patient has one of the exceptional forms of IL-12Rb1 deficiency, with recurrent CLV due to Salmonella enteritidis. Although common presentations for Salmonella infection in individuals with IL-12Rb1 deficiency are lymphadenopathy and bacteremia, it can be present clinically as CLV. Some infections such as Salmonella may be responsible for different types of vasculitis even though they are not common . In this respect, clinicians should be aware of possible infectious causes of vasculitis, and children presenting with unusual recurrent infections caused by non typhoidal Salmonella, BCG, or NTM should be investigated for IFN-γ / IL-12 pathway defects.

C8 DEFİCİENCY WİTH OR WİTHOUT RECURRENT MENİNGİTİS İN A TURKİSH FAMİLY

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The complement system is an important part of the innate immune defense and also plays a major role in shaping the adaptive immune response. These functions are required for a good defense against infections, especially bacteria. The C8 deficiency is a rare disease that is associated with recurrent neisserial infections, especially meningits caused by *N. meningitidis*.

The patient, a seven years old girl was admitted to hospital with high fever and diffuse, purple-coloured skin lesions. Her symptoms gave the diagnosise meningococcal meningitis. She had also earlier been diagnosed with the same disease when she was 5 years old. A sister to the patient had died from meningitis at 3 years of age. She has also one older and one younger sister. There is no consanguinity between her parents. The laboratory analyses of the classical pathway measured as complement hemolytic activity (CH50) and C8 concentration revealed no activity and absence of C8, respectively. Analysis of serum from her younger sister showed the same results, while her older sister's CH50 and C8 levels were found normal. Thus, our patient and her younger sister were diagnosed with hereditary C8 deficiency. The genetic analyses have not been completed yet. We here report the third and fourth cases of C8 deficiency in Turkish patients.

GRANULOMATOUS SKIN LESIONS, SCROTAL EDEMA AND SEVERE LOWER LIMB EDEMA: RARE AND REMARKABLE MANIFESTATIONS OF A CASE WITH COMPLETE IFN-γ RECEPTOR-1 DEFICIENCY AND REVIEW OF LITERATURE

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Interferon-g receptor-1 (IFNgR1) deficiency is caused by mutations in IFN-γ receptor-1 gene and is characterized mainly by susceptibility to mycobacterial disease. We report a boy with complete recessive IFNgR1 deficiency, afflicted by recurrent mycobacterial diseases with *M. Bovis, M tuberculosis, M. avium intracellulare* and *M.fortuitum*. Genetic analysis showed a homozygous mutation (106insT) in *IFNgR1* gene leading to complete IFNgR1 deficiency. In addition, he had atypical mycobacterial skin lesions caused by *M.avium intracellulare* and he developed scrotal and lower limb lymphedema secondary to compression of large and fixed inguinal lymphadenopathies. To our knowledge, the patient is the first case with interleukin-12/interferon − γ pathway defect and severe lymphedema. Defects in the IL-12/IFN − γ pathway must be considered in patients with disseminated or recurrent mycobacterial infections and in patients with severe viral infections, especially in countries where BCG vaccination is part of the national health programme. It must be kept in mind that these patients may develop granuloma-like skin lesions and severe lymphedema. HSCT must be applied at the earliest time before developing organ damages.

THE PHENOTYPE – GENOTYPE RELATIONSHIP IN SEVERE CONGENITAL NEUTROPENIA PATIENTS

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Purpose: Severe congenital neutropenia is a rare hereditary disease presented with infections such as sepsis, abscess, omphalitis and gingivitis in early life. We evaluated the association between clinical findings and mutation analysis of our severe congenital neutropenia patients.
Materials and Methods: The clinical, laboratory findings of 7 patients with severe congenital neutropenia were obtained and the diagnosis was confirmed by analysis of mutation in all family members (parents and children).
Results: The most common clinical presentation included formation of abscesses and presence of otitis and gingivitis. The mutation analysis by DNA sequencing revealed *HAX-1* mutation in 4 and *G6PC3* mutation in 3 patients. Prominent superficial vein, inverted nipple and triangular face were observed in patients with *G6PC3* mutation. Moreover, two patients with *G6PC3* mutation have colitis. Furthermore, developmental delay, convulsion, inability to speak and learning difficulties were seen in 2 patients with *HAX1* mutation.
Conclusion: In patients with severe, recurrent infections assessment of neutrophil count and consideration of various clinical presentations of severe congenital neutropenia is critical in the establishment of early diagnosis and successful therapy of disease. Additionally, genetic cancelling and mutation analysis should be offered for those patients.
Key words: Kostman disease, severe congenital neutropenia, *HAX1, G6PC3.*

CHRONIC MUCOCUTANEOUS CANDIDIASIS, AUTOIMMUNE THYROIDITIS AND CEREBRAL MYCOTIC ANEURISM; STAT1 MUTATION

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Chronic mucocutaneous candidiasis (CMC) is a heterogenous group with recurrent chronic Candida infections spesifically involving nails, skin and oropharynx. Several immunodeficiencies as DOCK-8 deficiency, severe combined immune deficiency, autoimmune polyglandular syndrome type 1 (APECED), IL-12Rβ1 and IL-12p40 deficiencies, CARD 9, STAT-3 and STAT-1 can cause CMC.
We report here a 3 years old boy, born to consaginous parents with onicomycosis, moniliasis, recurrent pneumonia, recurrent herpetic lesions, autoimmune thyroiditis and trombocytopenia. Last admission was due to generalized tonic-clonic convulsion and mycotic aneurism on middle cerebral artery was detected. Flow cytometry revealed CD4 lymphopenia, immunoglobulin values were in normal range. Polymorphism on exon 6 for AIRE gene (T/C heterozygot G227G) and heterozygot STAT1 mutation (c.501 > A; Q167H) were detected.
Various STAT1 GOF mutations (affecting the Coiled-coin domain or the DNA-binding domain) have been systematically associated with susceptibility to CMC. Autoimmune manifestations associated with STAT-1 mutations have been attributed to increased type 1 interferon. The aneurism formation is not elucidated whether it's due to Candida infection or vascular damage directly affected by STAT-1 mutation.
THE EVALUATION OF OUR PATIENTS WITH CHRONIC GRANULOMATOUS DISEASE

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Purpose: Chronic granulomatous disease (CGD) is a rare genetic disease of phagocytic system. Affected patients commonly present with bacterial infections associated with pneumonia, abscesses and lymphadenitis. In this study, we investigated the clinical and laboratory findings of our CGD patients.
Materials and Methods: The demographic data (age at diagnosis, initial presenting symptoms, family history, follow-up period), mutation analysis, therapy options, complications, radiological findings and prognosis were evaluated retrospectively.
Results: Among 9 CGD patients, autosomal recessive form was detected in 4 of them. The age at onset was statistically lower in X' linked CGD patients than AR form (11.2 ± 7.6 mo vs 43.5 ± 21.5 mo; p = 0.001). Respiratory tract infections (sinusitis, otitis, pneumonia) and recurrent abscesses were more commonly seen at onset. Microbiological culture revealed *A. fumigates* from lung biopsy in one patient and *S.marcescens* from blood specimen in other ones. BCGitis was observed in one patient and five patients received anti-TB therapy. Non-infectious complications were granulomatous uveitis, recurrent pericardial effusion, skin granuloma, noduler formation in lung and brain area.
Conclusion: Due to high rate of consanguinity, autosomal recessive inheritance was observed highly in our patient cohort. Since, patients with CGD are susceptible to Tuberculosis and BCG complications; initiation of tuberculosis prophylaxis is advisable in countries where BCG is still administrated at birth.
Key words: Chronic granulomatous disease, consanguinity, BCG.

ENIGMAS OF PRIMARY IMMUNODEFICIENCY AND MYCOBACTERIAL INFECTION IN IRAN

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Background: Defects of the immune system in Primary immunodeficient diseases (PIDs) predispose individuals to recurrent infections. Complex genetic components for susceptibility to mycobacterial disease have been suggested. Natural human immunity to the mycobacteria group, including Mycobacterium tuberculosis(MTB), Bacille Calmette-Guérin (BCG) or nontuberculous mycobacteria (NTM) relies on the functional IL-12/23-IFN-γ integrity of macrophages (monocyte/dendritic cell) connecting to

T lymphocyte/NK cells. Restricted defective molecules in the circuit and recently discovered CYBB responsible for autophagocytic vacuole and proteolysis have been identified in around 60% of patients with the Mendelian susceptibility to the mycobacterial disease (MSMD) phenotype. Primary defects in oxidase activity in chronic granulomatous disease (CGD) lead to severe, life-threatening infections. The role of phagocytic respiratory burst in host defense against mycobacterium tuberculosis was controversial. Previous studied showed that the critical role at reactive oxidants is to serve as intracellular signals for activation of microbicidal enzymes, rather than excretions a microbicidal effect perse.The role of phagocytic respiratory burst in host defense against M. TB is further supported by recent studies discovered immunological defects secondarily affecting phagocyte respiratory burst function and resulting in primary immunodeficiencies with varied phenotypes, including susceptibilities to pyogenic or mycobacterial infections.

The patients with severe PID's like SCID have broader diverse infections susceptibility and mycobacterial infections as well, however, Common variable immunodeficiency (CVID) mostly characterized by a deficiency of immunoglobulins and recurrent sinopulmonary infections.

Method: We overview the clinical rate of mycobacterial disease in our PID cases and evaluate the complex cases.

Results: Two hundred PID cases were evaluate between 1996-2013 in our clinic, Among 5% of them which diagnosed as MSMD nearly all presented with mycobacterial infection.8% diagnosed as CGD and interestingly 60% of them have been experienced mycobacterial disease sometimes in their life, as disseminated BCG or late onset complications of BCG including osteomyelitis or MTB once or more than one episode through their life. Also we have presented a CVID patient with disseminated TB and granulomatouse hepatitis, TB arthritis , peritonitis and a patient with LAD and nontubercolouse mycobacterial infectiouse abcesses of her skin.

Conclusion: PID cases Like CGD, MSMD or CVID which are living in area's with high prevalence of mycobacterial infection could have quiet different presentations and the study of these complex cases has provided essential insights into the functioning of the immune system. Despite the conventional view we have confirmed that the generation of ROIS by phagocytic respiratory burst may play a role in the defense of the host against M. tuberculosis by clinical evidence.

USE OF THE STIMULATED NBT REDUCTION SLIDE TEST FOR PRENATAL DETECTION OF CHRONIC GRANULOMATOUS DISEASE – A CASE REPORT

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Chronic granulomatous disease (CGD) is a rare disease caused by mutation in any of the five components of the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase in phagocytes, resulting in recurrent, life-threatening bacterial and fungal infections of the affected individuals. Our proband male patient presented at age of 2 years with bilateral pneumonia and positive serology for Aspergillus sp. The phorbol myristate acetate (PMA) stimulated nitroblue tetrazolium (NBT) test showed no reduction (0%) in our patient and partial reduction (58%) in his mother. Analysis of the CYBB gene showed a deletion of nucleotide G (c.1237delG) exon 10 causing frame shift mutation and early termination of translation (p.Val413Serfs). This mutation was not previously described. At the moment of diagnosis, his mother was already pregnant, 19th week of gestation. Fetal ultrasound showed that she was carrying a male fetus. The fetal blood sample, obtained by the percutaneous umbilical cord blood sampling, showed male karyotype and the PMA stimulated NBT test showed 100% reduction. There were no complication during pregnancy or delivery and a healthy boy was born. The proband patient underwent allogenic HSCT, his sister was the identical sibling donor. In the cases where the family-specific mutations are unknown, partial or complete gene deletions can be recognized by multiplex ligase-dependent probe amplification (MLPA) or array comparative genomic hybridization (aCGH) analysis of genomic DNA. The other possibility is cheap and accurate PMA stimulated NBT test used for more than three decades, since Levinsky RJ *et al* described first group of patients. It can clearly distinguish between affected CGD patients, carriers and healthy controls.

CLINICAL AND IMMUNOLOGIC FEATURES OF PATIENTS WITH THE PHENOTYPE OF AR-HIES: PATIENTS WITH AND WITHOUT DOCK8 DEFICIENCY

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Hyper-IgE syndromes (HIES) are characterized by recurrent sinopulmonary infections, pneumonia and abscesses, eczema, elevated serum IgE and eosinophilia. We presented here 15 patients with Dock-8 deficiency and 11 patients with the overlapping features with AR-HIES. We compared the clinical and laboratory features of our patients with previously reported patients with Dock-8 deficiency. 26 patients admitted and diagnosed as AR-HIES at Hacettepe University department of Pediatric Immunology from 2007 to 2013 were evaluated. Fifteen out of 26 patients were diagnosed as Dock-8 defect by molecular analysis. Features of the patients with AR-HIES Dock-8 Deficient and non-Dock-8 deficient group are given in the Table 1.

All patients with Dock-8 deficiency presented with cutaneous viral infections or early onset and severe atopic dermatitis. Many have also food allergy and/or asthma. Neurological complications and malignancy were seen in 20% and 27% respectively. Sixty seven percent of patients had low T; 83 %, low CD4 levels; 100%, high IgE. The latter features were shared between patients with or without Dock-8 deficiency, except atopic dermatitis which was mild when present in patients without Dock-8 deficiency and IgE levels were only mildly high or normal.

We identified STK4 and coronin 1A deficiency in two siblings each among the 11 patients who showed overlapping features with AR-HIES and do not have Dock-8 deficiency.

Our results showed that patients with Dock8 deficiency have early onset and more remarkable eczema, food allergy, asthma, more marked eosinophilia, higher IgE, low IgM levels and development of malignancy. These features may be helpful in differentiation Dock8 patients from patients without Dock-8 deficiency. It seems routine lymphocyte subset study results are not helpful for this differentiation.

PATIENTS	Dock-8 n = 15(%)	Non-Dock8 n = 11(%)
Cutaneous viral infections		
HSV	85	40
VZV	16	33
HPV	38	60
MC	33	20
Abscesses	27	10
Mucocutaneous candidiasis	14	20
URTI	100	100
Pneumonia	93	60
Bronchiectasis	35	30
Allergic Symtoms		
Eczema	100 (severe)	27 mostly mild, (dermatitis 40%)
Food allergy	70	-
Asthma	30	-
Autoimmunity		
Sclerosing cholangitis	20	-
Autoimmune hemolytic anemia	-	14
Other autoimmune manifestations	-	45%(3 Leukocytoklastic vasculitis, 1 hypothyroidism, and 1 immune thrombocytopenic purpura
Malignancy	27 (2 siblings from 2 families died of lymphoma, 1 developed multiple malignancy (squamous cell Ca, leiomyosarcoma, basal cell Ca	A sibling died of lymphoma
Nerological complication	20	1 patient (epilepsy, brain infarct)
Outcome	3 died (one with post -BMT comp., 2 with malignancy	All alive

IMMUNORECONSTITUTION IN THE FIRST THRE YEAR AFTER HSCT IN A NEWLY ESTABLISHED TRANSPLANTATION UNIT

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HSCT might be curative for some PIDs. Our immunology and transplantation center was newly established. We retrospectively reviewed all children with PID who diagnosed and received HSCT at Ondokuz Mayıs University or somewhere between June 2010 and December 2013. Twenty-two patients were identified. Four of them were referred to us for HSCT from other centers. The median age was 6 months (1 month–10 yr) at HSCT. Patients' diagnoses were SCID (n = 11), CHS (n = 2), Leukocyte adhesion deficiency (n=2), MHC Class II deficiency (n=2), Chronic granulomatous syndrome (n = 2), HLH (n = 1), WAS (n = 1) and Omenn's syndrome (n = 1). Seven patients received HLA-matched related HSCT; twelve haploidentical HSCT and two matched unrelated HSCT. One SCID patient died just after her diagnosis. Two patients developed BCGosis secondary to reactivation of pretransplant vaccination. One of them died due to hemophagocytic bone marrow aplasia, and the other has recovered. Five patients had graft failure; two of them received no conditioning regimens because of general health status and the other because of CMV infection. At a median follow up of 6 months (range 0-64), 15 patients are alive, with overall survival of 68 %. We conclude that; our clinic undertakes an important duty in our region for PID patients. Also, different PID's could be seen in our region.