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ABSTRACTS

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PO- 001

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

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

PO-002

Wiskott-Aldrich Syndrome with Normal Sized Platelets

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

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

PO - 056

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

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

PO - 057

NEMO: Description of an Atypical Clinical Case

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

PO - 058

Aberrant NK Cell Phenotype in a Patient with CD25 Deficiency

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

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

PO - 059

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

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

PO - 060

Report of Four Cases of Activated PI3 Kinase Delta Syndrome

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

PO - 061

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

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