The Interplay Between Immunodeficiencies, Allergies, Immune Dysregulation, and Lymphoproliferation: EAACI 2025

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INBORN errors of immunity (IEI) are rare conditions caused by genetic factors that impair the development or function of the immune system. Currently, 559 IEIs are recognised, and this number is expected to grow with advancements in genomic sequencing and molecular immunology. Although IEIs typically present with an unusual tendency for recurrent and/or severe infections, patients often experience other manifestations, including atopy, immune dysregulation, haematological manifestations, and an increased risk of cancer, which highlights the overlap between immunology, rheumatology, allergology, and haematology.

Keeping faith with its dual vocation as a society of allergology and clinical immunology, the European Academy of Allergy and Clinical Immunology (EAACI) Congress 2025 made an effort to provide updates and educational content in the field of rare immunological diseases. Here, the authors review the most impactful presentations and their findings.

MONOGENIC ATOPIC DISEASES

In the NAIS Symposia,[1] Anna Sediva, University Hospital Motol, Prague, Czechia, unravelled the perturbed immunological pathways in 'primary atopic disorders' (PAD), a group of monogenic IEI characterised by allergic inflammation as a predominant characteristic.[2] In PAD, pathways critical to the development of atopy include focal defects in immune cells and epithelial barrier function, as well as global metabolic changes. These lead to chronic Type 2 T helper (Th2) and eosinophil-mediated allergic inflammation, promotion of IgE-class switching in B cells, disruption of peripheral tolerance, and abnormal mast cell degranulation.[2]

In the thematic symposia 'Diagnostic Challenges in Patients with Inborn Errors of Immunity with Different Manifestations of Immune Dysregulation',[3] Riccardo Castagnoli, University of Pavia, Italy, proposed a practical approach to identify PAD. Features raising suspicion include early-onset, severe allergic manifestations, failure to respond to standard treatments, IgE levels >2,000 kU/L, and possible additional manifestations like autoimmunity, lymphopenia, or recurrent infections. Additional red flags include growth delay/short stature, connective tissue abnormalities, neurodevelopmental delay, or syndromic features.

The prototype condition is autosomal dominant hyper-IgE syndrome (AD-HIES), characterised by eczema, skin abscesses, chronic mucocutaneous candidiasis, and recurrent pneumonias, resulting from loss-of-function variants in the *STAT3* gene. Phenocopies of AD-HIES arise from defects in proteins within the STAT3 signalling pathway, such as IL-6 receptor (IL-6R) and Zinc Finger Protein 341 (ZNF341). Other notable related diseases include Comel-Netherton disease, autosomal recessive HIES due to DOCK8 deficiency, ERBIN deficiency, and Loeys-Dietz syndrome.[2] A condition caused by gain-of-function (GOF) variants in *STAT6* is the most recently described PAD, leading to Th2 skewing with early-onset atopic dermatitis, food allergies, eosinophilic oesophagitis, asthma, and short stature.[4]

For IEI with atopy, Th2-biologics and JAK inhibitors (JAKi) may be beneficial, although data on their safety and efficacy are limited. To provide insight in this field, the EAACI Immunodeficiencies Working Group (WG) has launched the ATO-PID task force (TF) to analyse published cases reports and case series of IEI treated with biologics or small molecule inhibitors due to their atopy. Unpublished results from a meta-analysis on 139 patients were presented during the Immunology Section Business Meeting by Federica Pulvirenti, Academic Hospital Policlinico Umberto I, Rome, Italy. Data collected showed that anti-Th2 biologics and JAKi are highly effective in treating atopy in IEI, especially skin manifestations, with a favourable safety profile for dupilumab and omalizumab, while the safety profile of JAKi requires careful individual assessment. The ATO-PID TF has also promoted a digital survey to collect consensus statements on indications, concerns, and monitoring strategies related to the use of anti-Th2 and JAKi in treating atopy in IEI. The survey also aimed to collect unpublished patient data. The WG also promoted a TF on drug hypersensitivity reactions (DHR) in IEI, launching a survey to obtain data on DHR classification,[5] diagnosis, and treatment in IEI.[6]

AUTOIMMUNITY AND AUTOINFLAMMATION IN INBORN ERRORS OF IMMUNITY

During the thematic symposium 'Diagnostic Challenges in Patients with Inborn Errors of Immunity with Different Manifestations of Immune Dysregulation',[3] Mahir Serbes, Çukurova University, Adana, Türkiye, addressed the apparent paradox of immune dysregulation in IEI. The prevalence of autoimmunity in patients with IEI accounts for up to 30%, with about 20% of patients presenting with dysregulation as the initial manifestation, especially autoimmune cytopaenias, conditions affecting the gastrointestinal tract, and autoimmune endocrinopathies.[7,8] Common variable immunodeficiency (CVID) and combined immunodeficiencies showed the highest prevalence of autoimmunity. Features that should raise the suspicion of IEI include early onset of autoimmunity, presence

of polyautoimmunity, resistance to conventional treatments, severe clinical presentation with refractory manifestations, association with infections, and a positive family history. Genetic testing is crucial to allow a definitive diagnosis, due to the high phenotypic overlap among distinct IEIs, and to identify patients eligible for targeted therapies. Treatment includes immunosuppressants as well as biologics. Selected patients can be candidates for haematopoietic stem cell transplantation or gene therapy, which represents the only definitive cure for IEI.

Among IEIs with dysregulation, patients with genetic variants of *CTLA4* and *LRBA* display signs of immune dysregulation, lymphoproliferation, and hypogammaglobulinaemia. The diseases arise, respectively, from haploinsufficiency of the gene encoding for *CTLA4*, an inhibitory receptor that regulates T cell activation, and biallelic loss of the gene encoding LRBA, a protein whose deficiency causes a secondary defect of *CTLA4*.[9]

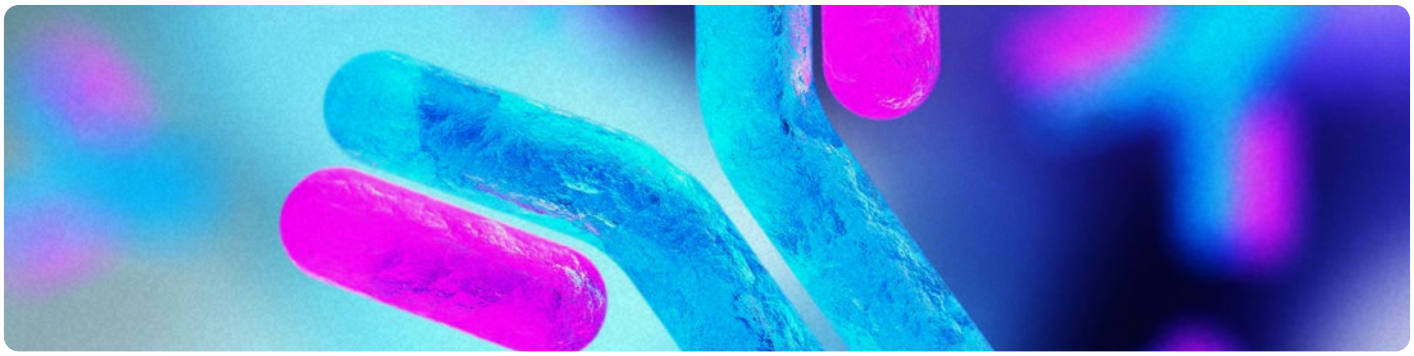
In the JMA session 'Inborn Errors of Immunity: Increasing Awareness in Clinical Practice',[10] Ayça Kykim, Istanbul University, Türkiye, provided an update on the management of IEI. In a Turkish multicentric study of 150 patients with genetic variants of *CTLA4* and *LRBA*,[11] the treatment with abatacept, a synthetic and soluble *CTLA4* approved for rheumatological indications, was shown to improve lymphoproliferation and immune dysregulation, and also served as bridging treatment for haematopoietic stem cell transplantation. In the same session Petter Brodin, Karolinska Institutet, Stockholm, Sweden, focused on interferonopathies, a group of autoinflammatory diseases characterised by variable clinical phenotypes.

Interferons (IFN), classified as Type I (α, β), Type II (γ), and Type III (λ), are crucial for the immune response. Diagnosis of interferonopathies relies on early patient history and clinical signs, such as recurrent fevers, skin vasculopathy, interstitial lung disease, neurological manifestations, and elevated inflammatory markers. IFN signature gene analysis (a blood test assessing IFN effects) confirms interferonopathy. Whole-exome or whole-genome sequencing is used to identify the specific genetic anomaly. Notably, complex conditions include STING-associated vasculopathy with onset in infancy linked to *STING1* mutations, and chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE) related to *PSMB8* mutations. Therapeutic options like JAKi and anifrolumab (a monoclonal antibody targeting Type I IFN receptor) effectively block IFN signalling and reduce inflammation.

> **The prevalence of autoimmunity in patients with inborn errors of immunity accounts for up to 30%, with about 20% of patients presenting with dysregulation as the initial manifestation**

INBORN ERRORS OF IMMUNITY AND LYMPHOPROLIFERATION

In the 'Diagnostic Challenges in Patients with Inborn Errors of Immunity with Different Manifestations of Immune Dysregulation' symposia,[3] Francesco Cinetto, University of Padua, Italy, highlighted lymphoproliferation as a key feature of IEI when associated with hypogammaglobulinaemia or immune dysregulation, especially autoimmune cytopaenias. In IEI, lymphoproliferation can manifest as chronic lymphadenopathy, splenomegaly, or lymphoid infiltration of the lungs, liver, and gut, with resulting organ dysfunction. Historically, autoimmune lymphoproliferative disease (ALPS), a condition mediated by defects in the FAS-regulated apoptosis of lymphocytes, has been regarded as the prototype of IEIs with lymphoproliferation and autoimmunity. However, in recent years, many other conditions have been identified, characterised by lymphoproliferation and autoimmune cytopaenias as primary manifestations, including defects of *CTLA4*, *LRBA*, *NFKB1*, *PIK3CD*, *PIK3R1*, and *STAT3* GOF. For these conditions, in 2024, the term 'autoimmune lymphoproliferative primary immunodeficiencies (ALPID)' was proposed.[12] Among autoimmune lymphoproliferative primary immunodeficiencies, activated



PI3Kδ syndrome (APDS) is a monogenic IEI resulting in lymphadenopathy, splenomegaly, an increased risk of developing lymphomas, and immunodeficiency. APDS arises from GOF mutation in the *PI3KCD* gene and a loss-of-function mutation in the *PIK3R1* gene, both leading to hyperactivation of the PI3Kδ signalling pathway, crucial in lymphocyte growth, differentiation, and survival.

In her speech on IEI management, Kykim reported that leniolisib, a PI3Kδ inhibitor recently released for treating APDS, reduced the signs of lymphoproliferation (lymph node and spleen size), increased the number of circulating naïve T cells, and reduced serum IgM levels.[10]

CLOSING REMARKS

In conclusion, in IEI, infections are just the tip of the iceberg of a multifaceted and complex phenotype. Advancements in the fields of genetics and molecular diagnostics are contributing to the elucidation of pathogenic pathways involved in IEI and are revealing targets for precision medicine. Delays in diagnosis, due to symptom overlap and the rarity of these diseases, can lead to serious complications. Increasing physician awareness and prompt referrals to specialised centres are vital for better patient outcomes.

> **In recent years, many other conditions have been identified, characterised by lymphoproliferation and autoimmune cytopaenias as primary manifestations**

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