Hyper IgE Syndromes (HIES), clinical phenotypes, molecular characteristics and therapeutic options

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Several well-defined genetically determined primary immunodeficiency diseases (PID) are associated with elevated serum IgE levels. The “classic” HIES are rare PIDs inherited in autosomal dominant (AD) or autosomal recessive (AR) manner. Patients with AD-HIES often present with Staphylococcus aureus abscesses, recurrent episodes of pneumonia with pneumatocel formation, very high IgE levels, and eczema. The entity was reported in 1966 as Job syndrome, and as Hyper IgE syndrome in 1972 when elevated IgE levels and coarse facial features were noticed. Other findings include hyperextensible joints, delayed shedding of primary teeth, scoliosis and bone fractures with minimal trauma. In 2010, several groups reported that AD-HIES/Job syndrome is caused by heterozygous mutations in STAT3 which belongs to the STAT family of transcriptional regulators. The generation of both mutated nonfunctional and wild type STAT3 alleles results in decreased wild type STAT3 dimers (~25%) which affect the development of IL–17 producing TH17 effector T cells, that play a prominent role in controlling infectious agents commonly observed in HIES. However, the precise mechanisms by which heterozygous STAT3 mutations cause the multitude of pathologies characteristically seen in AD–HIES patients are only partially understood. A second form of HIES (AR-HIES) complicated by recurrent viral infections and involvement of the central nervous system but without connective tissue and bone abnormalities was recently associated with DOCK8 mutations. Other single gene defects resulting in PID with eczema, increased serum IgE, and recurrent infections include Omenn Syndrome (caused by hypomorphic mutations in RAG1/RAG2, ARTEMIS, ADA or RMRP); Wiskott-Aldrich Syndrome caused by mutations in the *WAS* gene; Immune Dysregulation, Polyendocrinopathy, Enteropathy, X-linked syndrome (IPEX) caused by mutations in the gene *FOXP3;* and Netherton syndrome caused by mutations in *SPINK5*. These syndromes, unlike atopic dermatitis, are caused by single gene defects and have in common abnormal cognate and innate immunity, increased susceptibility to infections, elevated IgE and therapy resistant eczema. Treatments include symptomatic measures (antibiotics, antifungals and IVIG for Job Syndrome and Netherton Syndrome; immune suppressive therapy for IPEX) and hematopoietic stem cell transplantation (Omenn Syndrome and DOCK8 deficiency).