

Hyper Immunoglobulin E Syndrome – an Overview

Introduction

Hyper Immunoglobulin E (IgE) syndrome (HIES) is a rare primary immunodeficiency syndrome characterized clinically by elevated serum IgE levels, recurrent skin infections, recurrent lung infections, eczema, and connective tissue and skeletal abnormalities (1). While the prevalence of disease is currently estimated at <1 in 1 million (2), the true prevalence is likely higher since HIES can be difficult to diagnose. Diagnosis of HIES is complicated by the non-specificity of some symptoms, such as elevated serum IgE levels and skin rashes, and the atypical presentation of others. HIES-related pneumonias in particular are often not recognized, since they tend to lack characteristic symptoms such as fever and cough. A family history indicative of HIES may also not always be obvious, since HIES shows variable expressivity and penetrance, ranging from 33-100% (3-6). In addition, many cases of HIES are due to de-novo mutations. At the same time, treatment of HIES patients with aggressive antimicrobial prophylaxis is crucial, since bacterial and fungal superinfections accompanying recurrent pneumonias are a major cause of mortality (7). Since about 22% of HIES has been associated with mutations in the gene *STAT3*, genetic testing can confirm diagnosis of HIES, helping to recognize HIES-related pneumonias and facilitate prophylactic treatment with antibiotics. Genetic testing can also allow detection of at-risk individuals in family members of HIES patients, facilitating timely diagnosis and treatment.

In addition to *STAT3*-related HIES, which typically shows autosomal dominant inheritance, a rare autosomal recessive form of familial HIES associated with mutations in the *TYK2* gene has been reported (Table 1). *TYK2*-related HIES usually occurs in the context of very severe immunological features but lacks many of the connective tissue and skeletal abnormalities seen in the autosomal dominant form of the disease (8).

Table 1: Genetic Causes of Familial HIES

Gene (Protein)	% HIES (inheritance)	References
<i>STAT3</i> (signal transducer and activator of transcription 3)	6-22% (AD)	(3, 4, 6, 9)
<i>TYK2</i> (tyrosine kinase 2)	<1% (AR)	(10)

AD (autosomal dominant); AR (autosomal recessive)

Molecular Pathophysiology

STAT3 (signal transducer and activator of transcription 3) codes for a transcription factor that, as a component of the JAK/STAT signaling pathway, is involved in regulating transcription of many different genes in response to certain extra-cellular stimuli. The *STAT3* protein is activated by becoming phosphorylated by Janus kinases (JAKs) in response to upstream triggers. Once phosphorylated, *STAT3* proteins dimerize, bind to specific DNA sequences in the promoters of genes, and activate their transcription. In T lymphocytes, *STAT3* activities are central to the tight regulation of several different cytokines, including IL-6, IL-12, IL-17, and IFN- γ (reviewed in (1, 11)). Loss-of-function mutations in *STAT3* can result in a myriad of cytokine-related issues including increased inflammation, increased IgE levels, and a breakdown of host defense to bacterial and fungal infections (reviewed in (1)).

Clinical Presentation

The clinical features of HIES are summarized in Table 2. HIES typically presents as a pustular rash on the face and scalp of newborns, often infiltrated with *Staphylococcus aureus*. In early childhood, immunological manifestations almost always include eczema, boils, recurrent pneumonias, and mucocutaneous candidiasis. The late childhood/adolescent period is typi-

cally marked by more aggressive pneumonias (with pustular pneumatocele formation) and skin manifestations, but also non-immunological manifestations which can include cranio-facial abnormalities, retained primary teeth, fractures, scoliosis, and hyperextensibility. Age of onset of HIES is usually in the newborn period, but diagnosis may be delayed until both immunologic and non-immunologic features are present (12).

Table 2: Clinical features of HIES	
Immunologic (frequency)	
<ul style="list-style-type: none"> • Newborn rash (81%) • Eczema (100%) • Boils (87%) • Recurrent pneumonias (87%) • Mucocutaneous candidiasis (83%) • Peak serum IgE > 2000 IU/ml (97%) • Eosinophilia (93%) • Increased incidence of lymphoma (unknown) 	
Non-immunologic (frequency)	
<ul style="list-style-type: none"> • Asymmetric face, broad nose, deep set eyes, prominent forehead (83%) • Retained primary teeth (72%) • Mild fractures (71%) • Scoliosis > 10 degrees (63%) • Hyperextensibility (68%) • Focal brain hyperintensities (70%) • Chiari 1 facial malformations (18%) • Craniosynostosis (unknown) • Arterial aneurysms (unknown) • Degenerative joint disease (unknown) 	

Adapted from (1)

Diagnosis

While almost all HIES patients show elevated IgE levels (>2000 IU/ml) accompanied by eosinophilia, this finding alone is not sufficient for diagnosis of HIES since patients with allergic skin rashes or a variety of other primary immunodeficiency disorders may have serum IgE levels in the HIES range. Clinical diagnosis of HIES is therefore based on the classic “diagnostic triad,” which is defined by the presence of elevated IgE levels, pneumonia, and skin abscesses (13). Radiographs

and CT scans can show pulmonary abnormalities consistent with recurrent lung infections and skeletal abnormalities including minor fractures and scoliosis. Lung and skin biopsies will often show *Staphylococcus aureus* infiltrates. Other lung pathogens commonly found are *Streptococcus pneumoniae* and *Haemophilus influenzae* (reviewed in (12)). However, the diagnostic triad for HIES is only present in about 77% of patients (14). In unclear cases, a clinical diagnosis of HIES can be confirmed through genetic testing, since published studies have shown a causal relationship to certain variants in *STAT3* (reviewed in (1)). In clear cases of HIES, genetic testing of the index patient can identify the familial mutation and allow identification of at-risk family members.

Treatment

Therapeutic options for HIES (reviewed in (1, 13)) mainly revolve around treatment of lung and skin infections with prophylactic antibiotics and topical steroids and antifungal creams for the dermatitis associated with skin infections. Other treatments include dental extraction of primary teeth and orthopedic care for fractures and scoliosis. A cure for HIES is currently not available; bone marrow transplantation has been tested in a few HIES patients, but was of short-lived success (15, 16).

References

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