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Hyper-IgE syndrome update

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Autosomal dominant hyper-IgE syndrome (AD-HIES) or Job's syndrome is a primary immunodeficiency with a wide array of clinical features caused by dominant negative mutations in STAT3. In recent years, not only the clinical phenotype of the disease has been expanded with recognition of features such as arterial aneurysms, but also our understanding of the pathogenesis of the disease has greatly improved.

Keywords: autosomal dominant hyper-IgE syndrome; Job's syndrome; signal transducer and activator of transcription 3; Th17 cells

Introduction

So went Satan forth from the presence of the LORD, and smote Job with sore boils from the sole of his foot unto his crown.

—King James Bible

First described in 1966, Job's syndrome is characterized by the triad of eczematoid dermatitis and recurrent skin and pulmonary infections.¹ In 1972, Buckley *et al.* recognized elevated IgE levels as part of the clinical spectrum, hence the current reference to hyper-IgE syndrome (HIES).² Over the next few decades the multisystem nature of the disease was delineated,³ and in 2007, dominant-negative mutations in signal transducer and activator of transcription 3 (STAT3) were identified as the link between recurrent infections and connective tissue abnormalities.^{4–6} STAT3 is integral to signal transduction for multiple cytokines and widely expressed across tissue types.^{4,5,7–10} The last several years of research has brought a deepened understanding of both the clinical phenotype and the pathogenesis of the autosomal dominant form of the disease (AD-HIES). More recently autosomal recessive syndromes with IgE elevation have been genetically characterized, largely from mutations in DOCK8. This review will focus on the HIES due to STAT3, which is the more common and better described disease.

Immunologic and infectious disease manifestations

AD-HIES is characterized by eczematoid rashes, skin abscesses, recurrent sinopulmonary infections, mucocutaneous candidiasis, and malignancies (Table 1).^{3,6,11–13} Rashes usually start within the first few weeks of life, typically presenting as pustular or eczematoid eruptions on the scalp and face.^{14,15} A biopsy may show eosinophilic infiltrate. Rashes may resolve or persist and are consistent with eczematoid dermatitis and, like eczema, appear to be *Staphylococcus aureus* driven. Antistaphylococcal therapy, along with topical antiseptics (i.e., bleach baths¹⁶), is part of the routine regimen and are typically quite effective in controlling the rash.

The initial description of Job's syndrome included skin infections that lacked the usual features of warmth and erythema—so-called “cold” abscesses, which are nearly a universal feature of the disease.¹ Associated chronic signs of inflammation may or may not be present. Recurrent boils usually abate with good skin care and antistaphylococcal maintenance therapy (such as trimethoprim-sulfamethoxazole), but may persist in problem areas such as the axilla or groin.

Recurrent sinopulmonary infections common in HIES are predominately caused by *S. aureus*, with *Streptococcus pneumoniae* and *Haemophilus* species less frequently associated.^{3,17} Healing after these

Table 1. Clinical features of hyper-IgE syndrome

Immunologic (% frequency)	Nonimmunologic (% frequency)
Eczema (100)	Intraoral lesions (93)
Peak serum IgE > 2,000 IU/mL (97)	Characteristic facies (83)
Eosinophilia (93)	Minimal trauma fractures (71)
Boils (87)	Coronary artery tortuosity or dilation (70)
Recurrent pneumonias (87)	Focal brain hyperintensities (70)
Mucocutaneous candidiasis (83)	Hyperextensibility (68)
Newborn rash (81)	Scoliosis (63)
	Retained primary teeth (>60)
	Hypertension (54)
	Coronary aneurysms (37)
	Chiari 1 malformation (18)
	Degenerative joint disease (unknown)
	Craniosynostosis (unknown)

pyogenic pneumonias is aberrant, with bronchiec-tasis and pneumatoceles frequently resulting (Fig. 1). Once parenchymal lung damage is present, the spectrum of pulmonary pathogens changes and becomes more similar to those seen in cystic fibrosis. *Pseudomonas aeruginosa* becomes common and dif-ficult to eradicate, and pulmonary nontuberculous mycobacteria occurs at a rate similar to that in cys-tic fibrosis.¹⁸ Filamentous molds such as *Aspergillus* and *Scedosporium*, which HIES leukocytes appear to kill normally *in vitro*, may occupy the pneumatoce-les.¹⁹ These secondary infections are very difficult to treat and are major causes of morbidity and mortal-ity for these patients, due to recurrent exacerbations of infection and pulmonary hemorrhage.²⁰ Pneu-matocele management is difficult. Although resec-tion is appealing for its ability to decrease the risk of secondary infection and hemoptysis, surgical resec-tion carries a fairly high frequency of complication due to bronchopleural fistulae and impaired lung expansion. These in turn can lead to soiling of the pleural space and persistent infection.

Susceptibility to nonfilamentous molds includes *Pneumocystis jiroveci* pneumonia (PCP), mucocu-taneous candidiasis, and the endemic dimorphic fungi. Similar to T cell immunodeficiencies (for example, severe-combined immunodeficiency syn-drome or congenital HIV), PCP can manifest in in-fancy, prior to pyogenic pneumonias,^{17,21} and thus raises concern for immunologic evaluation. How-ever, PCP in HIES is infrequent, and even less

common outside of infancy. Chronic antifungals may be needed to control mucocutaneous candidia-sis. *Histoplasma*, *Coccidioides*, and *Cryptococcus* can cause isolated gastrointestinal tract disease,^{22–25} and coccidioidal and cryptococcal meningitides have been reported.^{26,27}

AD-HIES is associated with an increased risk of malignancies—most notably non-Hodgkin’s lym-phoma (NHL), with the majority being of B cell origin and aggressive histology.^{12,13} Other reported malignancies have included Hodgkin’s lymphoma, leukemia, and cancers of the vulva, liver, and lung.²⁸

Nonimmunologic manifestations

The pleiotrophic nature of STAT3 accounts for the multitude of changes in HIES, not only immuno-logical but also craniofacial, musculoskeletal, dental, and vascular abnormalities.^{3,6,12,13,29–31} Character-istic facial features become apparent in late child-hood and early adolescence, with increased interalar distance, prominent forehead and chin, coarse skin, and facial asymmetry.^{3,6} Although these changes are apparent to the human eye, the characteristic facial features have been difficult to identify statistically, except for nasal alar width. The craniosynostosis and Chiari type I malformations generally do not require surgical correction.^{30–32}

Musculoskeletal abnormalities include hyperex-tensibility, scoliosis, minor trauma fractures, and osteopenia.³ Scoliosis occurs commonly and may be severe enough to require placement of spinal

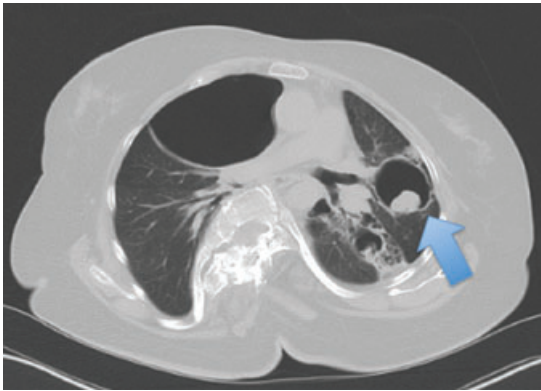


Figure 1. Chest CT showing pneumatocoeles with aspergilloma (arrow) in a 40-year-old woman.

rods. About 50% of HIES individuals have minimal trauma fractures, and many have osteopenia, although there is not close correlation between bone mineral density and propensity to fracture. There is also hyperextensibility of the joints, which may account for degenerative joint disease at younger ages than in the general population. Particularly striking is cervical spine disease in the fourth and fifth decade of life that may require surgical stabilization (Fig. 2).

Failure to exfoliate primary teeth and the need for surgical extraction of some or all primary teeth is a common finding in HIES individuals.^{3,33} Almost all HIES patients also have abnormalities of the oral cavity, including high arched palate, hard palate midline sagittal fibrotic thickening, deep grooves—and even pyramidal or ovoid cleft—on the tongue, and buccal mucosa with multiple mucosal fissures.³⁴ The recent recognition of defects in IL-11 signaling in cases of isolated craniosynostosis and impaired primary tooth deciduation is confirmation that this STAT3-mediated pathway is impaired in HIES as well.³⁵

Vascular abnormalities have been recognized in recent years and include aneurysms, dilation, and tortuosity of middle-sized arteries, and lacunar infarctions.^{20,32,36,37} Myocardial infarction has been reported as the result of coronary artery aneurysms in one HIES man. There are also case reports of bilateral berry aneurysms of the carotids and of middle cerebral artery mycotic aneurysm. These observations prompted further investigation of vascular abnormalities in the HIES population.^{32,36,38,39} Cardiac CT and MRI in HIES individuals found

that coronary artery aneurysms and tortuosity are a common feature of the disease. Seventy percent of HIES patients had coronary artery tortuosity or dilation, compared to 21% of a control group. HIES has an increased incidence of hypertension but a paucity of atherosclerosis, indicating that STAT3 is involved in vascular remodeling.⁴⁰

Focal hyperintensities are seen on brain MRI in the majority of individuals with HIES, increasing in number with age. The clinical significance of these lesions remains unknown; they are usually not associated with neurologic abnormalities.³² They may represent focal areas of demyelination, and whether they are due to ischemia or infection or poor astrocyte activity is still unknown.

Laboratory abnormalities

Laboratory abnormalities in HIES include eosinophilia and IgE usually elevated above 2,000 IU/uL. The IgE level may decline over time and occasionally reaches normal levels in adulthood despite persistent symptoms.³ Interestingly, individuals with HIES have very little in the way of allergies or anaphylaxis to foods, a marked difference from those with DOCK8 deficiency. Serum IgG and IgM are usually normal, and serum IgA is normal or low; however, impaired specific antibody responses are seen in some with HIES. Lymphocyte phenotyping often shows diminished memory T cells (CD45RO⁺) and memory B cells.⁶ HIES has also been associated with decreased CD27⁺ B cells.⁴¹

Genetics

In 2007, mutations in STAT3 were identified as the cause of autosomal dominant HIES.^{4,5} Mutations are dominant negative and inhibit the activity of the wild-type allele.⁵ STAT3 is necessary in embryogenesis, as homozygous STAT3 knockout mice do not survive.⁴² Disease-causing mutations in STAT3 are largely missense or in-frame deletions located primarily in the SH2 and DNA-binding domains.^{4,5,7–10} In general there does not seem to be a clinically relevant genotype–phenotype correlation in many of the features of HIES; however, there is a modest increase in some of the non-immunologic features in the SH2 domain group, including high palate and increased interalar distance, which may explain an increased frequency of sinusitis in this group. There was also increased

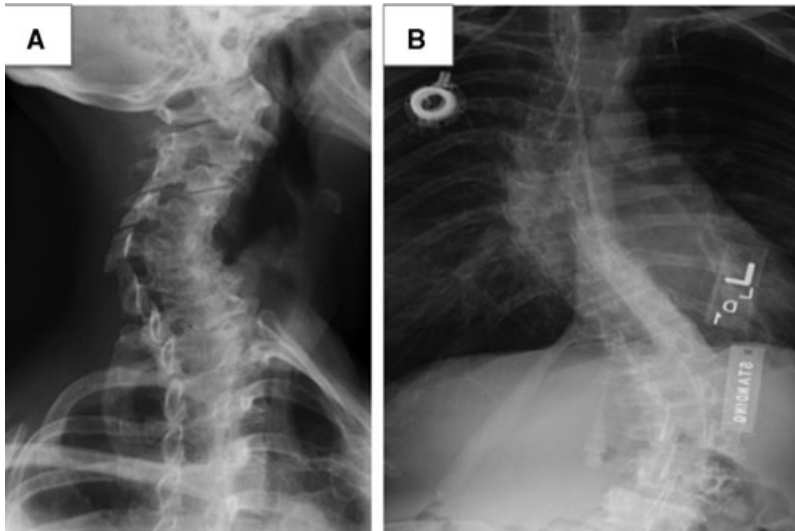


Figure 2. (A) Cervical spine disease in a 55-year-old woman. (B) Severe scoliosis is seen in $>50\%$ of AD-HIES individuals.

scoliosis in the SH2 domain group compared to those with DNA-binding site mutations.⁴³ Increased frequency of sinusitis was noted in patients with SH2 domain mutations, which may reflect facial anatomical differences rather than immunological aberrations.⁴³

HIES should be suspected in individuals with elevated IgE and both of the immunologic and somatic features as described. A scoring system was developed prior to identification of the genetic etiology to aid in diagnosis of HIES and is still helpful to predict who is likely to have STAT3 mutations.⁴⁴

Pathogenesis

Since the identification of mutations in STAT3 in HIES in 2007, great strides have been made in understanding the pathogenesis of the disease. HIES is a disease of both too much inflammation, as exhibited by the exuberant purulence seen in pneumonias and the subsequent pneumatocele formation, as well as too little inflammation—which is indicated by the presence of cold abscesses. STAT3 is integral to signal transduction for multiple cytokines, including IL-6, IL-10, IL-11, IL-17, IL-21, IL-22, IL-23, leukemia inhibitory factor, oncostatin M, cardiotrophin-1, cardiotrophin-like cytokine, and ciliary neurotrophic factor through the shared signal-transducing molecule gp130. This pathway controls both proinflammatory (for example, IL-6) and anti-inflammatory (for example, IL-

10 and suppressors of cytokine signaling (SOCS)) proteins.

Mutations in STAT3 lead to failure of Th17 CD4 cell differentiation, which is STAT3-dependent; this explains some of the susceptibility to infection seen in HIES.^{7,8,45,46} This signaling abnormality, first demonstrated via an association between defective IL-17 function and mucocutaneous candidiasis in humans, has been confirmed by the recognition of patients with mucocutaneous candidiasis and autoantibodies to IL-17, as well as by patients with mutations in IL-17F or the IL-17R.^{47–49} IL-17 signaling is also involved in *S. aureus* skin infections in mice.⁵⁰ IL-22 and IL-17 are thought to play a role in host defense through upregulation of antimicrobial peptides such as human beta defensin 2 (BD2) and CC-chemokine ligand 20 (CCL20).⁵¹ Human BD2 is important in the atopic dermatitis that is commonly associated with *S. aureus*.^{52,53}

The saliva of individuals with HIES has low levels of critical candidacidal peptides, including histatins and BD2, which are induced by IL-17.⁵⁰ Saliva is highly enriched with beta defensins and histatins, which exert direct candidacidal activity.⁵⁴ IL-17 directly activates the promoters for mouse BD3 and human BD2.⁵⁵ IL-17A, but not IL-22, has direct effects on human salivary glands, which may explain the lack of histatins in the saliva of HIES patients and their susceptibility to mucosal candidiasis.⁵⁰

The skin and lung infections of HIES may also be due to impaired Th17 cell differentiation and signaling, and their susceptibility to epithelial infections. Keratinocytes and bronchial epithelial cells display a much stronger dependence than other cell types on Th17 cytokines for their production of chemokines and antibacterial peptides.⁵⁶ Skin and lung epithelial cells efficiently secrete antimicrobial peptides only when stimulated with a combination of Th17 cytokines and classical proinflammatory cytokines (e.g., TNF- α , IL-1 β , IFN- γ). When normal keratinocytes and bronchial epithelial cells were stimulated with activated HIES T cell-derived cytokines, secretion of these factors was impaired compared to epithelial cells incubated with control T cell-derived cytokines. For nonepithelial cells, such as fibroblasts, endothelial cells, and macrophages, antibacterial factors were secreted efficiently when stimulated with proinflammatory cytokines that were not STAT3-dependent, such as IL-1 β .⁵⁶

Impaired IL-11 signaling causes craniosynostosis, delayed tooth eruption, and supernumerary teeth.⁵⁷ Inactivation of IL-11 signaling was caused by homozygous missense mutations in IL-11R alpha in three unrelated consanguineous Pakistani families associated with craniosynostosis and delayed tooth eruption.⁵⁷ These missense mutations (specifically Arg296Trp) rendered IL-11R alpha unable to stimulate STAT3-mediated signal transduction, mimicking what is seen in STAT3 mutations.⁵⁷

Other nonimmunologic aspects of HIES appear to relate to abnormalities of tissue remodeling. Lung healing after pneumonia or surgery is impaired, frequently leading to progressive parenchymal damage. Because matrix metalloproteinases (MMPs) regulate tissue remodeling, we examined MMP levels in the plasma of HIES patients. In a group of 37 HIES patients with STAT3 mutations, MMP-8 and MMP-9 were approximately threefold higher than control, while MMP-3 was about one-third the normal level.⁵⁸ MMP-8 exhibits threefold greater enzymatic activity against type I collagen than the other interstitial collagenases, and has been shown to be involved in acute lung inflammation.⁵⁹ MMP-9 has been associated with abdominal aortic aneurysms through its role in vascular smooth muscle migration and macrophage infiltration.^{60,61} MMP-3 plays a role in fibrinolysis and angiogenesis, and is important for vascular and cardiac matrix remodeling. Further study is necessary to determine how MMP

dysregulation may occur and whether this can be altered to improve tissue remodeling.

The pathogenesis of the vascular abnormalities in HIES may relate to MMP or TGF- β dysregulation.^{62–65} Other disorders that involve dysregulation of TGF- β include Marfan syndrome and Loeys–Dietz syndrome, which have similar vascular abnormalities as well as scoliosis and hyperextensible joints.^{66,67}

Treatment

The mainstay of therapy for HIES revolves around proper skin care and prevention and aggressive treatment of infections. Since HIES patients may lack the classic signs and symptoms of infections, such as fevers, chills, or rigors, a careful history, physical exam, and appropriate imaging are important to catch infections.

Prophylactic antibiotics targeted against *S. aureus* (for example, trimethoprim/sulfamethoxazole) are used to decrease the frequency of pneumonia with the goal of preventing parenchymal lung damage. Skin care usually includes oral antistaphylococcal prophylactic antibiotics and bleach baths or chlorhexidine washes, which help to improve eczematoid dermatitis and prevent abscesses. Antifungal prophylaxis is not routinely given but may be helpful in HIES individuals with chronic *Candida* infections such as onychomycosis. Antifungal agents that also treat *Aspergillus* (for example, itraconazole, voriconazole, and posaconazole) are used in those with fungal lung infections or colonization. Anti-*Aspergillus* treatment may be considered for any HIES patient with pneumatoceles, as these place patients at a higher risk for developing *Aspergillus* infections.

Hypertension is seen fairly commonly in HIES and should be treated due to its possible association with vascular abnormalities.⁴⁰ Antibody production defects in HIES are variable, as has been reported.⁶⁸ This apparently intrinsic variation in the B cell repertoire in HIES has bedeviled blanket recommendations for immune globulin replacement in HIES. Some reports claim fewer infections in immune globulin recipients, and this is to be expected in selected cases. At this point it seems appropriate to test antibody responses and to consider replacement in those cases for which defects are demonstrated. However, anti-staphylococcal prophylaxis is probably appropriate for all patients.^{69–71}

The role of bone marrow transplantation (BMT) in HIES is unclear. The initial report of HIES BMT claimed failure to correct the infection susceptibility and IgE elevation. The first patient transplanted suffered from lymphoma and died posttransplant.⁷² A second case was reported to recur with HIES-related features four years posttransplant, despite full donor engraftment in all lineages.⁷³ Recently, two children transplanted for high-grade non-Hodgkin lymphoma were subsequently reported to have STAT3 mutations. These children had successful myeloablative HLA-matched sibling BMTs that resulted in full engraftment. Ten and fourteen years after BMT both immunologic and nonimmunologic features of HIES were reported to be resolved.⁷⁴ Interestingly, not only did the osteoporosis improve (pretransplant *t* score of -4.04 and posttransplant *t* score of -0.8), but there was also resolution of characteristic facies. This successful curative treatment of AD-HIES by BMT is provocative, and suggests that there are likely other patients transplanted in childhood for lymphoma who may be identified through looking back. This approach may be important as many individuals suffer from progressive lung and other diseases, which might be prevented with early BMT.

Conclusion

In summary, HIES is a primary immunodeficiency characterized by defects in immunity, connective tissue, skeleton, the brain, and vascular tissues, all due to mutations in STAT3. The pathogenesis of HIES has already shed light on the role of IL-17 in chronic mucocutaneous candidiasis, and will likely continue to shed light on a variety of more common ailments, such as scoliosis, eczema, staphylococcal infections, aneurysms, atherosclerosis, and osteoporosis.

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Conflicts of interest

The authors declare no conflicts of interest.

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