

Hyper IgE syndrome: an update on clinical aspects and the role of signal transducer and activator of transcription 3

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Purpose of review

Hyper IgE syndrome (HIES) is a primary immunodeficiency characterized by eczema, recurrent skin and lung infections, elevated serum IgE, and connective tissue and skeletal abnormalities. We present newly recognized aspects of the clinical phenotype and discuss recent genetic and immunologic findings.

Recent findings

In 2007, mutations in signal transducer and activator of transcription 3 (*STAT3*) were determined to be the cause of autosomal-dominant HIES. Mutations lead to disruption of *STAT3*-dependent pathways, which are crucial for signaling of many cytokines, including IL-6 and IL-10. On the one hand, cells from *STAT3*-defective patients have a proinflammatory profile with elevated TNF α and IFN γ ; on the other hand, *STAT3* mutations result in the inability to produce IL-17 or form Th17 cells.

Summary

HIES was previously defined on the basis of clinical manifestations and laboratory markers that were not specific to the disease. With the identification of *STAT3* mutations as the cause of HIES, we can definitively characterize the disease at molecular and immunologic levels. Future study of HIES and *STAT3* will help us understand eczema, IgE regulation, infection susceptibility, coronary artery disease, scoliosis, and bronchiectasis as well as provide mechanistic insights into treatment.

Keywords

hyper IgE syndrome, Job's syndrome, recurrent infections, signal transducer and activator of transcription 3, Th17 cells

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Introduction

Hyper IgE recurrent infection syndrome (HIES) was first described as 'Job's syndrome', in reference to the Biblical figure Job who was 'smote with sore boils' [1]. Buckley *et al.* [2] later recognized a syndrome of extremely elevated serum IgE with eczema and recurrent skin and lung infections, which they named HIES. Subsequently, the two reports [3,4] were found to be describing the same disease, which is now called by both names. HIES is one of the few primary immune deficiencies with immunologic and infectious manifestations as well as prominent somatic features. The recognition of mutations in signal transducer and activator of transcription 3 (*STAT3*), encoding a signal transduction protein key to many complex pathways as the cause of HIES, has helped explain many aspects of the complex phenotype that is HIES [5^{••}–10^{••}].

Clinical manifestations

HIES is a multisystem disease with varied clinical manifestations (Table 1). Affected individuals may have some

but not all the features of HIES, depending on the age at which they are examined.

Skin

A rash in the newborn period is usually the first clinical manifestation of HIES. The rash typically starts on the face and scalp in the first few weeks of life, and is usually pustular and eczematoid [11,12]. Biopsies show eosinophilic infiltrates and bacterial cultures typically grow *Staphylococcus aureus*. The rash of HIES often persists throughout childhood, but can be controlled with anti-staphylococcal therapies, consisting of antibiotics, topical antiseptics such as diluted bleach, or both.

Boils also begin early in life and are nearly universal, unless antistaphylococcal therapies are initiated early. Classic signs of inflammation, such as warmth and tenderness are variable, sometimes resulting in the 'cold' abscesses reported in the initial description of Job's syndrome [1]. However, frank pus is recovered on aspiration and *S. aureus* is typically cultured. The boils abate with good skin staphylococcal control, but problem areas, such as the axilla and groin, may persist.

Table 1 Clinical features of hyper IgE syndrome

Immunologic (% frequency)	Nonimmunologic (% frequency)
Newborn rash (81)	Characteristic face (83)
Boils (87)	Retained primary teeth (72)
Recurrent pneumonias (87)	Minimal trauma fractures (71)
Eczema (100)	Scoliosis > 10 degrees (63)
Mucocutaneous candidiasis (83)	Hyperextensibility (68)
Peak serum IgE > 2000 IU/ml (97)	Focal brain hyperintensities (70)
Eosinophilia (93)	Chiari 1 malformations (18)
Increased incidence of lymphoma	Craniosynostosis (unknown)
	Arterial aneurysms (unknown)
	Degenerative joint disease (unknown)

Lung

Recurrent pyogenic pneumonias start in early childhood. The most common infecting organisms are *S. aureus*, *Streptococcus pneumoniae*, and *Haemophilus influenzae* [3,4]. Similar to the variability seen with the boils, the extent of pneumonia may be out of proportion to the systemic signs of illness (e.g. fever and purulent sputum), leading to delayed diagnosis. Cough is surprisingly diminished in HIES pneumonias. Bronchoscopy may be needed to establish the specific bacterial diagnosis and also assists in clearance of copious but viscous pus. Pneumatocele formation and bronchiectasis typically follow these pyogenic pneumonias. Structural abnormalities tend not to subside, but serve as sites for future infections with Gram-negative bacteria (typically *Pseudomonas*), molds (usually *Aspergillus* or *Scedosporium*), or nontuberculous mycobacteria [4,13]. These secondary infections cause morbidity and mortality due to hemoptysis, extrapulmonary dissemination or both [13]. Surgical resection of these cysts is controversial, as the site of future serious infection may be removed, but the expansion and healing of the residual lung may be impaired, leading to difficult postoperative management.

Other infections

Mucocutaneous candidiasis is common in HIES, typically manifesting as thrush, vaginal candidiasis and onychomycosis [4]. Much less frequently, disseminated histoplasmosis and cryptococcosis occur, typically in isolated nonpulmonary locations such as in the intestine or tongue [14,15]. *Pneumocystis jirovecii* pneumonia (PCP) has been described, occurring both as the initial pulmonary infection in infants and following a course similar to that in infants with congenital HIV, and in older individuals complicating chronic lung disease [16].

Craniofacial abnormalities

HIES has a characteristic facial appearance that develops during childhood and adolescence, characterized by asymmetry, broad nose, and deep-set eyes with a prominent forehead [3,4]. However, despite the typical facies that can be recognized by the human eye, statistical anthropometric precision has been difficult to achieve

except for nasal alar width. The facial skin often has a coarse, porous texture. Both craniosynostosis and Chiari I malformations occur, but typically do not require surgical correction [17–19].

Musculoskeletal abnormalities

Musculoskeletal abnormalities in HIES include scoliosis, minimal trauma fractures, osteopenia, hyperextensibility and degenerative joint disease [4]. Scoliosis is common, and often appears during adolescence, similar to the case with idiopathic scoliosis, but may also be associated with leg length discrepancy or is worsened by lung damage or resections. Minimal trauma fractures occur in about half of individuals with HIES, and frequently involve the ribs and long bones. Osteopenia and osteoporosis also occur, but appear to be independent of the minimal trauma fractures. Osteoclast-mediated bone resorption is abnormal in HIES and likely relates to osteopenia and fractures [20,21]. Despite this, bone healing after fractures or surgery is typically normal. Hyperextensibility of the small and large joints is frequent and may contribute to early degenerative joint disease, especially in the cervical spine.

Dental abnormalities

Most individuals with HIES fail to exfoliate their primary teeth normally, often requiring surgical extraction of some or all primary teeth to allow the secondary teeth to emerge normally [4,22]. Characteristic variations of the oral mucosa, tongue, roof of mouth and cheeks include central depressions of the tongue that may relate to *Candida* infections and central band-like protrusions of the palate [23].

Vascular abnormalities

Vascular abnormalities are newly recognized in HIES [13,17,24,25]. A coronary artery aneurysm resulting in myocardial infarction (MI) in one HIES man prompted a closer examination of arterial abnormalities in others [24]. Computed tomography and MRI show that coronary artery tortuosity, dilation, and aneurysm formation are common. However, except for the one report of MI, all have been asymptomatic (Gharib, *et al.* unpublished data). One woman had bilateral berry aneurysms of the carotids and another had a middle cerebral artery mycotic aneurysm [13]. Lacunar infarctions have been described at a younger age than is typical (in the fourth decade of life), and T2-weighted hyperintensities, which may reflect small vessel abnormalities, are frequently observed on brain MRI at a much younger age than is typical [17].

Malignancies

HIES is associated with an increased rate of non-Hodgkin's lymphoma (NHL), the majority of which is B-cell origin and aggressive histology [26]. Several

individuals responded to treatment and were apparently cured, but there was an increased mortality, which may in part be due to delayed diagnosis. Other reported malignancies have included Hodgkin's lymphoma, leukemia, and cancers of the vulva, liver and lung [27].

Laboratory abnormalities

The two most consistent laboratory abnormalities in HIES are eosinophilia and elevated serum IgE. Age-adjusted IgE elevation may be present at birth in cord blood and typically peaks at levels substantially above 2000 IU/ml. Over time, however, the serum IgE may decline, even into the normal range in some adults, despite persistent symptoms of HIES [4]. Eosinophilia is common but does not correlate with the IgE level. Serum IgG, IgA, and IgM are usually normal, although mild deficiencies may be present in some individuals. Lymphocyte phenotyping often shows diminished memory T cells (CD45RO⁺) [3].

Genetics

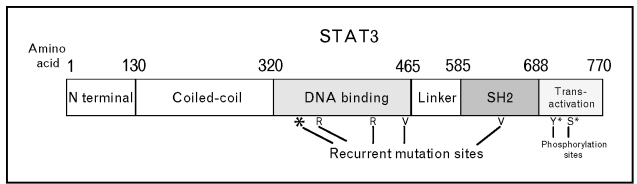
HIES is transmitted in an autosomal dominant pattern but there are also numerous sporadic cases. All racial groups are affected without gender preference [4]. The signal transducer and activator of transcription 3 (*STAT3*) gene is located on chromosome 17. *STAT3* has N-terminal, coiled-coil, DNA binding, src homology (SH2), and transactivation domains [28]. The majority of HIES mutations reside within the DNA binding, SH2 and transactivation domains [5^{••}–10^{••}]. The DNA-binding region mediates attachment to *STAT3*-responsive promoter elements in numerous genes. The SH2 domain mediates *STAT3* dimerization and binding to other protein targets. The transactivation domain contains phosphorylation sites involved in *STAT3* activation. The mutations identified to date are heterozygous and predicted to be protein positive, due to missense changes, in-frame deletions, and splice site mutations leading to exon skipping [5^{••}–10^{••}] (Table 2). Several mutational

Table 2 Published mutations within signal transducer and activator of transcription 3 causing hyper IgE syndrome

Mutation (nucleotide/amino acid change)	Exon	Number of reported mutations	Reference
994 C→T	H332Y	9	[10 ^{••}]
1003 C→T	R335W	10	[7 ^{••}]
1020 delGAC	K340N/T341del	10	[7 ^{••}]
1027 G→C	V343L	10	[7 ^{••}]
1139(+1)g→t	del 371–80	12	[7 ^{••}]
1140(–2)a→g	del 371–80	12	[7 ^{••}]
1144 C→T	R382W	13	[5 ^{••} –8 ^{••} , 10 ^{••}]
1145 G→A	R382Q	13	[5 ^{••} –9 ^{••}]
1145 G→T	R382L	13	[5 ^{••}]
1150 T→C	F384L	13	[5 ^{••}]
1151 T→C	F384S	13	[5 ^{••}]
1152 T→A	F384L	13	[7 ^{••}]
1175 C→T	T389I	13	[6 ^{••}]
1234 A→C	T412S	14	[8 ^{••}]
1268 G→A	R423Q	14	[5 ^{••}]
1294 G→A	V432M	15	[9 ^{••}]
1309 C→T	H437Y	15	[6 ^{••}]
1310 A→C	H437P	15	[9 ^{••}]
1387delGTG	V463del	16	[5 ^{••} , 6 ^{••} , 8 ^{••} , 10 ^{••}]
1393 T→G	S465A	16	[5 ^{••}]
1407 G→T	Q469H	16	[7 ^{••}]
1414 A→G	N472D	16	[8 ^{••}]
1832 G→A	S611N	20	[5 ^{••}]
1858 A→G	T620A	20	[7 ^{••}]
1861 T→G	F621V	20	[5 ^{••}]
1865 C→T	T622I	20	[5 ^{••}]
1907 C→T	S636F	21	[7 ^{••}]
1909 G→A	V637M	21	[5 ^{••} , 7 ^{••} , 10 ^{••}]
1909 G→T	V637L	21	[5 ^{••}]
1913 A→G	E638G	21	[7 ^{••}]
1915 C→G	P639A	21	[5 ^{••}]
1924 A→G	K642E	21	[8 ^{••}]
1930 del CAG	Q644del	21	[5 ^{••}]
1931 A→C	Q644P	21	[9 ^{••}]
1939 A→G	N647D	21	[5 ^{••}]
1954 G→A	E652K	21	[5 ^{••}]
1970 A→G	Y657C	21	[5 ^{••}]
1994 T→A	I665N	21	[8 ^{••}]
2069 del30	del 690–699	21	[7 ^{••}]
2125 A→G	K709E	22	[8 ^{••}]
2137 G→C	V713L	22	[7 ^{••}]

del, deletion.

Figure 1 STAT3 protein



Recurrent ('hotspot') mutations indicated are those that have been found in more than one independent family.

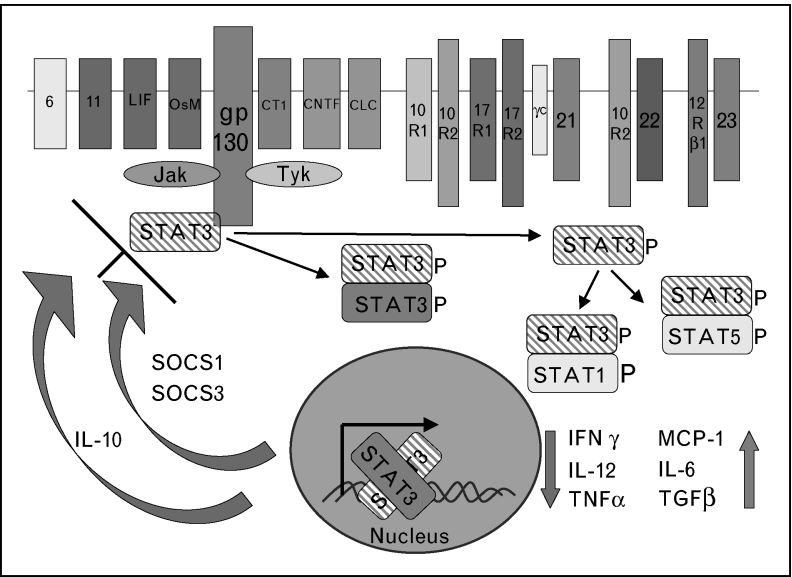
hotspots at which multiple independent mutations are found lie within the DNA-binding domain and the SH2 domain, the most common being R382W/Q and V637M/L, respectively [5^{••}] (Fig. 1). Somatic mosaicism has been reported in one individual [5^{••}].

STAT3 acts through a Janus kinases (JAK)-STAT signal transduction pathway, initiated by binding of extracellular ligand to its corresponding receptor [29,30]. STAT3 is integral to signal transduction for multiple cytokines (Fig. 2) including IL-6, IL-11, leukemia inhibitory factor, oncostatin M, cardiotrophin-1, cardiotrophin-like cytokine and ciliary neurotrophic factor through the shared signal transducing molecule, gp130. IL-10, IL-17, IL-21, IL-22, and IL-23 use STAT3 both directly and indirectly. Suppressors of cytokine signaling (SOCS) proteins act on STAT3 as part of their control of inflammation, putting STAT3 at the center of both proinflammatory and anti-inflammatory responses.

For example, IL-6 binds its transmembrane receptor, IL6Ra and gp130, initiating dimerization of gp130-containing complexes and recruitment of STAT3 to the cytoplasmic tail of gp130. JAK1 molecules are involved in the phosphorylation of STAT3, which is then released into the cytoplasm where it homodimerizes or heterodimerizes with STAT1 or STAT5. Phosphorylation of STAT3 tyrosine 705 appears to be impaired in cells from HIES patients with SH2-domain mutations, but not in those with DNA-binding domain mutations [7^{••}]. Phospho-STAT3 dimers translocate to the nucleus where they bind specific promoters to upregulate transcription of specific genes. In HIES, the exact mechanism by which STAT3 mutants inhibit function has yet to be elucidated, as STAT3 mutants can translocate to nucleus [5^{••}]. The mutant alleles clearly exert a dominant negative effect in transfection experiments [6^{••}]. The ability of DNA-binding domain STAT3 mutants to bind DNA is compromised [6^{••}].

Homozygous STAT3 knockout mice are embryonic lethal, indicating a crucial role of STAT3 in embryogenesis [31]. *Stat3*^{+/-} mice are reported to be phenotypically normal, suggesting that haploinsufficiency is unlikely to cause HIES. This is further supported by the failure to find null alleles in HIES patients. The embryonic lethality of *Stat3*^{-/-} mutants necessitated tissue-specific mutants to study the roles of Stat3 in mouse development. Targeted *Stat3* deletion in the mouse pulmonary epithelium led to acute lung injury with an exaggerated

Figure 2 STAT3 signaling pathways



Mutant STAT3 is shown with cross-hatching. The up and down cytokine regulation shown in the lower right reflect normal STAT3 activity. STAT3 also regulates SOCS expression, which downregulates STAT3 activity. Therefore, mutations in STAT3 lead to aberration of cytokine transduction and regulation. MCP-1, monocyte chemoattractant protein; SOCS, Suppressors of cytokine signaling; STAT3, signal transducer and activator of transcription 3; TGFβ, transforming growth factor beta.

inflammatory response when exposed to hyperoxia [32]. Disruption of *Stat3* in mouse hematopoietic tissues resulted in decreased bone density, increased osteoclastogenesis and increased levels of IFN γ and TNF α [33,34]. Conditional knockout of *Stat3* in mouse keratinocytes caused impaired wound healing and spontaneous skin ulcers [35]. Deletion of *Stat3* in astrocytes led to increased perilesional inflammation and demyelination in mice with spinal cord injuries [36]. These observations in mice seem to recapitulate parts of the clinical phenotype of HIES such as bone fractures, pulmonary disease, neurologic findings, and skin manifestations.

Immunology

STAT3 regulates a wide variety of downstream targets, which differ depending on cell type. It is involved in inflammation, cell growth and differentiation, and even malignant transformation [37]. STAT3 is activated by not only the IL-6 family, but also the IL-10 family, interferons, granulocyte colony-stimulating factor, and leptin.

Prior to the identification of *STAT3* mutations as causing HIES, several studies suggested that aberrant Th1/Th2 distribution with low IFN γ production and neutrophil chemotactic defects contributed to the infection susceptibility in HIES [38–45]. Leukocytes from HIES patients show upregulation of proinflammatory cytokines by protein and by message [5^{••}]. Lipopolysaccharide, *S. aureus* Cowan strain, and heat-killed *Listeria monocytogenes* induced higher levels of TNF α and IL-12 in HIES patients than in normal individuals. Consistent with the impairment in STAT3 signaling, IL-6 stimulation resulted in less monocyte chemoattractant protein-1 from HIES patients' peripheral blood mononuclear cells (PBMCs) than from PBMCs of normal individuals. The proinflammatory state may in part be due to dysregulation of STAT3-dependent IL-10 signaling [46]. Mice conditionally devoid of STAT3 in macrophages and neutrophils had high levels of TNF α , IL-1, IFN γ , and IL-6, thought due to impaired IL-10 production [47].

Th17 CD4 cells are important in host defense though recruitment of neutrophils and macrophages to sites of infection [48[•]]. Their differentiation is dependent on IL-6 signaling and STAT3 [49,50]. Microarray analysis of PBMCs from HIES patients showed decreased levels of IL-17 expression after stimulation with heat-killed *S. aureus* [39]. Mouse CD4⁺ T cells deficient in STAT3 had reduced expression of IL-17 and impaired differentiation into Th17 cells [49,50]. Recently, it was demonstrated that individuals with HIES have significantly diminished ability to form IL-17-producing CD4 lymphocytes (Th17 cells) [7^{••}–9^{••},51^{••}]. As mice deficient in Th17 cells are susceptible to infections with Gram-negative organisms such as *Klebsiella* as well as

Candida species, the lack of IL-17 in HIES may explain some of the susceptibility to *Candida* and other extracellular bacteria in HIES [51^{••},52,53].

STAT3 is important in other pathways involved in immune function. The IL-22 receptor shares a common IL-10 receptor component, which signals through STAT3. IL-22 expression is also dependent on Th17 cell production. In epithelial cells, IL-22 regulates expression of human beta defensins 2 and 3 (hBD2 and 3), antimicrobial peptides important in innate immunity [54]. hBD2 in particular may be important in atopic dermatitis, which is commonly associated with *S. aureus* superinfections [55]. Activated CD4⁺ T cells from HIES patients produced significantly less IL-22 than CD4⁺ T cells from normal individuals [9^{••}]. Further analysis of IL-22 in human cells with *STAT3* mutations will be important in studying the susceptibility to infection in HIES patients.

IL-21 is also dependent on STAT3 signaling and is important in humoral immunity. Mice lacking the IL-21 receptor produce abnormally high levels of IgE after immunizations [56]. In contrast, in humans, IL-21 synergizes with IL-4 to increase IgE production in naïve B cells after stimulation with CD40 ligand [57]. In B cells derived from HIES patients, there was decreased IgE production upon stimulation with CD40 ligand, IL-4 and IL-21 compared with B cells from normal donors. Therefore, it is hypothesized that the elevated IgE levels seen in HIES patients may be due to the loss of suppression of IL-21. However, the exact mechanisms leading to abnormal IgE production in HIES has yet to be determined.

Therapy

Therapeutic options for HIES currently revolve around prevention and treatment of infections and skin management. Cells derived from HIES patients have increased proinflammatory cytokines upon stimulation with bacterial-derived antigens [5^{••}], so it would seem that patients should have exaggerated symptoms of infection such as fever or sepsis. On the contrary, affected individuals often lack classic signs and symptoms of invasive infections. Therefore, careful history and examination need to explore infectious causes of new symptoms, even if they may seem trivial. There is no specific treatment for HIES at present, so therapy relies on prevention of infection with prophylactic antimicrobials and antiseptics. Diluted bleach baths are helpful for staphylococcal-driven skin eruptions, accompanied by aggressive antimicrobial therapy when necessary. Anecdotal reports suggest that some patients have fewer infections with regular immunoglobulin therapy, but immunoglobulin synthetic defects are not common in HIES [58–60].

The role of bone marrow transplantation remains unclear [61,62].

Conclusion

In summary, HIES is a complex primary immunodeficiency with immunologic, infectious, connective tissue and skeletal abnormalities resulting from *STAT3* mutation. Better understanding of the discrete mechanisms of the phenotypes of HIES should deeply enrich our understanding and treatment of more common diseases. Although HIES is rare, eczema, staphylococcal infections, scoliosis, osteoporosis and arterial aneurysms are common.

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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 590).

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