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Hyper-IgE syndromes

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Summary: The hyper-immunoglobulin E (IgE) syndromes (HIES) are primary immunodeficiencies characterized by the clinical triad of recurrent staphylococcal abscesses, recurrent cyst-forming pneumonia, and an elevated serum IgE level of >2000 IU/ml. Most cases are sporadic; however, multiplex families displaying autosomal dominant (AD) and autosomal recessive (AR) inheritance have been described. In most sporadic and AD cases, the HIES clinical triad is part of a multisystem disorder including abnormalities of the soft tissue, skeletal, and dental systems. In contrast, those with AR-HIES have severe molluscum contagiosum and other viral infections and may develop severe neurological complications. Unlike patients with sporadic HIES and AD-HIES, those with AR-HIES lack skeletal or dental involvement and do not develop lung cysts. Additional variants of HIES are discussed in this review. The etiology of HIES is still unresolved. Recent research points toward a skewed T helper 1 (Th1) cell/Th2 cell ratio and the involvement of chemokines. Therapy for HIES is directed at prevention and management of infections by using sustained systemic antibiotics and antifungals along with topical therapy for eczema and drainage of abscesses. Anti-staphylococcal antibiotic prophylaxis is useful. Interferons, immunoglobulin supplementation, or low-dose cyclosporine A have been reported to benefit selected patients, but they are not generally indicated.

Introduction

Hyper-immunoglobulin E (IgE) syndromes (HIES) [also called Job's syndrome, Online Mendelian Inheritance in Man (OMIM) #147060 and #243700] are very rare primary immunodeficiencies (incidence $<10^{-6}$), characterized by the clinical triad of high serum levels of IgE (>2000 IU/ml), recurring staphylococcal skin abscesses, and pneumonia with pneumatocele formation. The most recent complete review on HIES in English has been written by Erlewyn-Lajeunesse in 2000 (1).

Most cases are sporadic, but both autosomal dominant forms of HIES (AD-HIES) (2) and autosomal recessive forms (AR-HIES) (3) have been described. Skeletal symptoms such as hyperextensibility of joints, scoliosis, osteoporosis, and retained primary teeth are associated with the autosomal dominant form (4). An autosomal recessive disease characterized by severe recurrent viral infections, extreme eosinophilia, and devastating neurological complications that are often fatal in childhood, but without skeletal or dental abnormalities, has recently been described (3).

Immunological Reviews 2005
Vol. 203: 244–250
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Immunological Reviews
0105-2896

HIES usually presents very early in life. Early diagnosis can prevent complications due to pneumatocele formation, for example, by the instigation of prophylactic antistaphylococcal treatment. The authors, under the umbrella of the European Society for Primary Immunodeficiencies (<http://www.esid.org> and <http://www.esid-registry.org>), the Pan American Group for Immunodeficiencies (<http://www.clinimmsoc.org/pagid/>), and the USIDnet (<http://www.usidnet.org>), are currently establishing a world-wide registry for HIES in order to better characterize this very rare disorder.

History

'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.' With this citation from the book of Job 2:7, Davis, Schaller, and Wedgwood (5) coined the term Job's syndrome in 1966. They reported two red-haired, fair-skinned girls who had frequent sinopulmonary infections, severe dermatitis, and recurrent staphylococcal skin infections that were remarkable for their lack of the features of classical inflammation, including warmth, hence the term 'cold' abscesses.

The syndrome was further defined and clarified by Buckley *et al.* (6), who noted similar infectious problems in two boys with severe dermatitis, characteristic facies, and elevated IgE levels, leading to the term Buckley's syndrome. Following this report, elevated levels of IgE and a defect in neutrophil chemotaxis were identified in the two girls from the initial report (7), showing that Job's syndrome and Buckley's syndrome represented the same condition. This syndrome is now often referred to as hyper-IgE recurrent infection syndrome (8). In a detailed analysis, the group at the National Institutes of Health showed HIES to be a multi-system disease, based on 19 clinical features in a cohort of 30 patients (4). The identification of recurrent infections and failure of primary dental deciduation in HIES led Fischer (9) to speculate that Hanno Buddenbrook (Thomas Mann, Buddenbrooks, 1901) may have suffered from this condition.

In 2003, an autosomal recessive disease with eosinophilia and IgE elevation was identified in consanguineous Turkish and Mexican families, suggesting an autosomal recessive form of HIES (3). Distinct features readily differentiate the autosomal dominant HIES from this autosomal recessive syndrome.

The AD-HIES

Clinical features

The clinical features of HIES encompass the immune system, connective tissue, skeleton, and dental development with variations in the severity of the symptoms. The most common

clinical features and laboratory parameters are summarized in Table 1.

The immune system. Eczema, recurrent skin abscesses, pneumonia with pneumatocele formation, mucocutaneous candidiasis, elevated serum IgE, and eosinophilia are the most common features of immunodeficiency and immune dysregulation in HIES. However, HIES typically first manifests with a newborn rash (10, 11).

The spectrum of infections. HIES is characterized by staphylococcal infections. Pneumonias are mainly caused by *Staphylococcus aureus*, *Streptococcus pneumoniae*, or *Haemophilus influenzae*. The pneumatoceles that typically follow the resolution of cured bacterial pneumonias are frequently superinfected by *Pseudomonas aeruginosa* and *Aspergillus fumigatus*. The most common opportunistic infection in HIES is mucocutaneous candidiasis. However, several cases of *Pneumocystis (carinii) jiroveci* have been reported (4). Cryptococcosis (12) and histoplasmosis (13–15) have also been reported. Less common infections include disseminated candidiasis (16) and necrotizing bacillus Calmette-Guérin infection after vaccination in a newborn who was later diagnosed with HIES (17). Severe herpes simplex infection occurs rarely in AD-HIES (18) but is more consistent with the autosomal recessive type of HIES (see below).

The skeletal system. Facial abnormalities and hyperextensibility were recognized in the original reports (5, 6). A skeletal phenotype and the characteristic facies were identified subsequently (4, 19, 20). Recurrent pathological fractures are further evidence of the multisystem nature of HIES, occurring in about half of patients and mainly affecting the long bones and ribs rather than the spine (4). Scoliosis is seen in about

Table 1. Incidence of clinical and laboratory findings in patients with typical sporadic or autosomal dominant hyper-immunoglobulin E (IgE) syndromes

Immune system	
Eczema	100%
Skin abscesses	87%
Recurrent Pneumonia (3 or more, proven by X-ray)	87%
Pneumatocelles	77%
Mucocutaneous candidiasis	83%
Skeletal symptoms	
Characteristic face	83%
Wide nose (interalar distance > 2 SD above norm)	65%
Failure of dental exfoliation (>3 teeth)	72%
Hyperextensibility	68%
Recurrent pathologic fractures	57%
Scoliosis (>10°)	63%
Laboratory findings	
Serum-IgE (>2000 U/ml or >10 times the age-specific upper norm)	97%
Eosinophilia (>2 SD above norm)	93%

two-thirds of patients, but the reasons for this are complex. Scoliosis may arise from leg length discrepancy, following thoracotomy (e.g. removal of a lung cyst), from anomaly of a vertebral body, or spontaneously in adolescence, similar to the case in idiopathic scoliosis. The latter skeletal findings contribute to the notion that midline anomalies are part of the HIES phenotype. Craniosynostosis has been reported in HIES but is much less common than the other skeletal features (21, 22).

The dental system. Anomalies in dentinogenesis are consistent features of HIES (4, 23). Reduced resorption of primary tooth roots is thought to lead to prolonged retention of primary teeth, which in turn prevents the appropriate eruption of permanent teeth (23).

The eye. Ophthalmologic pathologies such as extensive xanthelasma (24), giant chalazia (25), undefined tumors of the eye lid (26), and strabism (27, Grimbacher, unpublished data) have been reported.

Malignancies. Several malignancies, especially lymphomas, have been observed in HIES patients. Recent reports include anaplastic large cell lymphoma (24), peripheral T-cell lymphoma (28), and a pulmonary adenocarcinoma (29). The lymphoid neoplasms in HIES were reviewed in Leonard et al. (30).

Diagnosis of HIES

Several of the symptoms of HIES are also features of related conditions, which leads to difficulties in the diagnosis of HIES, especially in young patients and atypical, less severe cases (HIES-variants) (31). The lack of specific blood tests, other than elevation of IgE levels and eosinophilia, or specific immunologic or molecular markers, makes the diagnosis of HIES similar to the assembly of a puzzle, requiring the compilation of symptoms which develop over years. A scoring system was developed at the National Institutes of Health in order to assist linkage studies in families with multiple cases of HIES (2). The diagnosis rests on the recognition of defects in both the immune and somatic systems, re-emphasizing the complex nature of the disease.

Laboratory investigations

IgE. The importance of the elevated polyclonal IgE in the pathology of HIES is still not clear. IgE levels from 10 000 to as high as >100 000 IU/ml are characteristic of HIES, but the levels are not static (4, 8). Substantial fluctuation has been documented in the elevated levels of serum IgE over time without any obvious change in clinical presentation. Furthermore, some affected individuals have had declines in IgE into

the normal range, as they reach the third decade and later. High levels of IgE are not correlated with the level of eosinophilia or the susceptibility to severe infections; some older patients whose IgE levels were consistently below 2000 IU/ml still suffered recurrent infections (4). For newborns, normal levels are very low to undetectable; therefore, normal adult IgE levels in infants (100–200 IU/ml) are pathological. Physiologic IgE levels increase very slowly after birth. An IgE level 10-fold above the 95th percentile of the age norm appears a reasonable level at which to entertain the diagnosis of HIES.

Blood cell count and complement. Most HIES patients have eosinophilia at least 2 SDs above the norm (usually more than 700 cells/ μ l). However, there is no correlation between eosinophilia and IgE levels or eosinophilia and infectious complications of HIES. Total white blood cell counts are typically in the normal range when no infection is present, and they often fail to elevate even in the setting of acute infection.

Etiology

Despite more than 35 years of research, the underlying cause of HIES is still not known. Hill and colleagues (7) believed that impaired neutrophil chemotaxis caused the susceptibility to infection, but this defect proved to be inconsistently present (8). More recent studies have focused on the T helper 1 cell (Th1)/Th2 cytokine imbalance, because a predominant Th2 response or a defective Th1 response with interleukin-12 (IL-12) and interferon- γ (IFN- γ) is thought to favor the IL-4, IL-10, and IL-13 cytokine profile, which might facilitate Ig class switching toward IgE. Borges et al. (32) examined blood from 10 patients with HIES and found decreased *in vitro* IL-12 production, particularly after specific stimulation with staphylococcal antigens, a major pathogen in HIES. These findings were supported by a Dutch HIES family in which affected members showed skewing toward the Th2 phenotype due to a significant reduction of the IFN- γ /IL-10 ratio after stimulation with heat killed *S. aureus* or *Candida albicans* (33). Gudmundsson et al. (34) reported an increased expression of IL-13 (but not IL-4) in six HIES patient CD4⁺ helper T cells. Ohga and coworkers (35) demonstrated reduced expression of TGF- β and IFN- γ genes in the circulating activated T cells from five HIES patients. They showed that the transforming growth factor- β (TGF- β)/IL-4 ratio in either human leukocyte antigen (HLA)-DR⁺ or HLA-DR^{neg} T cells was the most powerful discriminator between HIES and atopic dermatitis or chronic granulomatous disease. The latest support and refinement for the 'IFN- γ hypothesis' in HIES came from Ito et al. (36), who found in

three patients with HIES that IFN- γ mRNA transcription and translation were intact, but the secretion of IFN- γ into the medium was defective as determined by confocal laser scanning microscopy of HIES patient cells. The conflicting observations regarding transcription, translation, and secretion from these several studies taken together have yet to be resolved. If IFN- γ is dysregulated in HIES, it may not be alone. Chehimi et al. (37) used an early generation gene array to show that HIES patients had a wide range of abnormal chemokine gene expression. It should be noted that, in patients with defects in the IFN- γ /IL-12 pathway, none of the common features or infections of HIES are seen, suggesting that the simple reduction of IFN- γ or IL-12 is not etiologic (reviewed in Rosenzweig and Holland, this volume).

As at least one form of HIES is a monogenic but complex multisystem disease that affects the skin, bone, teeth, lung, and immune system, the relevant defect must cause anomalies in all of these tissues. Thus, the aberration is unlikely to be solely in the B-cell and T-cell system but may affect the monocyte-macrophage lineage or endothelial cells.

Genetics

More than 200 HIES patients have been documented in the literature. Although first described in Caucasians with red hair (5), HIES occurs in all ethnic groups and almost equally in both genders. Most pedigrees of HIES families are consistent with an autosomal dominant inheritance. Father to son transmission excludes X chromosome linkage in some families (2, 38).

An HIES patient with mental retardation who was found to have an interstitial deletion of 15–20 cM on chromosome 4q drew attention to this region (39). Linkage analysis of 19 families with 57 HIES patients demonstrated linkage to the proximal arm of chromosome 4q (2). However, six of the 19 families did not demonstrate linkage to this region of 4q, suggesting genetic heterogeneity.

Hershey et al. (40) identified a polymorphism in the IL-4 receptor (Q576R) linked to atopic eczema and suggested a link to HIES. However, analysis of 20 HIES patients showed no correlation of the Q576R allele with the HIES phenotype, and a linkage study with seven autosomal dominant HIES families ruled out linkage to the IL-4 receptor locus on chromosome 16 (41).

HIES could be caused by mutation of a single gene, mutations in different genes of a common pathway (genetic heterogeneity), or deletion of several genes in a short chromosomal region.

A single founder effect of typical sporadic or autosomal dominant HIES is very unlikely, as the genetic background of the patients varies considerably and the disease was probably always

fatal before antibiotics were available. Several different mutations are most probably the cause of the genetic defect in HIES.

The AR-HIES

In 2004, 13 HIES patients from six consanguineous families with severe recurring infections (pneumonia and abscesses), eczema, high IgE, and eosinophilia were described (3) and fulfilled the criteria for HIES.

Clinical features in AR-HIES

Infections. The patients with AR-HIES had recurrent or severe infection of *S. aureus*, *H. influenzae*, *Proteus mirabilis*, *P. aeruginosa*, and *Cryptococcus*. Several patients also had severe chronic refractory *Molluscum contagiosum* infections. Seven of 13 patients suffered recurrent aphthoid herpes simplex infections, which also caused keratitis. One patient suffered recurrent varicella zoster infections. The increased susceptibility to viral infections in AR-HIES is quite distinct from the dominant and sporadic form. A defect in T cells is possible in this condition, especially taking into account recurrent fungal infections in 10/13 patients. Whereas postinfection pneumatocele formation is almost pathognomonic in AD-HIES and typical sporadic HIES, no pneumatoceles occurred in any of the patients with AR-HIES, even though the incidence of pneumonia was the same. This helps distinguish AR-HIES and can be of use in the differential diagnosis. Autoimmune hemolytic anemia was seen in two patients with AR-HIES, and one patient had pericardial effusion, which may also have been an indication of autoimmunity. Thus, in contrast to AD-HIES, AR-HIES includes autoimmunity.

CNS and neurological symptoms. In the AR-HIES cohort, seven of 13 patients had neurological symptoms, which varied from partial facial paralysis to hemiplegia. Of these patients, four died of these neurological complications. The neurological complications may be manifestations of a possible hypereosinophilic vasculitis or occult infections, but the underlying etiology of the neurologic syndrome is still not clear.

Connective tissue. AR-HIES patients did not have skeletal abnormalities, fractures, dental abnormalities, or the characteristic facies seen in AD-HIES.

Laboratory investigations in AR-HIES

All AR-HIES patients had elevated IgE serum levels comparable to those in AD-HIES patients. Furthermore, serum levels of the other Ig isotypes were also raised, suggesting a non-specific stimulation of the humoral response. The eosinophilia was

more severe in AR-HIES patients than in AD-HIES patients, with values up to 17 500/ μ l (normal <700).

Etiology of AR-HIES

Lymphocyte phenotyping of patients with AR-HIES was normal with regard to the number of cells, but showed defective proliferative responses to specific antigens, suggesting that any lymphoid defects in AR-HIES are qualitative in nature most likely involving T cells. This hypothesis is supported by viral and fungal infections in AR-HIES. Neutrophil function seems to be normal in AR-HIES.

Genetics of AR-HIES

All patients are from consanguineous parents and are thus assumed to have an autosomal recessive mode of inheritance (3). Linkage analysis of this AR variant is complicated by the high mortality rate, but it appears that more than one genetic locus is involved. A comprehensive comparison of clinical and laboratory findings of both forms of HIES, the more frequent classic one and the rare AR-HIES, is summarized in Table 2.

Hyper-IgE overlap syndromes

In rare cases of other defined genetic diseases, the classical triad of HIES with recurrent skin abscesses, recurrent pneumo-

nia, and extreme elevations of IgE is also fulfilled. Antoniadis et al. (42) reported the coexistence of HIES and Dubowitz syndrome (defined by postnatal growth retardation, microcephaly, and characteristic facial appearance), and Boeck et al. (43) reported the coexistence of pentasomy X and HIES. Boeck et al. (44) also reported the coexistence of HIES and Saethre–Chotzen syndrome (defined by acrocephalosyndactyly, hypertelorism, and ptosis), caused by mutations in the TWIST gene.

Therapy of HIES

There is as yet no cure for HIES. Prophylactic antibiotic treatment and symptomatic treatment are desirable. Intensive care of skin lesions, prompt antibiotic/antimycotic treatment for infections, and surgical drainage of abscesses are the mainstay of HIES management. The prophylactic use of antibiotics against *Staphylococcus* markedly reduces the incidence of skin abscesses and staphylococcal pneumonias.

Dermatitis is often exacerbated by a superinfection with *S. aureus*. Systemic antibiotics are often indicated in addition to topical agents such as antibacterials, moisturizing creams, and topical steroids (as with atopic dermatitis). As yet very little is known about the use of drugs such as tacrolimus in HIES.

Mucocutaneous candidiasis, which manifests typically as onychomycosis, vaginal candidiasis, and thrush, is usually very responsive to oral triazole antifungals.

One remarkable feature of HIES is that patients are frequently unaware of how severely ill they are. Despite radiographic evidence of pneumonia or serious dermal pathology, they may be afebrile and feel well, presumably due to the same absence of inflammation that permits the 'cold' abscesses. It may be difficult to persuade such a patient to submit to invasive diagnostic testing or prolonged courses of therapy. High-dose intravenous antibiotics for a prolonged course are often required to eliminate infectious agents. Ideally, identification of the infectious agent should be carried out before starting antibiotics, but if it is not possible, empiric acute coverage for a new pneumonia should consider *S. aureus*, *H. influenzae*, and *S. pneumoniae*. Empyema is relatively common and requires drainage. The typical complication of pneumonia in HIES is the formation of pulmonary cysts, which occasionally disappear but most often persist. In persistent cavities, bacterial (e.g. *P. aeruginosa* or other Gram-negative rods) or fungal (e.g. *Aspergillus*) superinfections occur. These infections are very difficult to manage, because they are frequently in the setting of extensive bronchiectasis. Lung resection is difficult, because the expansion of residual lung that is needed following lobectomy is

Table 2. Summary of clinical differences between classic hyperimmunoglobulin E (IgE) syndromes (HIES) and AR-HIES

	HIES, classic form	HIES in consanguineous families
Inheritance pattern	Autosomal dominant	Autosomal recessive
Chronic eczema	Yes	Yes
Recurrent abscesses	Yes	Yes
Recurrent pneumonia	Yes	Yes
Pneumatoceles	Yes	No
IgE (IU/ml)	1875* to 58 200	1700–45 000
Absolute eosinophil count	726–2034/ μ l	2500–18 000/ μ l
Cerebral symptoms	Yes†	Yes
Vasculitis	No	Yes
Molluscum contagiosum	No	Yes
Herpes virus complications	No	Frequent
Recurrent bone fractures	Yes	No
Scoliosis	Yes	No
Hyperextensibility	Yes	No
Retained primary teeth	Yes	No
Lethality	Adulthood	Childhood

*IgE levels at diagnosis; authentic cases can have normal IgE levels in adulthood.

†Patients with the classical forms of HIES have high rates of unidentified bright object (UBOs; T2 hyperintensities) in the brain (66% of patients) and an elevated rate of lacunar infarction (15%) (C. Collura-Burke and S. M. Holland, personal communication).

markedly impaired in these patients. Therefore, the excision of pulmonary cysts must be undertaken with great caution in HIES.

The role of long-term prophylactic antibiotic therapy has not been strictly investigated in HIES patients, but the consensus favors prophylactic therapy with an anti-staphylococcal antibiotic such as cotrimoxazole, a semisynthetic penicillin, or an oral cephalosporin. Development of resistance to infectious agents has been less of an issue in HIES patients than the threat of severe infections and the attendant lung destruction.

Immune modulators have been clinically unsuccessful in HIES management. Levamisole, the only substance tested so far in a double blind study, caused adverse effects when compared to a placebo (45).

IFN- γ has been used in HIES but showed inconsistent effects on IgE levels and infection susceptibility (46). Aihara et al. (47) used IFN- γ in two Japanese patients, which triggered auto-immune thrombocytopenia in one of them. The use of IFN- γ or IFN- α in cases of drug-resistant viral infections in AR-HIES has not been studied.

Cyclosporine A has been used successfully in Israel (48, 49) and Spain (Dr N. Matamoros, personal communication).

Intravenous Ig infusion therapy (IVIG) may influence the IgE levels due to an increased (or induced) Ig catabolism or IgE neutralization via an anti-idiotypic network. As integrity of antibody formation, especially against encapsulated organisms, appears to be impaired in HIES, the use of IVIG is reasonable to consider. Two recent case reports used moderate- or high-dose IVIG with good (50) or partial (51) success. Five patients are being treated in Spain with IVIG with reasonable success (Dr N. Matamoros, personal communication). Prospective studies with firm immunologic, microbiologic, and infection endpoints are encouraged (please contact Corresponding author).

Given the overall impression that has prevailed that HIES is a disorder of the immune system, it is not surprising that bone marrow transplantation has been attempted in two cases of typical AD-HIES. A 46-year-old man with a B-cell lymphoma received peripheral stem cell transplantation from his HLA-

identical sister following irradiation. Posttransplant he was maintained on prednisone and cyclosporine A. Serum IgE values fell, and no HIES characteristic infections occurred. However, the patient died 6 months after transplant due to an interstitial pneumonia (52). A 7-year-old girl with severe HIES underwent successful bone marrow transplantation from a matched unaffected sibling. Initially, her IgE fell dramatically, and her skin lesions improved. After the discontinuation of immune suppression and in the presence of complete donor engraftment, her IgE levels returned to pretransplant levels, and she developed recurrent skin abscesses (53). Possible explanations for this outcome include persistent plasma cells, occult persistence of recipient hematopoiesis, or perversion of the donor marrow to the HIES phenotype by the recipient somatic compartment.

The causes for different forms of HIES may be diverse, and some treatments (e.g. IFN- γ , cyclosporine, IVIG, and bone marrow transplant) may work in one patient but not in another. Unfortunately, there are no validated predictive tests of what regimen may be helpful. Patients with AR-HIES have a more severe course with very different complications than those with AD-HIES. Therefore, they may be more likely to profit from bone marrow transplant. IVIG has a relatively narrow side-effect profile and should be evaluated in a prospective clinical study (Grimbacher, Matamoros, and Ehl, personal communications).

Summary

In order to improve the quality of life and prognosis of HIES patients, it is essential to be aware of the features such as retained primary teeth, pathologic fractures, and scoliosis that are associated with HIES. Therapy involves antibiotic and antimycotic prophylaxis and treatment as early as possible, and occasionally surgery for abscess drainage. However, as the etiologies of the different forms of HIES are variable and complex, one therapeutic approach may benefit one but not necessarily all patients with HIES.

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