Clinical Manifestations, Etiology, and Pathogenesis of the Hyper-IgE Syndromes

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ABSTRACT: Autosomal dominant Hyper-IgE syndrome (AD-HIES) is a rare primary immunodeficiency characterized by eczema, recurrent skin and lung infections, elevated serum IgE, and various connective tissue, skeletal, and vascular abnormalities. Mutations in signal transducer and activator of transcription 3 (*STAT3*) have recently been found to account for most cases; however, the pathogenesis of the varied features remains poorly defined. A distinct syndrome, known as autosomal recessive HIES (AR-HIES) manifests as severe eczema, recurrent bacterial and viral skin infections, and sinopulmonary infections. As opposed to *STAT3* deficient HIES, AR-HIES lacks the connective tissue and skeletal manifestations but has an increase in neurologic abnormalities. In this review, we discuss the clinical presentations, genetic etiologies, and immunologic abnormalities of these two syndromes. In addition, we discuss animal models of *STAT3* deficiency that provide insight into the pathogenesis of HIES. Further understanding of how *STAT3* results in the diverse manifestations of HIES will allow us to develop more specific therapies for HIES as well as for many of the manifestations, such as scoliosis, recurrent staphylococcal infections, and eczema, which are common in the general population. (*Pediatr Res* **65:** 32R–37R, 2009)

Job's syndrome was described in 1966 in reference to the Biblical Job who was "smote with sore boils" (1). Buckley *et al.* (2) refined the syndrome after detection of extremely elevated serum IgE in conjunction with eczema and recurrent boils and pneumonias. Autosomal-dominant hyper-IgE syndrome (AD-HIES) is now recognized as a multisystem disorder with various connective tissue, skeletal, and vascular abnormalities (3,4). Dominant-negative mutations in signal transducer and activator of transcription 3 (*STAT3*) are responsible for most cases of AD-HIES (5–8). However, the pathogenesis of both the clinical manifestations and the immunologic abnormalities remains poorly understood. Autosomal recessive HIES (AR-HIES) is a distinct clinical entity characterized by elevated IgE, recurrent skin and lung infections, and eczema, susceptibility to viral infections, such as *Molluscum contagiosum* and an ill-defined CNS involvement but lacks the connective tissue manifestations of AD-HIES

(9). The etiology of most cases of AR-HIES remains unknown. We will review the clinical manifestations, genetics, immunologic findings of HIES, and the pathogenesis of these unique diseases.

Clinical Manifestations

Immunologic features. AD-HIES typically presents in the first few weeks of life with a newborn rash (Table 1). This pustular rash is often most pronounced on the face and scalp, in a pattern most consistent with neonatal acne or eosinophilic dermatitis (10,11). Scrapings of the rash show eosinophilia. The rash may improve or progress to an eczematoid rash often worsened by *Staphylococcus aureus* infection. Control of eczema is typically most successful with antistaphylococcal therapy, either with antimicrobials or antiseptics, such as dilute bleach. Recurrent *S. aureus* boils usually start in early childhood. Although frank pus is present upon aspiration of the boils, cardinal features of inflammation, such as heat, erythema, and tenderness, are often absent.

Recurrent pyogenic pneumonias usually start in early childhood. *S. aureus* is the most common pathogen, with *Streptococcus pneumoniae* and *Haemophilus influenzae* also occurring frequently (3,4). Similar to the *S. aureus* boils, purulent sputum is present, but individuals often lack systemic signs of inflammation, such as fever, and may be quite well appearing. Healing of the pneumonia is often aberrant with pneumatoceles and bronchiectasis (Fig. 1). These structural abnormalities are then sites of fungal (typically *Aspergillus*) and Gram-negative (typically *Pseudomonas*) infection, which are major causes of morbidity and mortality (12). Mold infections can invade blood vessels leading to life-threatening hemoptysis and/or disseminate to extrapulmonary sites of infection.

Opportunistic infections are also seen in HIES. *Pneumocystis jiroveci* pneumonia can occur in infants as their first pneumonia (13). Disseminated histoplasmosis and *Cryptococcus* have been described in unusual sites such as focal intestinal disease (14,15). Mucocutaneous candidiasis manifests as fingernail, vaginal, and oral disease (4).

Somatic features. HIES is distinguished from many of the other primary immunodeficiencies by its many extraimmunologic features. A characteristic facial appearance develops through childhood and adolescence, characterized by facial asymmetry, a broad fleshy nose, and porous skin (3,4). Arnold Chiari I malformations (cerebellar tonsillar protrusion into the foramen magnum) are present in ~20% of patients and cra-

Table 1. *Clinical features of AD-HIES*

Immunologic (approximate percent frequency)
  Peak serum IgE >2000 IU/mL (97)
  Recurrent pneumonias (87)
  Parenchymal lung abnormalities (bronchiectasis/pneumatocoele) (70)
  Boils (87)
  Moderate-severe eczema (95)
  Newborn rash (80)
  Mucocutaneous candidiasis (83)
  Recurrent sinusitis or otitis (80)
  Eosinophilia (90)
  Lymphoma (5)
Somatic (approximate % frequency)
  Characteristic face (85)
  Hyperextensibility (70)
  Retained primary teeth (70)
  Minimal trauma fractures (65)
  Scoliosis >10 degrees (60)
  Coronary vasculature anomalies (60)
  Arnold Chiari I malformations (40)
  Focal hyperintensities on brain MRI (75)

Figure 2. Cervical spine x-ray of a 48-y-old with AD-HIES showing severe degenerative spine disease.
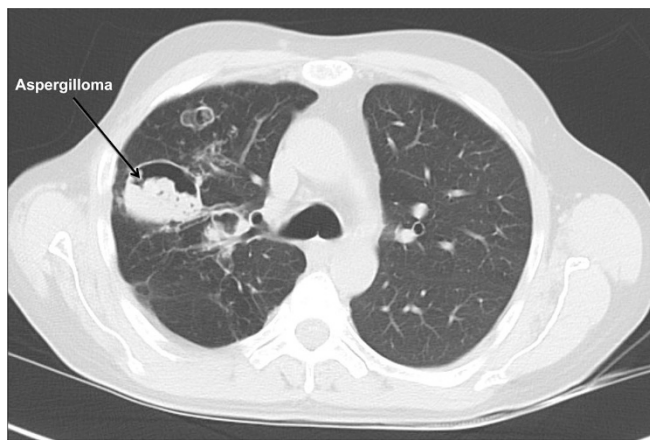
Figure 1. Chest CT of an individual with AD-HIES showing pneumatocoeles complicated by aspergilloma.

niosynostosis is seen in some individuals (16–18). Surgical repair of the craniosynostosis and Chiari I malformations is usually not indicated. Failure of primary dentition exfoliation is common and primary teeth often need to be removed for the secondary teeth to emerge (19). Oral mucosal manifestations include central ridges and fissures of the roof of the mouth, central depressions of the tongue, and oral mucosa variations of the cheek (20).

Minimal trauma fractures, osteopenia, hyperextensibility, scoliosis, and degenerative joint disease are common (3,4). Minimal trauma fractures of the ribs and long bones occur in about half of individuals with HIES and may occur independent of osteopenia. Varying degrees of scoliosis are common and may be severe enough to require rod placement. The scoliosis may develop during adolescence in a pattern similar to idiopathic scoliosis, but also occurs secondary to leg length discrepancy, lung disease with volume loss, or lung resections. Degenerative joint disease, especially of the spine, often manifests in the third and fourth decade of life and may require surgical repair (Fig. 2).

Vascular abnormalities are common in HIES (21–23). One man suffered a myocardial infarction due to a large left anterior descending coronary artery aneurysm (22). On further investigation, coronary artery dilatation, aneurysms, and tortuosity are common in adults with HIES, but are usually asymptomatic. Aneurysms have also been described outside of the coronary arteries, including bilateral berry aneurysms of the carotids in one woman and a mycotic middle cerebral aneurysm in another (12). On brain imaging, lacunar infarctions and T2-weighted hyperintensities, potentially suggestive of small vessel disease, occur at a younger age than expected (Fig. 3) (16).

Esophageal dysfunction is poorly understood in adults with HIES (our unpublished observations). Manifestations include choking episodes and inability to tolerate pills or large chunks of food. Esophageal diverticula and strictures occur and esophageal dilation may be required.

Similar to several other primary immunodeficiencies, there is an increased incidence of both Hodgkin's and non-Hodgkin's lymphoma in AD-HIES (24). Other reported malignancies include leukemia and cancers of the vulva, liver, and lung (25,26).

Laboratory abnormalities in HIES are most significant for eosinophilia and elevated serum IgE. The IgE typically peaks over 2000 IU/μL, but may decrease over time and even reach normal values in adulthood (4). Clinical manifestations of HIES may persist despite normalization of IgE. RAST testing for specific antigens may yield positive results; however, this is confounded by the overall high IgE level; clinically apparent allergies do not seem to be increased in HIES. Serum IgG, IgA, and IgM are typically normal.

White blood cell counts in HIES are usually normal, although relative neutropenia has been seen. Leukocytosis and acute phase reactants, such as C-reactive protein during infection, may not be as high as expected. Lymphocyte phenotyping shows decreased memory T cells, and antibody responses are variable (3,23,27).

Genetics

Dominant-negative mutations in *STAT3* account for most cases of AD-HIES (5–8,28,29). Many cases are sporadic, but when familial, all individuals carrying the mutation have the
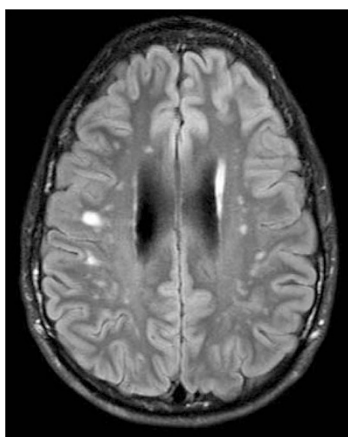
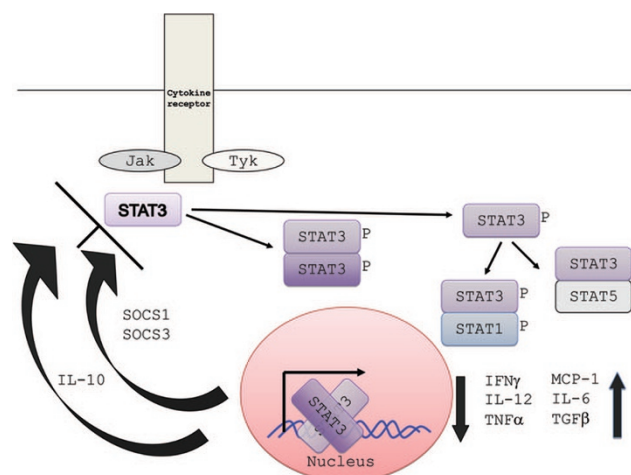**Figure 3.** Brain MRI of a 21-y-old with AD-HIES showing multiple focal hyperintensities.

Figure 4. STAT3 signaling pathway. Multiple cytokines, including IL-6, IL-10, IL-21, IL-22, and IL-23 activate STAT3 phosphorylation. Dimerized STAT3 enters the nucleus to affect transcription of various genes. STAT3 can also dimerize with other STATs. Normal STAT3 signaling leads to the up-regulation and down-regulation of the cytokines shown in the right lower corner. IL-10 and SOCS (suppressors of cytokine signaling) can down-regulate STAT3 activity.

HIES phenotype. Mutations have been found in all races and many ethnicities. Most of the reported mutations are missense mutations accounting for one amino acid change, but in-frame deletions of one amino acid, or exon skipping have been reported as well. Mutations have been largely concentrated in the SH2 domain (mediating protein–protein interactions) and DNA binding domain (mediating protein–DNA interactions) of *STAT3*, with a few reported mutations in the trans-activation domain. There are several mutational hot spots, but no clear phenotypic distinctions have emerged between these two regions. One man has somatic mosaicism for *STAT3* mutation and a milder HIES phenotype (5).

Null alleles have not been reported in HIES and heterozygous deletions in mice are phenotypically normal, indicating that the mutations exert a dominant-negative effect on the normal allele. Laboratory constructs of AD-HIES mutations show dominant-negative effect with STAT3 target binding activity ∼25% of normal (7).

STAT3 Function

STAT3 is one of six STAT proteins that are major signal transducers involved in many diverse pathways (30). Many cytokines transmit signals through Janus kinase (Jak)-STAT pathways (31). The intracellular components of cytokine receptors often bind to one of four Jak proteins (Jak1, Jak2, Jak3, Tyk2) leading to STAT recruitment and phosphorylation. Phosphorylated STAT then dimerizes by the Src homology 2 (SH2) domain, translocates to the nucleus leading to activation of STAT-regulated genes. STAT3 is involved in the signal transduction of many cytokines, including but not limited to IL-6, IL-10, IL-21, IL-22, and IL-23, and plays an integral role in wound healing, angiogenesis, cancer, and immunity (Fig. 4) (30).

The clinical phenotype of HIES is one of both excessive and inadequate inflammation. The prolonged local inflammation in the lung leading to pneumatocoeles is an example of excessive inflammation, with the susceptibility to infections including opportunists and the characteristic "cold" boils being examples of inadequate inflammation. This dichotomy is expected as both pro- (*e.g.*, IL-6) and anti-inflammatory (*e.g.*, IL-10) cytokines signal through STAT3.

Evidence of proinflammatory cytokines is present in the cytokine and microarry data of individuals with HIES as well as through myeloid specific *Stat3* knock out mice (5,32,33). Increased expression of TNF-alpha and IFN-gamma, likely due in part to impaired IL-6 signaling, is evident in myeloid-specific *Stat3* knockout mice (33). These findings reflect the immunologic data of individuals with *STAT3* mutations in whom leukocyte microarrays show increased proinflammatory activity, such as increased TNF-alpha at rest and after stimulation (5). In addition, *in vitro* HIES peripheral blood mononuclear cells have increased proinflammatory cytokine secretion (TNF-alpha, IFN-gamma, and IL-12) after stimulation with specific agonists (5,32).

However, the absence of hematopoietic *Stat3* in mice is also associated with impaired B cell numbers in the bone marrow and the periphery (34). Mice with *Stat3* deficient bone marrow have both poor B cell differentiation and enhanced apoptosis of B-cell progenitors. The correlation of these murine findings with human disease is not clear. Patients with HIES usually have normal B cell numbers, as well as normal IgG, IgM, and IgA, but the number of B-memory cells is diminished (27). In one study, there was no correlation between the ability to mount specific antibodies and the relative number of memory B cells, making the clinical significance of the lack of memory B cells unclear.

In mice and humans, STAT3 is integral to Th17 cell differentiation and IL-17 production. One of the most consistent immunologic findings in HIES is the near total absence of Th17 cells and severely impaired IL-17 production (28,29,35,36). Th17 CD4 cells are thought to be important in host defense through recruitment of neutrophils well as up-regulation of antimicrobial peptides (37). The significance of diminished IL-17 production in humans is still being elucidated, but mice that are deficient in IL-17 are prone to *Candida* and *Klebsiella* infections (38,39). Th17 cells are also

important for IL-22 secretion, which is critical for beta-defensin production (40). Lack of beta-defensins has been implicated in susceptibility to *S. aureus* in individuals with eczema (41). Therefore, the *S. aureus* abscesses of HIES may in part reflect decreased defensins secondary to the lack of Th17 cells. Beta-defensins are also expressed in the lung and might in part explain the susceptibility to pneumonias (42).

Further evidence of impaired immunity is the greatly diminished monocyte chemoattractant protein-1 levels in HIES patient peripheral blood mononuclear cells after IL-6 stimulation (5,6). Monocyte chemoattractant protein-1 is a chemokine involved in chemotaxis and the simulation of several cytokines. In addition, C-reactive protein, an acute phase reactant produced in response to IL-6, is often diminished in acute infections.

The extreme elevation of IgE in HIES remains poorly understood. There were initial hypotheses that the elevated IgE might reflect impaired IL-21 signaling, because IL-21 receptor knockout mice have elevated IgE (43). However, human B cells differ from those of mice in that IL-21 actually acts synergistically with IL-4 to increase IgE production (44). Therefore, lack of IL-21 might be associated with less IgE, not more. Perhaps, the increased IgE reflects a lack of suppression of IL-21 or lack of IL-4 inhibition by IL-10 or IFN-gamma. It is noteworthy that this cardinal feature of HIES has not yet been clearly explained.

Somatic Features of HIES

Homozygous *Stat3* knockout mice die *in utero*, but many tissue specific *Stat3* knockouts are viable. It is through these conditional knockout animals that much of the function of *Stat3* has been deduced (45). Poor wound healing, eosinophilia, osteoporosis, cardiomyopathy, lung, and brain abnormalities are seen in these tissue-specific deletants.

In pulmonary epithelium-specific *Stat3* knockout models, hyperoxia caused excessive inflammation and pulmonary injury with associated alveolar enlargement (46). This may relate to the pneumatocoeles of HIES that are thought to be related to an exuberant inflammatory response.

In hematopoietic *Stat3* knockouts, mice have increased TNF-alpha and IFN-gamma levels as well as increased osteoclastogenesis and decreased bone density (47). The bone findings may relate to the minimal trauma fractures and osteopenia observed in HIES. This may relate to the inhibitory effect on osteoblasts of TNF-alpha, or to abnormal IL-10 signaling, because IL-10 typically inhibits osteoclast activity (48).

The hyperintensities seen on brain MRI in HIES may relate to increased inflammation, demyelination, and astrocytosis after neurologic injury, as seen in astrocyte-specific *Stat3* knockout mice (49). As IL-6 is involved in astrocyte differentiation, these findings may relate to disrupted IL-6 signaling.

Cardiac myocyte-specific *Stat3* deficiency in mice leads to cardiac dysfunction with early cardiac failure and increased infarct size after ischemic insult (50). Cardiac myocytes stimulated with LPS had increased TNF-alpha levels and subsequent inflammation and dysfunction (51). Cardiomyopathy has not been a reported feature of HIES, but has not been

examined systematically. Coronary artery tortuosity and aneurysms have been found in HIES, as well as decreased atherosclerosis (21–23). The pathogenesis and implications of these findings remain to be determined. Some mouse models of atherosclerosis have increased Stat3 expression, suggesting that a lack of *Stat3* functioning may be associated with decreased atherosclerosis, but this has not been evaluated (52).

Poor wound healing after skin biopsy has been associated with mouse keratinocytes deficient in *Stat3* (53). These mice have normal initial hair growth, but then abnormal hair follicles form in subsequent growth cycles with resultant epidermal hyperplasia and keratosis. Wound healing is thought to be normal in HIES, but the skin is often porous with a doughy texture. The oral mucosa variants may reflect aberrant responses to infection, such as *Candida*, or injury. The pathogenesis of the eczema of HIES is not well understood.

Therapy of AD-HIES

Therapy of HIES remains largely supportive, but will likely be refined greatly in the next several years as the pathogenesis of HIES is delineated and animal models created. Treatment of eczema and prevention of *S. aureus* abscesses are most successfully accomplished with antiseptics such as bathing in bleach (120 mL of bleach in tub of water for 15 min three times weekly) or swimming in chlorinated pools. Antimicrobial prophylaxis prevents recurrent sinopulmonary infections, with trimethoprim-sulfamethoxazole a frequent choice. Pneumonias should be treated aggressively to try to prevent parenchymal damage; bronchoscopy may help isolate causative pathogens and clear pus. Active suspicion of pneumonia is necessary because systemic symptoms of illness are often lacking.

If pneumatocoeles and bronchiectasis are present, antimicrobial prophylaxis often needs to be broadened to cover Gram-negative bacteria and fungi. Management of pneumatocoeles is complex, as these cysts when secondarily infected carry significant risk for morbidity and mortality; however, surgery is not without risk, as HIES patients may have trouble re-expanding their lungs and soilage of the pleural space can occur.

Immunomodulatory agents in HIES have not been well studied. Intravenous immunoglobulin (IVIG) may decrease the number of infections for some individuals and is the most frequent immunomodulator used (54,55). Levamisole, an antihelminthic that stimulates T- and natural killer cell function, was found to be inferior to placebo (56). IFN-gamma *in vitro* showed promise, but clinically had mixed results (57). Histamine-2 antagonists and cyclosporine may be helpful (58,59). Omalizumab, the MAb against IgE, has not been studied. Bone marrow transplantation has been performed but is likely not fully corrective (60).

Autosomal Recessive Hyper-IgE Syndrome

A similar but distinct syndrome was reported by Renner *et al.* (9), characterized by extremely elevated serum IgE, severe eczema, recurrent skin bacterial and viral infections as well as sinopulmonary infection. Compared with AD-HIES, these

individuals lack the somatic features, such as the characteristic facies, scoliosis, and the failure of baby teeth to exfoliate. In addition, although pneumonias occur in AR-HIES, pneumatocoeles do not form.

AR-HIES has a much higher rate of cutaneous viral infections such as *Molluscum contagiosum*, Herpes simplex, and varicella infections. They also have frequent neurologic disease, ranging from facial paralysis to hemiplegia, in some cases due to CNS vasculitis. Mortality is high at a young age in AR-HIES with sepsis more frequent than in AD-HIES.

Eosinophilia and elevated serum IgE are the most consistent laboratory findings and may be more dramatic than in AD-HIES. Autoimmune cytopenias may occur. Other immunologic studies, such as lymphocyte phenotyping, do not have characteristic findings.

The etiology of most cases of AR-HIES is unknown, but autosomal recessive inheritance is assumed because of consanguinity and multiple affected siblings. One patient has been found to have a homozygous mutation of *Tyk2* with a four-nucleotide deletion resulting in a premature stop codon (61). This patient had the common features of AR-HIES such as eczema, viral infections, and recurrent sinopulmonary infections, but he also had *Bacille Calmette–Guerin* and *Salmonella* infections, infections classic for IL-12/IFN-gamma defects. Mutations of Tyk2 have been absent in the other reported cases of AR-HIES (62).

Conclusion

HIES was the last major primary immunodeficiency for which the genetic etiology was unknown. *STAT3* mutations account for most cases of this multifaceted disease. Understanding the pathogenesis of the immunologic and the somatic features has already been greatly aided by genetic dissection of this disease. It is to be hoped that understanding the pathophysiology of these rare conditions will shed light on the more common problems in the general population, such as eczema, scoliosis, osteoporosis, and *S. aureus* infection.

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