Review Article

Hyperimmunoglobulin E syndrome: Genetics, immunopathogenesis, clinical findings, and treatment modalities

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The hyperimmunoglobulin E syndromes (HIESs) are very rare immunodeficiency syndromes with multisystem involvement, including immune system, skeleton, connective tissue, and dentition. HIES are characterized by the classic triad of high serum levels of immunoglobulin E (IgE), recurrent staphylococcal cold skin abscess, and recurrent pneumonia with pneumatocele formation. Most cases of HIES are sporadic although can be inherited as autosomal dominant and autosomal recessive traits. A fundamental immunologic defect in HIES is not clearly elucidated but abnormal neutrophil chemotaxis due to decreased production or secretion of interferon γ has main role in the immunopathogenesis of syndrome, also distorted Th1/Th2 cytokine profile toward a Th2 bias contributes to the impaired cellular immunity and a specific pattern of infection susceptibility as well as atopic-allergic constitution of syndrome. The ophthalmic manifestations of this disorder include conjunctivitis, keratitis, spontaneous corneal perforation, recurrent giant chalazia, extensive xanthelasma, tumors of the eyelid, strabismus, and bilateral keratoconus. The diagnosis of HIES is inconclusive, dependent on the evolution of a constellation of complex multisystemic symptoms and signs which develop over the years. Until time, no treatment modality is curative for basic defect in HIES, in terms of cytokines/chemokines derangement. Of note, bone marrow transplant and a monoclonal anti-IgE (omalizumab) are hoped to be successful treatment in future.

Key words: Autoimmune disease, eye, hyperimmunoglobulin E syndrome, immunodeficiency, ocular, omalizumab, *Staphylococcus aureus*

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INTRODUCTION

The hyperimmunoglobulin E syndromes (HIESs), also called "hyperimmunoglobulin E (IgE) recurrent infection syndrome" (Online Mendelian Inheritance in Man [OMIM] 243,700),[1] are very rare complex immunoregulatory multisystem disorders[2] of unknown cause that affect the immune system, skeleton, connective tissue, and dentition. The prevalence and incidence of HIES (disease) are about 1: 100,000 and <10–6 per year, respectively; with equal sexual preponderance.[3,4] HIES is characterized by the classic triad of high serum levels of IgE at least ten times normal (>2000 IU/ml),[5] recurrent staphylococcal cold skin abscesses, and cyst-forming pneumonia which occurs in 77% of patients.[5] Abnormal neutrophil chemotaxis due to decreased production of interferon gamma (IFN-γ) is believed to be the underlying mechanism of disease.[6]

This syndrome was first reported is 1966 by Davis *et al.*, who presented two red-haired, fair-skinned girls with frequent sinopulmonary and staphylococcal skin infections, chronic dermatitis, and an abnormal inflammatory response.[7] They addressed this condition

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as Job's syndrome (OMIM 147,060)[1] based on its similarity biblical character whose body was covered with sore boils.[8] Elevated levels of IgE and a defect of neutrophil chemotaxis were identified in the two Job's syndrome girls.[9] This shows that Job's syndrome and hyper-IgE syndrome are probably the same disorder.

In 1972, Buckley *et al*. discussed two boys with similar problems such as severe dermatitis, recurrent cutaneous, pulmonary, and joint abscesses as well as coarse facies and growth retardation with markedly elevated serum IgE levels and eosinophilia.[10] This was referred to as Buckley's syndrome.[11]

These two syndromes were later found to fall in the same category and were introduced under the new title of HIES. To date, approximately 250 cases have been reported in literature.[2] The HIES also has well been described by Hill and Quie[12] in 1974, Donabedian and Gallin in 1983, and Belohradsky *et al*.[13] in 1987. A systemic evaluation of thirty patients established that HIES is a multisystem disorder characterized by susceptibility to infection, elevated levels of serum IgE, eosinophilia, distinctive facial appearance by the age of 16 years, retained primary dentition, bone fragility, hyperextensible joints, scoliosis, and craniosynostosis.[5]

We planned this review synthesis to provide a framework within which HIES could be explained by its clinical manifestations, genetics, laboratory findings, and pathogenesis. Diagnostic issues and therapeutic options of the entity are outlined as well.

METHODS

A thorough electronic literature was performed on PubMed, Medline, Scopus, EMBASE, and Web of Science databases using the following keywords and terms: "Hyper immunoglobulin-E syndrome;" "HIES;" "job syndrome;" "Buckley syndrome;" "job-Buckley syndrome;" "hyper immunoglobulin E-recurrent infection syndrome." Our search strategy was based on previous studies.[14] No limitation on publication date was applied. Retrieved review articles were excluded primarily. Eligible study designs were as follows: controlled or noncontrolled clinical trials, experimental interventions, case–controls, cross-sectionals, case reports/series, and letters/correspondences. With no language limitation, all of the articles were examined for direct relevance to one of the following topics: pathogenesis, prevalence, clinical features, genetics, and treatment strategies. After exclusion of irrelevant articles, we narrowed our results down to 76 articles.

PRESENTATION

Despite the presence of systemic anomalies in a high percentage of HIES patients, their manifestation may be postponed until late childhood or early adolescence with variable expression.[2] As well, there is prominent variability in the collection of signs and symptoms that establish the diagnosis.

Lack of specific blood tests and immunologic or molecular markers make the diagnosis of HIES difficult, especially in atypical less severe cases (HIES-variants).[1,5,15] Recognition of the early presenting findings of HIES can lead to earlier diagnosis as well as the institution of prophylactic measures.

When other relatives are involved, the diagnosis may be made during the neonatal period. This is based on a distinctive newborn rash as a papulopustular eruption that mainly involves the scalp, face, neck, axillae, and diaper area. In the majority of cases, this finally develops into eczematoid dermatitis that persists sometimes for years and differs from atopic dermatitis by its tendency to generalize following superinfection with *Staphylococcus aureus*[16] and often require antibiotic treatment. There are also some key clues to the diagnosis including markedly elevated serum IgE levels and cold abscesses or pneumatocele that may develop later in the course of HIES.[17] Thus, IgE levels lower than the arbitrary cutoff point of 2000 IU/ml can be seen in infants with HIES.[5]

With a negative family history, HIES diagnosis should be considered in children with frequent respiratory and cutaneous infections or recurrent abscesses superimposing chronic eczema typically in the absence of other atopic conditions. Conclusively, the constellation of recurrent otitis media or pneumonia in the 1st month of life in the setting of characteristic eosinophilic pustular folliculitis (EPF) of the scalp necessitates detailed investigations for HIES. Additional supportive associations include recurrent candidal infections, osteopenia, and pathologic bone fractures.[17]

Although serum IgE levels are in general markedly elevated, and some have IgE levels in the tens of thousands, this hyper-IgE-state is not a constant finding, and serum IgE levels may change irrespective of the severity of skin disease and infections; may even become normal in the late course of the disease.[17] Therefore, HIES is, in fact, a descriptive title for this condition. Another important aspect of HIES is peripheral eosinophilia due to increased production of the granulocyte-monocyte colony-stimulating factor (GM-CSF); however, this abnormal laboratory finding does not necessarily correlated with disease activity either.[5,18]

PATHOGENESIS

Although exact immunologic defects and underlying causes of HIES are not completely understood; several immune

system dysregulations play role in the pathogenesis of disease. Of note, the most common features of HIES are as the following increased serum IgE, eosinophilia, increased GM-CSF, decreased C3b receptors on neutrophil, decreased adhesion molecule L-selectin, lowered IFN-γ production or secretion, lack of transforming growth factor (TGF)-β, poor response to interleukin 12 (IL-12) stimulation, and abnormal neutrophil chemotaxis.[2,15]

As a well-known notion, in normal conditions, IgE synthesis is enhanced by Th2 cytokines (IL-4 and IL-13) and repressed by Th1 cytokines (IFN-γ and IL-12). In addition, eosinophils are influenced by cytokines which are secreted from T-helper cells. Th2 cytokines (mainly IL-4, IL-10, and IL-13) induce IgE switching; IL-5-mediated activation, and differentiation of eosinophils[19] and Th1 cytokines (IFN-γ and IL-12) repress IgE synthesis.[6] In case of HIES, IgE synthesis is a complex process sustained by interactions between T- and B-cells and the cytokine profile of T-helpers. HIES consists of Th1/Th2 imbalance and dysregulation of cytokines and chemokines production.[20] The inconsistency of chemotactic defects and variations of disease course over time[21] and raised IgE titers may be secondary to the predominance of Th2 cytokines (IL-4, IL-13, and IL-6).[21] Despite repressed Th1 response, the Th2 response may not be overactive. Thus, not only IgE synthesis, regulated by the IL-4/IL-13 pathway (mainly IL-13) is maximal but also IgE catabolism may be impaired.[21]

A major part of the immunologic dysfunction lies on the cellular and humoral immune responses. IFN-γ as an indicator of the Th1 cytokines - mainly produced by T-cells and NK-cells - activates cellular immune responses; however, Th2 cytokines (IL-4, IL-10) mainly enhance of the humoral immune system. The low IFN-γ secretion could be responsible for bias toward Th2 cell dominance which then results in susceptibility to infections and neutrophil chemotactic defect and markedly elevated serum levels of IgE.[22-24] Because Th1 cytokines are important for stimulating the defense against intracellular microorganisms,[24] defects of IFN-γ-mediated immunity appear to be the pathogenic mechanism of severe disseminated mycobacterial infections. Disseminated bacillus Calmette–Guérin (BCG) infection has been reported in one HIES patient without central nervous system (CNS) involvement and in another with CNS involvement with multiple brain abscesses.[25]

Occurrence of chronic local or systemic fungal infections such as mucocutaneous and nail bed candidiasis as well as mycobacterial, *Pneumocystis carinii,* or *Cryptococcus neoformans* infections in HIES patients reflects abnormal cellular immune response owing to defective IL-12/IL-18/IFN-γ axis with resultant impaired IFN-γ biosynthesis.[21] Impaired IL-12/IL-18, IFN-γ axis in HIES patients is evidenced by decreased expression of IL-12 RB2 in cells from HIES patients, which leads to failed synergistic stimulation of T-cells by combination of IL-12/IL-18.[26] Moreover, the release of IFN-γ is the principal step in defense against these pathogens with activation of innate also adaptive cellular immunity.[21] The previous studies had shown that recombinant human IFN-γ enhances chemotactic activity of neutrophil through a rise in intracellular free calcium and inhibition of IgE production.[22,27] However, autoimmune thrombocytopenia had been reported as an adverse drug effect of recombinant IFN gamma in a patient with HIES.[28]

Although the precise mechanism behind low IFN-γ production in HIES remains elusive, Ito *et al*.[26] demonstrated that transcription of IFN-γ messenger ribonucleic acid and the production of its protein molecules progresses normally but selective insufficiency in the secretion of IFN-γ persists. Confocal laser scanning microscopy clearly demonstrated the accumulation of IFN-γ in the cytoplasm of lymphocytes in patients with HIES. Ito *et al*. suggested that impaired intracellular secretory mechanisms or a faulty IFN-γ structure could be a possible mechanism for selective insufficiency in IFN-γ secretion.

IL-12 is an enhancer of IFN-γ production and also suppresses IgE production.[6] Enhancement of IFN-γ production by IL-12 in patients with HIES is significantly lower compared to healthy controls.[23] Borges *et al*.[23] reported that HIES lymphocytes have an impaired IL-12-mediated IFN-γ production, despite favorable IL-12 production, due to decreased IL-12 RB2 receptor expression. Consequently, the principal immune system defect in HIES consists of IFN-γ deficiency mainly by a defective upstream IL-12 signaling error.[2] This defect favors naive T-cell differentiation into Th2 cells and thus has a direct effect on the production of cytokines such as IL-13.

Ohga *et al*.[29] demonstrated reduced expression of TGF-β and IFN-γ genes in the circulating activated T-cells. IFN-γ and TGF-β inhibit IL-4-dependent IgE synthesis. The underexpression of TGF-β and IFN-γ in naturally activated T-cells leads to a crucial cytokine derangement which contributes to a hyper-IgE state in HIES. In addition, since TGF-β plays a crucial role in the activation and differentiation of regulatory T-cells, the defective TGF-β expression as well as IFN-γ dysregulation are of key importance in the pathogenesis of both immunological aspects, such as the hyper-IgE state and potential defects in the regulatory T-cells in addition to constitutional problems in this syndrome.[29]

The impaired neutrophil chemotaxis has been assayed in response to endotoxin-activated serum, C5a, sodium caseinate, and fMet-Leu-phe,[30] but oxidative burst assay

using nitroblue tetrazolium test was normal.[24] As IFN-γ has a critical role in inflammatory reactions as a major activator of neutrophil, the defect of IFN-γ may be responsible for impaired chemotaxis of neutrophil that is important in the pathogenesis of at least recurrent abscesses and undue susceptibility to bacterial and fungal infections seen in this syndrome.[26] Another finding in HIES includes a deficiency of neutrophil receptor for C3b, an important chemotactic factor, and mediator of neutrophil phagocytosis.[31] In addition to decreased IFN-γ, production of inhibitory cytokines by lymphocytes, such as GM-CSF[22] and under expression of ENP-78 and IL-8 have a role in this impaired neutrophil chemotaxis.

The release of IL-10 is unaltered in HIES patients. The relatively high concentrations of IL-10, compared with IFN-γ, contribute to the atopic constitution of this syndrome such as high IgE level, eosinophilia, allergic reactions, and chronic dermatitis.[24] Chehimi *et al*.[6] suggested that the impaired ratio of IFN-γ to IL-4 and IL-10 might account for IgE or eosinophil imbalances. Furthermore, they described various abnormalities in chemokine gene expression such as under expression of chemokines, for example, epithelial neutrophil activating protein-78, monocyte chemoattractant protein-3, eotaxin, and osteopontin. In addition, Gudmundsson *et al*.[32] reported an increased expression of IL-13 in CD4+ helper T-cells. They showed that higher proportions of IL-13 expressing CD4+ cells and increased levels of IL-13 in HIES patients could be responsible in part for raised IgE as well as a factor in their skeletal features. IL-13 inhibits the growth of osteoblasts and stimulates them to produce IL-6 a potentiating osteoclast factor.[33]

HIES patients have reduced bone density and higher incidence of long bone fractures.[26] Bone fragility in these patients is associated with an imbalance in cytokine-secreting lymphocyte subpopulations.[34] In addition, underexpression of osteopontin is responsible for hypomineralized bones, pneumatocele formation, and infectious susceptibility and low IFN-γ and high PGE2 synthesis reflects a lack of IFN-γ inhibition of bone resorption with consequent cortical bone loss. It has been disclosed that HIES mononuclear cells release abnormally high levels of PGE2 and this factor is one of the crucial factors responsible for many of the musculoskeletal findings, including increased bone resorption and decreased bone density.[26] In two patients with HIES, inhibiting cyclooxygenase-induced PGE2 with aspirin reversed monocyte-induced bone degradation to normal.[35]. Imbalances of chemokines, which are produced by a range of nonhematopoietic cells, may explain why bone marrow transplantation has been ineffective in this syndrome.[34] In addition, Grimbacher *et al*.[11,15] suggested that there was upregulation of RGC32 (a CD14+ T-cell gene), decreased expression of IL-17 and CXC11 gene in HIES monocytes as well as an upregulation of Ig-related genes. Furthermore, mononuclear lineage cell (osteoclasts, osteoblasts) abnormalities could be responsible for bone and dental anomalies.

A distorted Th1/Th2 cytokine profile toward a Th2 bias, which seems to be a basic immune abnormality, contributes to the impaired cellular immune responses, and a specific pattern of infection susceptibility characteristic to HIES as well as chronic allergic dermatitis.[24] There is evidence of host defense abnormalities in HIES, for example, poor antibody responses to immunization[12,16-18] abnormal T-lymphocyte subsets, including low suppressor T-cell number, decreased percentage of T and B memory cells and severe decrease in Th17 cells, hypersensitivity to staphylococcal and *Candida* antigens, high IgE titer directed toward *Staphylococcus* and *Candida* and lack of anti-staphylococcal IgA.[22,36,37] It has been shown that HIES patients possess unique anti-*S. aureus* Ig composition, especially, uniformly elevated IgE to *S. aureus* and a deficiency of anti-*S. aureus* IgA. This implies that raised IgE titer has no causative correlation with recurrent infection and may even be immunoprotective.[38] The Th17 cells have a critical role in IL 22 secretion which is important in beta defensin production. The lack of beta defensin in patients with eczema is associated with susceptibility to *S. aureus* infection and pneumonia.[39,40]

The prevalence of autoimmune complications in HIES, as in other primary immunodeficiency states, is increased, most notably due to abnormalities of an incompetent immune system consisting of impaired neutrophil chemotaxis, complement or IgA deficiencies with lack of eradication of pathogens, and resultant exaggerated stimulation of an alternative, ineffective immune pathway which leads to damage to self-tissue[41] and development of autoimmune manifestations. In addition, pathologic activation of B-cell is associated with a shift in the immunoregulatory state that favors Type 2 over Type 1 cytokines. The decreased IL-2 production due to faulty Th1 response may alter the development of regulatory CD4+ CD25+ cells and fit the synthesis of autoantibodies by IL-4 activation.[42] Several cases of HIES in the literature (autosomal recessive [AR], sporadic variants) are reported to be associated with systemic lupus erythematosus (SLE), nephritic syndrome, and idiopathic thrombocytic purpura (ITP); and one case of bronchiolitis obliterans has been reported.[42,43]

Although the genetic basis of HIES is still relatively unknown, it is clear that genetic components have crucial role in the pathogenesis of the disease. The variable phenotype of HIES suggests that HIES may be caused by mutations in different genes in different families (including genetic heterogeneity)

or the deletion of contiguous genes in a short chromosomal region.[11]

In the literature, nineteen families with 57 cases of HIES were genotyped and underwent multipoint analysis in a candidate proximal 4q region that confirmed linkage to this region of 4q as a disease locus. However, these candidate-gene approaches of multiplex HIES families did not identify any linkage to this region of 4q, suggesting genetic heterogeneity.[1] Renner *et al*.[20] evaluated 13 human immunodeficiency virus-seronegative patients with suspected primary immunodeficiency who all fulfilled the classic clinical triad of HIES. They were from six consanguineous families and demonstrated an AR mode of inheritance for HIES. They concluded that the AR-variant of HIES represents a different distinctive disease entity from autosomal dominant HIES (AD-HIES) through complex linkage analysis that documented the involvement of more than one genetic locus.

To pursue the genetic localization of HIES, a quantitative phenotype HIES scoring system was developed at the national institute of health based on a systematic evaluation of thirty patients with HIES and seventy of their relatives based on the existence and severity of the following twenty clinical and laboratory features: newborn rash, eczema, skin abscesses, recurrent upper respiratory tract infections, pneumonia, parenchymal lung changes (bronchiectasis or pneumatocele), candidiasis, other severe infections, fatal infections, characteristic facies, increased interalar distance, high palate, retained primary dentition, joint hyperextensibility, pathologic fractures, scoliosis, midline anomalies, lymphoma, high serum IgE level, and eosinophilia. Then, on the basis of incidence and specificity of each finding for HIES, a point value was assigned where ≥15 points indicates the subject is likely to carry an HIES genotype, a score of 10–14 points to an indeterminate HIES genotype, and subjects with a score of <10 points are unlikely to have an HIES genotype.[1]

Although most cases are sporadic, HIES can be inherited as a single locus, AD trait with variable expressivity and also AR inheritance.[11,20] One of the involved genes in pathogenesis of HIES is STAT3 that causes autosomal dominant type of the syndrome.[44] Mostly, mutations of STAT3 occur in two regions, including the DNA binding domain and SH2 domain.[45] The presence multiple mutations of STAT3 gene calls to mind a ration for the multisystem involvement of the disease. It has been demonstrated that peripheral blood monocytes in the HIES patients with STAT3 mutations have more bone resorption activity comparing to healthy controls.[46] This explains the possible etiology of reduced bone density and consequent frequent bone fractures. Th17 cytokine plays a pivotal defensing role against mucocutaneous candidiasis. In addition, the mutations in STAT1 in HIES patients lead to defective Th17 responses. Hence, the defective response of Th17 is highly associated to mucocutaneous candidiasis.[47] Filaggrin plays role in preventing water loss leakage and entrance of infections microorganisms to the epidermis. Reportedly, mutation in filaggrin responsible for atopic dermatitis.[48]

CLINICAL MANIFESTATIONS

The clinical features of HIES involve the immune system, connective tissue, skeleton, skin, and dental development with variations in the severity and time of presentation.

Skin findings

A newborn rash, similar to atopic dermatitis, is a presenting feature of HIES in 78% of cases. It usually begins as pink to red papules that become pustules, exude pus, and turn into a crusted form. Lichenification and scales are either absent or mild. This rash, which is distributed on the scalp, face, neck, axillae, and diaper area, is typically pruritic owing to the histamine released by IgE-triggered intradermal mast cells. Although eczematous changes are seen in some patients, generalized xerosis and other signs of atopy may not be present. Eczema is seen to some degree in 100% of HIES patients; moderate to severe eczema in only 71%. The main clinical clues for differentiating HIES dermatitis from atopic dermatitis include a severe prolonged clinical course, beginning at an earlier age, atypical distribution on axillae, groin and perineum, chronicity of dermatitis, recurrent staphylococcal skin infections, cold abscesses and resistance to conventional therapy, and responsiveness to anti-staphylococcal antibiotics. Recurrent superantigen producing *S. aureus* infections superimpose HIES dermatitis, serve as the autosensitizing trigger and lead to generalizations of dermatitis. Despite well response to intensive antibiotic treatment, recurrences occur when prophylactic anti-staphylococcal antibiotics such as trimethoprim/sulfamethoxazole (TMP-SMX) are not taken.[2,11,16,17]

After the newborn period, skin findings include retroauricular fissures, weeping crusted external otitis, severe infected folliculitis of axillae and groin, folliculitis of the upper back and shoulders, cutaneous cold abscesses, chronic mucocutaneous, and nail bed candidiasis (*Candida* paronychia, onychodystrophy); these features differentiate HIES from atopic dermatitis. Older HIES patients show distinctive thick and doughy texture of the facial skin with dilated follicular ostia and pitted scarring.[16,17]

Infections and immunodeficiency

Cold abscesses and chronic candidiasis with 87% and 83% incidence, respectively, are the most common cutaneous

infections seen in HIES. Cold abscesses are pathognomic of HIES, but they are not essential to the diagnosis.[15]

Skin abscesses may occur anywhere, but the most common sites are the face and trunk and generally grow *S. aureus*. Besides, furunculosis and cold abscesses, *S. aureus* has been the causative agent in infections of the external ear.[15] Recurrent pneumonia, as a clinical hallmark of HIES, is seen in 87% of patients. The most common pathogen of acute pneumonia is once again *S. aureus*; next infecting organisms are *Haemophilus influenza* and *Streptococcus pneumonia*. The staphylococcal pneumonia with pneumatocele formation are essential for the diagnosis of HIES,[49] but they are not invariably present.

Long-term pulmonary complications, including bronchiectasia and pneumatocele, recurrent pulmonary abscesses, and bronchopleural fistulae had been seen in 77% of HIES patients.[15] Superinfection of the bronchiectatic lung and pneumatocele with *Pseudomonas aeruginosa* and *Aspergillus fumigatus* can further exacerbate lung destruction.

The less frequent pulmonary infections in HIES consist of *P. carinii*, nocardia, mycobacterium intracellulare pneumonia, disseminated pulmonary candidiasis, adult respiratory distress syndrome (ARDS) with disseminated intravascular coagulation (DIC) due to methicillin-resistant *S. aureus* (MRSA) sepsis. Upper respiratory tract infections, including sinusitis, bronchitis, otitis media, otitis externa, and mastoiditis are frequent in HIES. With regard to opportunistic infections in HIES, mucocutaneous candidiasis is the most common one; the gastrointestinal tract is also susceptible to these infections. Cryptococcosis and histoplasmosis of the colon and rectum with the simulated presentation of crohns disease and four cases of colon perforation and peritonitis have also been described.[18,50-52]

The less frequent infections include disseminated candidiasis and disseminated or local necrotizing mycobacterial infections following BCG immunization.[25,53,54] Systemic candidiasis has reported as endocarditis with a fungal mass on the tricuspid valve.[55] Other reported opportunistic infections are cryptococcal meningitis and generalized lymphadenopathy caused by trichosporonosis.[56]

One of the most distinctive indicators in AR-HIES is chronic refractory viral infections, especially herpes simplex virus (HSV) and molluscum contagiosum (MC), varicella-zoster virus (VZV), possibly due to a qualitative T-cell defect. Presentations of HSV infections include recurrent aphthoid lesions as large soft tissue masses around the nose and ear.[57]

Other systemic infections include recurrent bacterial arthritis and staphylococcal osteomyelitis at fracture sites bacteriemia and sepsis are rare.[5]

Eczema (100%), eosinophilia (93%), elevated serum IgE (97%), abscesses (87%), pneumonia (87%), and mucocutaneous candidiasis (83%) are the most common features of immunodeficiency and immune.[2,11]

Musculoskeletal and dental abnormalities

Distinctive coarse facial characteristics of HIES patients become universal by the age of 16 years,[2] and include facial asymmetry with hemihypertrophy, prominent forehead, deep-set eyes; broad nasal bridge, wide fleshy nasal tip, increased alar and outer canthal distance, mild prognathism, and rough facial skin with prominent pores.[16]

Midline facial anomalies such as cleft lip, palate, and tongue, high-arched palate and craniosynostosis have been reported but are unusual.[58] Scoliosis is seen in 63% of patients and may arise from diverse conditions such as discrepancies in leg length, anomaly of vertebral body after thoracotomy,[59] and an intrinsic susceptibility.[15] Other skeletal abnormalities are various and include osteopenia, joint hyperextensibility, joint deformities, genu valgum,[2] congenital spinal anomalies as well as bifid rib and pseudoarthrosis of rib, and frequent pathologic fractures that may reflect a higher than normal level of cytokine-mediated bone resorption.[32]

HIES has also been associated with one case of osteogenesis imperfecta tarda.[60] Impaired deciduation of primary teeth due to the persistence of epithelial root sheath in HIES patients is found quite consistently which in turn prevents the appropriate eruption of the permanent successors.[15,61] It is likely that the delay in dental root resorption, as well as the ineffective inflammatory responses causing pneumatocele formation, are both manifestations of impaired cytokine-mediated osteoclasts and macrophage activation.[5]

Ocular manifestations

Ophthalmologic pathologies that have been described in the literature include conjunctivitis, keratitis, spontaneous corneal perforation, endophthalmitis caused by *Candida* and *Streptococci*, recurrent giant chalazia,[62] extensive xanthelasma,[7] undefined tumors of the eyelid,[19] strabismus, and bilateral keratoconus.[63]

HYPER IMMUNOGLOBULIN E SYNDROME ASSOCIATION WITH AUTOIMMUNE DISEASES AND MALIGNANCIES

Although autoimmune diseases are observed in all forms of HIES,[20] especially AR-HIES; HIES has been

associated with SLE (five documented cases in the literature), dermatomyositis, membranoproliferative glomerulonephritis, nephrotic syndrome, ITP, hemolytic anemia, bronchiolitis obliterans, and pericardial effusion.[20,64]

Ulcerative colitis, alopecia areata, and celiac disease are all indicative of autoimmunity demonstrated in three cases of 22 patients in an Iranian survey from consanguineous families.[65] Ozgur *et al*.,[66] in May 2007, presented a child of acquired hemophilia with low levels of factor VIII owing to elevated factor VIII inhibitor levels. The case had clinical and laboratory features suggestive of AR-HIES. Association of HIES with autoimmunity has been theorized by impaired neutrophil chemotaxis and deficiency of complement or IgA. In addition, distorted Th1/Th2 with a dominant Th2 response and/or a defective Th1 cytokine profile leads to altered development of regulatory T-cells and favors the production of autoantibodies by IL-4 activation and inappropriate stimulation of B-cells and class-switching.

Several malignancies have been reported in HIES, suggesting HIES patients may be at increased cancer risk. Multiple cases of lymphomas have been reported in HIES patients, including Hodgkin's lymphoma,[66] non-Hodgkin's lymphoma[67] also Burkitt's and an unusual histiocytic variant.[68]

Lymphogenesis in HIES may be multifactorial, including chronic antigenic polyclonal B-lymphocyte stimulation by viruses, poor T-cell control of B-cell proliferation, defective immunosurveillance, and cytokine irregularities. Many of the involved patients have had advanced stage or extranodal disease and poor outcome.[67]

Other cancer types, including acute myelocytic lymphoma, vulvar and liver cancer, and metastatic tongue squamous cell carcinoma have been reported in HIES patients; however, lymphoma is the most frequently reported malignancy.[67] A high index of suspicion of lymphoma should be exercised in HIES patients who present with lymph node enlargement.

Other rare associations with HIES include ventricular aneurysm with myocarditis, autism, and mental retardation.[62,69]

Causes of death in hyperimmunoglobulin E syndrome

The most significant causes of death in HIES patients include pulmonary insufficiency from recurrent pneumonia with their consequences such as pneumatocele and lymphoma.[70] Cystic lungs may become super-infected with Gram-negative bacteria and fungal agents which are associated with mortality due to pulmonary fungal vascular invasion and systemic dissemination.

HYPERIMMUNOGLOBULIN E OVERLAP SYNDROMES

Coexistence of HIES classical triad with rare defined genetic diseases has been reported; dubowitz syndrome (postnatal growth retardation, microcephaly, and characteristic facial appearance) by Antoniades *et al*.,[71] pentasomy x by Boeck *et al*.,[72] and Saethre–Chotzen syndrome (acrocephalosyndactyly, hypertelorism, and ptosis) by Boeck *et al*.[73]

HYPERIMMUNOGLOBULIN E SYNDROME-AUTOSOMAL RECESSIVE VARIANT

In 2004, Renner *et al*. reported 13 patients from six consanguineous families which fulfilled the HIES criteria and had recurrent infection of *S. aureus*, *H. influenzae*, *Proteus mirabilis*, *P. aeruginosa*, and *Cryptococcus*. Several of them had chronic refractory MC infections, seven suffered from recurrent aphthoid HSV infections, one patient had recurrent VZV-infections, and ten of these 13 patients had recurrent fungal infections. AR-HIES is a primary immunodeficiency with classical immunologic findings of elevated serum IgE, hypereosinophilia, eczema, and recurrent staphylococcal infections of the skin and respiratory tract. In addition, CNS sequelae with high mortality, patients had neurological symptoms such as partial facial paralysis to hemiplegia, vasculitis, autoimmunity (hemolytic anemia, pericardial effusion) were noted.[20]

AR-HIES represents a distinct disease entity, which can be separated from AD-HIES by several major criteria. First, AR-HIES patients have no facial, skeletal, connective tissue, or dental abnormalities. Second, they have high incidence of devastating CNS complications with fatal outcome which may be manifestations of hypereosinophilic vasculitis or occult infection and vary from ruptured cerebral aneurysm and embolic stroke to vasculitis of cerebral arteries and subarachnoid hemorrhage. Third, types of infections and immunologic features differ from AD-HIES with regard to recurrent severe viral infections, especially HSV, VZV, and MC infections which are not encountered in sporadic or AD-HIES. There is also increased susceptibility to fungal infections that are quite distinct from the dominant and sporadic forms.[11,20] A defect in Th1 - T-cell function is possible, especially with taking into account recurrent fungal infections. Autoimmune diseases are observed in all forms of HIES but may be more frequent in AR-HIES. AR-HIES patients have significantly higher eosinophil counts when compared with AD-HIES patients. Whereas postinfection, pneumatocele formation is almost pathognomonic in AD and typical sporadic HIES, they do not occur in AR-HIES even though the incidence of pneumonia is the same.[18,28,70]

In the pathogenesis of AR-HIES, both humoral and cell-mediated immunity are responsible. Ig isotypes other

than IgE are also raised, suggesting a nonspecific stimulation of the humoral response. Lymphocyte immunophenotyping was found normal with regard to the number of cells, but defective proliferative responses to specific antigens suggest that any lymphoid defects in AR-HIES are qualitative in nature, and most likely involve T-cells. Neutrophil function seems to be normal.[20]

LABORATORY INVESTIGATIONS

The most prominent immunologic aspects in HIES patients consist of defective granulocyte chemotaxis when activated by endotoxin and/or formyl-methionyl-leucyl-phenylalanine phagocytic cell ingestion, metabolism, and bacterial killing are all normal.[19] Th1/Th2 cytokine imbalances include reduced expression of IFN-γ and TGF-β genes and increased expression of IL-13 in the activated T-cells, decreased TGF-β/IL-4, and TGF-β/IL-10 ratio,[15,24,29] a skewed toward Th2 response with IL-4, IL-10, and IL-13 cytokine profile and normal monocyte cytokine production including IL-6, IL-8, IL-12, tumor necrosis factor alpha.[11,24]

IgE – serum Ig electrophoresis shows normal IgG, IgM, and IgA and increased IgD and markedly increased IgE and also polyclonal B-cells stimulation by viruses and increased risk of cancer.[67] Significant fluctuations can be seen in serum IgE levels over time without any alteration in clinical presentation.[5] Fluctuations in the IgE levels and eosinophilia are not correlated and are not related to infection susceptibility, eczema, or disease severity.[11] A lower limit of 2000 IU/ml is used as an arbitrary cutoff for this syndrome. In newborns, normal levels of IgE are very low to undetectable, therefore, normal adult IgE levels in infants (100–200 IU/ml) are pathological. An IgE level ten times higher than the 95th percentile of the age norm seems to be an acceptable level for the diagnosis of HIES.[11] As IgE titers are not static, elevated IgE levels may decrease over time in some patients,[15] thus a normal IgE level should not exclude the presence of HIES in an adult. Anti-staphylococcal and Anti-*Candida* IgE titers are raised,[74] but relation to disease is not conclusive. IgE production may be elevated due to an increased number of B-cells making subnormal levels of IgE. Dreskin *et al*.[75] showed that IgE catabolism was defective in HIES.

Blood cell count - white blood cell counts are generally in the normal limits in the absence of infection and often fail to rise in the occurrence of active infection, but leukopenia, neutropenia as well as leukocytosis have been reported in HIES patients. Eosinophilia in the blood, sputum, and abscesses is seen in virtually all patients. The eosinophilia is at least two standard deviations above normal values (more than 700 cell/μL). There is no correlation between the eosinophil count and serum IgE titer or severity of infectious complications. Flow cytometry analysis revealed normal T-cell, B-cell, NK-cell but abnormal T-lymphocyte subsets including decreased CD8+ cytotoxic T-cells and decreased CD8+ CD45 Ro+ and CD8+ CD45 RA+ (decreased memory phenotype T-lymphocytes),[76] normal T-lymphocyte proliferative responses to mitogens but very low or absent responses to antigens and allogeneic cells from family member.[19] One of the twenty-two patients in the Iranian survey was deficient in CD4+ T-cells, and four had a reversed CD4/CD8 ratio.[64] There is also poor antibody and cell-mediated responses to neoantigens, abnormally low anamnestic antibody response, diminished antibody response to secondary immunization, normal total hemolytic complement activity, involvement of Th2-lymphocyte subsets, especially IL-4 and IL-5 secreting ones[15] and reduced T-suppressor activity.[76]

Complement levels have been normal when studied.[15] In some HIES patients, raised levels of urinary histamine have been described which was correlated with eczematoid dermatitis.[15]

DIAGNOSIS

HIES diagnosis is inconclusive due to lack of specific blood tests, except for elevated serum IgE levels, and eosinophilia or definite immunologic indicators.

Earliest clues to the HIES diagnosis in infancy are a papulopustular folliculocentric eruption of the scalp, face, neck, axillae, and diaper area with characteristic skin biopsy findings of spongiosis and perivascular infiltrate with a predominance of eosinophils (EPF). A baseline evaluation should include qualitative Igs and a complete blood count with differential, skin biopsy, and bacterial cultures of skin lesions.[2,11]

The diagnosis of HIES is suspected in a case of recurrent staphylococcal pneumonia or cutaneous abscesses complicating chronic eczema. The presence of osteopenia or bone fractures is also strongly supportive of the diagnosis. In conclusion, vigilance and alertness of many physicians in regard to early presenting findings of HIES as well as recognition of defects in both the immune and somatic systems can lead to timely diagnosis and institution of appropriate prophylactic measures, including anti-staphylococcal antibiotics such as TMP-SMX and antifungals such as fluconazole that is very effective in limiting the severity and activity of disease and its complications. The diagnosis of HIES is dependent on the evolution of a constellation of complex multisystemic symptoms and signs that affect the skin, bone, teeth, lung, immunity, and infectious susceptibility which develop

over the years. These findings are suggestive of an aberrant regulatory molecule that is shared in all of these tissues, such as monocyte-macrophage or endothelial cell lineage.[2,11]

THERAPEUTICS

At present, no treatment modality is curative for the underlying defect in HIES. Intensive care of dermatitis, immediate wide spectrum antibiotic/antifungal treatment of infections, and surgical drainage of abscesses are the cornerstones of HIES management.

The prophylactic use of anti-staphylococcal antibiotics markedly reduces the incidence of skin infections and staphylococcal pneumonias but its effect on the outcome is uncertain. Lifetime penicillinase-resistant penicillins are reported to be safe and effective but a growing problem is the occurrence of MRSA and complications such as sepsis, ARDS, and DIC.[77] TMP-SMX is a safe and effective substitution to penicillins and has anti-MRSA coverage. Importantly, stopping of prophylactic antibiotic therapy will often lead to disease recurrence. Development of multidrug-resistant bacteria has been less of an issue than the risk of severe infections, especially recurrent pneumonia with attendant lung destruction.[78,79]

Mucocutaneous candidiasis, with manifestations such as onychomycosis, vaginal candidiasis, and thrush, is best controlled by oral triazole antifungals.[78]

Despite evidence of acute pneumonia or extensive superinfected dermatitis, HIES patients may be afebrile and not seriously ill, presumably due to the absence of inflammatory responses that permits the cold abscesses and pneumatocele to form. Empiric antibiotic therapy for new pneumonia should cover *S. aureus*, *H. influenza,* and *S. pneumoniae*. Empyema is not uncommon and necessitates drainage.[79]

Many researchers have attempted to treat HIES by correcting the imbalance of cytokines and Igs. The common mechanisms of action of several immunomodulatory therapies occur by T-cell phenotype shift from Th2 to Th1 on the action of IgE or on neutrophil function.[6]

Since 1979, ascorbic acid and concurrent antibiotics or intravenous immunoglobulin (IVIG) have been reported to improve clinical outcome in HIES, but the true effectiveness is not documented.[80] The histamine receptor-2 (H2) antagonist, cimetidine, has been shown to reverse HIES chemotactic defect *in vitro*.[2,81] Cromoglycate with maximum 40 mg/kg/day has been used with good clinical effects.[82] Levamisole has been inferior to placebo in a blinded randomized trial with infections as a clinical end-point.[78] Isotretinoin improved eczematous dermatitis and abscesses in one patient at a dose of 1 mg/kg/day over 4 months.[83] Isolated cases of HIES also exist that received recombinant human G-CSF with successful results.[84]

Cyclosporine A (CSA) at a dose of 3–5 mg/kg/day has been shown to cause dramatic improvement in the clinical condition, decrease in serum IgE levels, and improve neutrophil chemotactic function[85,86] with no untoward side effects. Low-dose CSA should not come as first line or maintenance treatment but only as a short-term therapy in patients with difficult management or refractory disease. The possible mechanism of action is a shift away from Th2 response.

High-dose IVIG has both immunoregulatory and anti-inflammatory properties and decreases IL-4-dependent IgE production, induces IgE neutralization or increases IgE catabolism[2,11] and may alter the immune dysfunction, decrease the frequency of infections, and improve eczematoid dermatitis. Monthly moderate doses of IVIG, as an alternative to high-dose, has been used in patients whose disease is refractory to standard therapies[87] and has been associated with an enhanced Th1 response.

Plasmapheresis in few reports has also shown improvement in clinical conditions such as dermatitis and infections.[88]

Subcutaneous injection of IFN-γ with a dose of 0.05 mg/m^2 three times weekly has been shown to reduce IgE production as well as improving neutrophil chemotaxis. Deficient IFN-γ is one of the prominent immune dysfunctions in HIES.[28] Although initial research shows promise, its inconsistent effects on IgE levels and infection susceptibility proposed by King *et al*.[89] reported autoimmune thrombocytopenia[28] necessitates extreme caution when this therapeutic approach is being considered. On the other hand, the use of IFN-γ or IFN-α in cases of refractory viral infections in AR-HIES has not been evaluated. IFN-α has been used clinically with some effect on eczema and IgE levels but has not been shown to affect neutrophil chemotaxis *in vitro*.[90]

Causes for different variance of HIES may be diverse, therefore, one therapeutic approach may benefit one but not necessarily all patients with HIES. Patients with AR-HIES have a more severe course with a striking vasculitis of the CNS, intractable viral infections, and autoimmune complications more frequent than in other forms of HIES, and so they may be more likely to benefit from BMT.[11]

Recently, a monoclonal anti-IgE, omalizumab has been shown closely related to a decline in serum IgE with symptomatic improvement in atopic conditions.[91,92] In

HIES, cause and effect impression of hyper-IgE state have not been established, thus the benefit of omalizumab is unknown. It is hoped that omalizumab proves to be a successful treatment in the future.

CONCLUSION

HIES is a rare, multisystem primary immunodeficiency disease with unknown etiology. It has variable features, and there is no single laboratory or clinical investigation that can secure the diagnosis. It is associated with many dysregulations of immune system cytokines and genetic mutations. One of the important factors in immune system of HIES patients is Th17, which is nearly complete absence in these patients. Th17 has an important role in the recruitment of neutrophils for host defense and also it has been shown that dysregulation IL-17 leads the mice susceptible to *Klebsiella* and *Candida* infections. In addition to Th17, it seems that raised level of IgE is associated with IL-21 signaling because mice with IL-21 receptor knockout have elevated level of IgE. Hence, more studies needed to demonstrate the role of IL-21 signaling and Th17 cytokines in pathogenesis of disease. Moreover, it is important to clarify the genetic mutations in pathogenesis of disease. As more is understood about the immune and genetic defects in these patients, more therapeutic options with increased efficacy will become available.

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Conflicts of interest

There are no conflicts of interest.

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