REVIEW ARTICLE

Hyper-IgE syndrome

Suresh Kumar Angurana, Renu Suthar Angurana

Introduction: The hyper-IgE syndrome (HIES) is a relatively rare primary immunodeficiency with multisystem involvement characterized by increased susceptibility to recurrent bacterial and fungal infections, musculoskeletal, facial and dental abnormalities, eczema, eosinophilia, and elevated levels of IgE (1-5). In recent past, large and comprehensive studies of the clinical features of HIES revealed a more complete clinical picture of HIES involving the immune system, the skeleton and dentition. There is also varied severity of the different clinical findings with age and from individual to individual, even within the same family. Patients with HIES require constant vigilance with regard to infections and chronic lung disease and prompt treatment to prevent complications. With early diagnosis and treatment of infections, most patients with HIES can lead full lives, becoming productive adults.

History: Hyper-IgE syndrome was described first as "Job's syndrome" by Davis and colleagues(1) in 1966, referring to the Biblical Job, who was "smote with sore boils"(1). They reported two red-haired, fair-skinned girls with many episodes of pneumonia, eczema-like rash and recurrent skin boils remarkable for their lack of surrounding warmth, redness, or tenderness. In 1972 the syndrome was refined by Buckley and colleagues (2), who noted similar infectious problems in two boys who also had distinctive facial appearances and extremely elevated IgE levels. Since that time, the classic triad of eczema, recurrent skin and lung infections, and high serum IgE has been expanded to include skeletal, connective tissues, cardiac & brain abnormalities (6, 7).

Clinical Features: HIES is a multisystem disorder with wide spectrum of clinical features. The characteristic manifestations of this condition are newborn rash (81%), boils (87%), recurrent pneumonias (87%), pneumatocoeles (77%), eczema (100%), mucocutaneous candidiasis (83%), peak serum IgE > 2000 IU/mL (97%), eosinophilia (93%), and increased incidence of lymphoma. Non-immunologic features include characteristic facies (83%), retained primary teeth (72%), minimal trauma fractures (71%), scoliosis (63%), hyperextensibility of joints (68%), focal brain hyperintensities (70%), chiari 1 malformations (18%), craniosynostosis and arterial aneurysms (5).The first manifestation of HIES is usually newborn rash (8). Pustular and eczematoid rashes usually begin within the first month of life, typically first affecting the face and scalp. The rash can be quite significant, especially in childhood. Boils are a classic finding in HIES and are characteristic of the diagnosis. The degree of inflammatory symptoms, such as tenderness and warmth, often is quite variable or absent. The "cold" abscesses initially described by Davis and colleagues (1) are common. Despite the absence of external signs of inflammation, there is frank pus on aspiration, and Staphylococcus aureus usually is cultured. With prophylactic antibiotics, the occurrence of these boils typically diminishes substantially.

Recurrent pyogenic pneumonias are the rule. Pneumonias typically start in early childhood, and the most frequent bacterial isolates are Staphylococcus aureus, Streptococcus pneumoniae, and Haemophilus influenzae (5). Although the pneumonias typically respond promptly to appropriate antimicrobial therapy, the healing of the lungs is aberrant leading to formation of pneumatocoeles and bronchiectasis during the healing process and usually persist once the infection has cleared (5). These persistent structural abnormalities predispose the patient to secondary gram-negative bacterial infection (typically Pseudomonas) and fungal infections (typically Aspergillus or Scedosporium species) in addition to the primary pathogens which are typically indolent and are difficult to clear. These long-term infections are more frequently associated with mortality than the acute pyogenic infections, causing rupture into large pulmonary vessels with life-threatening hemoptysis or fungal dissemination to the brain (9).Mucocutaneous candidiasis is common in HIES, manifesting commonly as oral thrush, vaginal candidiasis, or onychomycosis (6). Systemic Candida infections are very rare and most likely are nosocomial in origin (e.g. an indwelling catheter infection). Disseminated Cryptococcus and Histoplasma infections also occur, although less frequently than candidiasis. Skeletal abnormalities include scoliosis, osteopenia, minimal trauma fractures, hyperextensibility, and degenerative joint disease. Scoliosis occurs in about 75% of patients, typically develop during adolescence (6). Hyperextensibility of both the large and small joints is frequent. Minimal trauma fractures and decreased bone

From the Department of Pediatrics, Advanced Pediatric Center, PGIMER, Chandigarh, India, 160012.
Correspondence to : Dr Suresh Kumar Department of Pediatrics, Advanced Pediatric Centre, PGIMER, Chandigarh, India

mineral density also are common but may occur independently of one another (6). Fractures tend to be of the long bones, ribs, and pelvic bones. The characteristic facial appearance include coarse facies, a prominent forehead, deep-set widely spaced eyes, a broad nasal bridge, a wide fleshy nasal tip, mild prognathism, facial asymmetry, and hemihypertrophy are common. The facial skin has a rough appearance with exaggerated pore size (6, 10). This characteristic appearance typically develops during childhood and adolescence. Retention of primary dentition is common past the age of normal primary dental exfoliation. This manifestation seems to be result of failure of the primary teeth to exfoliate and not due to failure of development or eruption of the secondary teeth (6). An increased risk of malignancy is associated with hyper-IgE syndrome (11, 12). Both Hodgkin's and non-Hodgkin's lymphoma (mostly B-cell origin) have been described. Other cancers described include leukemia and cancers of the vulva, liver, and lung (12).

Laboratory Findings: The two most consistent laboratory findings of Job's syndrome are elevated serum IgE level and eosinophilia (5). The serum IgE typically peaks above 2000 IU/mL and usually is elevated even at the time of birth. It is important to keep in mind the natural change in IgE levels over time: they usually are undetectable in cord blood and rise to the adult range slowly over the years. However, IgE levels may decrease with age and fall to normal range (1-90 IU/ml) in about 20% of the cases and it do not correlate with the disease severity (5). Therefore, when other features of HIES are present, normal IgE levels does not rule out the presence of HIES in older children and adults (5, 6). Eosinophilia almost always is present in these patients, but is not correlated with the serum IgE level. Total white blood cell counts usually are normal but may not increase appropriately during acute infection. Neutropenia has been reported but is uncommon. Serum IgG, IgA, and IgM typically are normal, although some individuals can have deficiencies in one or more of these immunoglobulins (5).

Genetics and Pathogenesis: There are two forms of HIES: a dominant form caused by mutations in STAT3, and a recessive form, for which a genetic cause is unclear (13). These two different types have distinct presentations, courses, and outcomes and share very little in terms of pathogenesis other than the elevation of IgE (5). The dominant form is characterized by non-immunologic features including skeletal, connective tissue, and pulmonary abnormalities in addition to recurrent infections and eczema. In contrast, the recessive form lacks the somatic features and has severe recurrent fungal and viral infections, as well as central nervous system manifestations, such as ischemic infarction, subarachnoid hemorrhage, and hemiplegia (5, 14). STAT3 mutations are responsible for majority of the cases of autosomal dominant HIES (5, 15). STAT3 is a major signal transduction protein involved in diverse pathways including wound healing, angiogenesis, cancer and is a key regulator of many immunologic pathways (5). Microarray analysis of leukocytes from STAT3-deficient humans showed significant up-regulation of pro-inflammatory genes at rest or after stimulation (13). Infections of the lung and skin may predominate because STAT3 is a key regulator of beta-defensins of the skin and lung through IL- 22 signaling (16).

Some of the earliest studies implicated abnormal neutrophil chemotaxis and an altered immunoglobulin profile as the primary immune defect in HIES (4, 17). As the name indicates, HIES is characterized by profound elevations of serum IgE levels. Specifically, IgE antibodies to S aureus have been found to be uniformly elevated in HIES (18). The high IgE may result from defects in STAT3-mediated IL-21 receptor signaling, as it was noted that heterozygous IL-21 receptor knockout mice have increased IgE (19).

Cytokine profile studies demonstrated that HIES patients have decreased levels of IFN-gama, a major activator of neutrophils (20). IL-12 is an enhancer of IFN-gama production and also suppresses IgE production. In the presence of S aureus, mononuclear cells of HIES patients release markedly less IFN-gama and even the addition of recombinant IL-12 cannot augment (21). So, the pivotal defect in these patients' immune system is a deficiency of IFN-gama that is mediated in part by a defective upstream IL-12 signaling error. Transforming growth factor beta (TGF-b) is another important cytokine that has been proposed to play a role in HIES. Vargas *et al* (22) found HIES patients have reduced L-selectin expression on quiescent and activated granulocytes and lymphocytes as well as increased oxygen radical production by stimulated neutrophils. This provides another mechanistic explanation of the impaired neutrophil chemotaxis and the marked tissue damage seen in HIES. They also found increased production of granulocyte-monocyte colony-stimulating factor by resting and activated mononuclear cells; this may explain the eosinophilia that often accompanies this disease. Additional alterations in HIES include a deficiency of neutrophil receptors for C3b, an important chemotactic factor and mediator of neutrophil phagocytosis (23).

HIES is not exclusively a disorder of too little inflammation and resulting inability to control invading micro-organisms. It is also a disorder of too much inflammation. The increased inflammation is evident in the lung, where tissue breakdown leading to formation of pneumatoceles may be a consequence of exuberant inflammation. In contrast, there are aspects of STAT3

deficiency that are more consistent with too little inflammation, such as the frequent "cold" abscesses and the relative paucity of symptoms compared with the extent of disease (5).In another recent study defective IL-10 signaling in hyper-IgE syndrome results in impaired generation of tolerogenic dendritic cells and induced regulatory T cells, which may contribute to inflammatory changes in HIES (24) .

Treatment: No definitive therapy is available for the treatment of hyper-IgE syndrome. The mainstay of treatment is the control of bacterial infections. Early incision and drainage followed by intravenous administration of antibiotics are used for cutaneous infections (5). Antibiotics are usually required for longer duration because disease in these patients respond more slowly. Intravenous antibiotic treatment for 2 weeks is typical. Ideally, treatment of pneumonia is guided by the etiologic agent. Bronchoscopy is helpful to recover the pathogen and to assist with clearance of mucus and pus, because these patients often do not have an adequate cough response (5). Because these patients often feel well and have minimal fever despite significant infection, it is good to have a low threshold for investigating slight changes, such as new cough, chest discomfort, or fatigue, even in the absence of fever (5). Antimicrobial prophylaxis to prevent S aureus skin and lung infection is among the most widely used treatments options (14). However, there have been no case-control studies to assess whether intermittent or long-term antibiotics affect outcome. In developing countries, long-term oral penicillin has been used safely and with dramatic improvement (25). Life-long penicillinase-resistant penicillins with intermittent culture-directed antibiotics and antifungals as required reported to be safe and effective (26). TMP-SMX is a safe and effective alternative to penicillin; importantly, it has anti-MRSA properties (27). Unfortunately, as more cases of multidrug resistant bacteria evolve, treatment options will become more complex.Intravenous immunoglobulin may decrease the number of infections in these patients (28). High-dose IVIg possesses both immune-regulatory and anti-inflammatory properties. It has been postulated that HIES patients could benefit from both effects. High-dose IVIg shown to lead to marked clinical improvement in patients with HIES (28). There are also isolated reports of monthly and moderate-dose IVIg being used as an alternative to high-dose IVIg (29). There are no case-control studies because of the rarity of the disease, but IVIg may have a role in patients whose disease is refractory to standard therapies, but cost is the major limiting factor in our setting.Levamisole was found to be inferior to placebo in a blinded, randomized study (30). IFN-gama has been used with mixed results (31). Case reports and small case series have shown successful treatment of HIES using disodium cromoglycate (32), isotretinoin (33), double-filtration plasmapheresis (34), and ascorbic acid (35). There are several reports on the use of cyclosporine for HIES (14). Low-dose cyclosporine (3-5 mg/kg) is not considered a first-line therapy, but as short-term therapy it has a role in patients with difficult to manage or refractory disease (14). Omalizumab (the monoclonal antibody against IgE) has not yet been studied, and it is unclear whether there may be any benefit (5). Recently, four bone marrow transplantations in HIES patients have been reported with short term improvement in HIES-related symptoms in the post-transplantation period only (36, 37, 38).

HIES is a complex multisystem disease requires a sophisticated multidisciplinary approach including close management of infectious disease, pulmonologists for diagnostic and therapeutic bronchoscopy and pulmonary toilet, orthopedists for scoliosis, fractures, and degenerative joints; dentists to address the retained primary teeth (5). Appropriate thoracic surgery is indicated for super-infected pneumatoceles or those persisting for more than 6 months. Patients with HIES require constant vigilance with regard to infections and chronic lung disease. With early diagnosis and treatment of infections, most patients with HIES lead full lives, becoming productive adults.

Conclusion: HIES is a multisystem immunodeficiency that has important relevance to the physicians. Although rare, HIES should be kept as differential diagnosis among other possibilities in a patient with recurrent pyogenic infections (especially Staphylococcal). Elevated IgE levels and eosinophilia are hallmark of this condition and molecular techniques help in confirmation of diagnosis. Prompt and aggressive treatment of infections and antibiotic prophylaxis lead to improved survival of these patients. As more is understood about the immune defects in these patients, more therapeutic options with increased efficacy will become available. Until then, it is up to the observant clinician to detect problems early before life-threatening complications develop.

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