Hyper IgE Syndrome

Chapter 17

Hyper IgE Syndrome (HIES) is a rare primary immunodeficiency disease characterized by eczema, recurrent staphylococcal skin abscesses, recurrent lung infections, eosinophilia (a high number of eosinophils in the blood) and high serum levels of IgE. Most cases of HIES are sporadic, but some familial cases of HIES have been reported, with either an autosomal dominant (AD) or autosomal recessive (AR) mode of inheritance.

Definition of Hyper IgE Syndrome

HIES is a rare primary immunodeficiency characterized by recurrent eczema, skin abscesses, lung infections, eosinophilia and high serum levels of IgE. Two form of HIES have been described, including an autosomal dominant (AD, or type 1) and an autosomal recessive (AR, or type 2) form. These two forms share overlapping clinical and laboratory features including eczema, recurrent infections, skin abscesses, high IgE level and increased eosinophil number. However, they also exhibit distinct clinical manifestations, courses and outcomes.

History of Hyper IgE Syndrome

HIES was described first as "Job syndrome" by Davis and colleagues in 1966, in two girls with many episodes of pneumonia, eczema-like rashes and recurrent skin boils remarkable for their lack of surrounding warmth, redness or tenderness (so-called "cold abscesses"). In 1972, the syndrome was refined and clarified by Buckley and colleagues who noted similar infectious problems in two boys who also had distinctive facial appearance and extremely elevated IgE levels. Following this report, elevated IgE was found in the two girls from the initial report, showing that Job syndrome and Buckley syndrome represented the same condition. In 2007, a heterozygous mutation in the gene encoding the transcription factor STAT3 was found to underlie most cases of AD (type 1)-HIES. In 2009 mutations and deletions in the DOCK8 gene were found to underlie the majority of cases with AR (type 2)-HIES.

Clinical Presentation of Hyper IgE Syndrome

AD-HIES, associated with heterozygous mutations in the transcription factor STAT3, is the more common form of HIES in the U.S. It commonly presents with respiratory infections and skin findings including newborn rash, eczema, recurrent skin abscesses and ear, sinus and lung infections resulting in formation of cavitary lesions in the lungs (pneumatoceles). Other frequent findings of STAT3 deficiency include mucocutaneous candidiasis (candida fungus on mucous membranes and/or skin), manifesting typically as thrush, vaginal candidiasis or candida nail infection (onychomycosis). Additional findings include connective tissue and skeletal abnormalities such as a typical facial appearance characteristic of patients with this syndrome, hyper-

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extensibility of their joints, retained primary teeth and recurrent bone fractures secondary to even minimal trauma.

AR-HIES with DOCK8 deficiency is particularly common in areas of the world with high consanguinity rates (intermarriage among close relatives), where its occurrence may exceed that of AD-HIES. AR-HIES similarly presents with eczema, skin abscesses, recurrent respiratory infections, candidiasis and other fungal infections. However, patients with AR-HIES are distinguished from those with AD-HIES by the occurrence of severe, recurrent viral infections caused by pathogens such as *Herpes simplex*, *Herpes zoster* and *Molluscum contagiosum*. They are also susceptible to allergic and autoimmune manifestations, including food allergy, hemolytic anemia (due to red blood cell destruction by antibodies) and vasculitis (inflammation within blood vessels). Patients with AR-HIES also have a high frequency of neurologic complications, including encephalitis (brain inflammation) and vascular brain lesions. The mechanisms of those complications may include viral infections of the central nervous system and autoimmunity. Finally, unlike their AD-HIES counterparts, those with AR-HIES do not manifest connective tissue or skeletal abnormalities.

Skin Affected by Hyper IgE Syndrome

A newborn rash or eczema is frequently the first manifestation of AD-HIES. Pustular and eczema-like rashes usually begin within the first month of life, first affecting the face and scalp. Skin abscesses are a classic finding in this disorder, caused by a particular susceptibility to infections with *Staphylococcus aureus*. The degree of inflammatory symptoms, such as tenderness and warmth, often is quite variable. The term “cold abscesses” is applied to those lesions that lack external signs of inflammation despite the presence of pus. The occurrence and severity of these abscesses is substantiallydecreased with prophylactic therapy with antibiotics against *Staphylococcus aureus*.

DOCK8 deficient patients also have severe eczema-like rashes, starting early in life, although not necessarily in the newborn period. They also suffer from recurrent skin abscesses, usually associated with *Staphylococcus aureus* infection. Severe recurrent or persistent skin viral infections with *Herpes simplex*, *Herpes zoster* and *Molluscum contagiosum* can also be features of DOCK8 deficiency. These infections can be persistent and are frequently difficult to treat.

Skin and nail infections with candida are common to both AD- and AR-HIES.

Lungs Affected by Hyper IgE Syndrome

Recurrent bacterial pneumonias are often encountered in patients with AD-HIES. Pneumonias typically start in childhood, and the most frequent bacterial isolates are *Staphylococcus aureus*, *Streptococcus pneumoniae*, and *Haemophilus influenzae*. Fungal lung infections, especially with *Aspergillus fumigatus*, are also common. Similar to the occurrence of cold skin abscesses, these pneumonias may present with fewer symptoms than

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would be expected in a person with intact immunity. This relative lack of symptoms and subsequent delay in clinical presentation may contribute to advanced disease and significant tissue damage before identification and initiation of appropriate therapy. However, the severity of lung tissue damage and the subsequent emergence of chronic lung disease are higher in patients with AD-HIES as compared to those with AR-HIES. Infection-induced tissue destruction in individuals with AD-HIES may give rise to pneumatocele formation (large cavities in the lung), which is a distinguishing feature of AD-HIES with STAT3 mutations.

Recurrent lung infections with both gram-positive and negative bacteria are common in patients with AR-HIES with DOCK8 deficiency, and they may also lead to chronic lung disease with damage to the airways (bronchiectasis) and lung tissues.

Skeletal and Connective Tissues Affected by Hyper IgE Syndrome

Involvement of both the connective and skeletal tissues is an important feature of AD-HIES with STAT3 mutations. An asymmetrical facial appearance with prominent forehead and chin, deep-set eyes, broad nose, thickened facial skin and a high arched palate are typical of this disease. These features evolve during childhood and become more established by adolescence. Patients with AD-HIES exhibit hyperextensibility of the joints. They frequently suffer bone fractures from seemingly insignificant trauma, and bone density may be reduced. Scoliosis is common and typically emerges during adolescence or later in life. Fused skull bones (craniosynostosis) and extra or abnormally formed ribs or vertebrae are also found more often in patients with AD-HIES than in the general population. None of these skeletal abnormalities are seen in DOCK8 deficient patients.

Teeth Affected by Hyper IgE Syndrome

Abnormalities affecting dentition is another common feature of AD-HIES with STAT3 mutations. Retention of primary (or baby) teeth even after the permanent teeth have erupted is a consistent finding. Reduced resorption of primary tooth roots leads to failure to shed primary teeth, which in turn prevents the appropriate eruption of permanent teeth. This abnormality is revealed on panoramic x-ray views as double rows of retained primary teeth overlaying the permanent ones. Surgical extraction of the retained primary teeth is necessary for healthy dentition in this disorder. Children who have had their retained primary teeth extracted have had normal eruption of their permanent teeth. In contrast to AD-HIES patients, those with AR-HIES due to DOCK8 deficiency patients do not manifest abnormalities in their dentition.

Other Clinical Findings of Hyper IgE Syndrome

Deep tissue abscesses are commonly encountered in patients with AD-HIES, most frequently caused by staphylococcal infections.

Both AD- and AR-HIES patients are at increased risk for malignancies, especially lymphomas. Other cancers described in STAT3 deficiency include leukemia and cancers of the vulva, liver and lung. Patients with DOCK8 deficiency are susceptible to papilloma virus-induced squamous cell carcinoma and to lymphomas. Autoimmune diseases have also been associated with both types of HIES, but it is most often seen in DOCK8 deficiency.

DOCK8 deficient patients have more symptomatic neurologic disease than those who have STAT3 deficiency. Neurologic manifestations may range from limited involvement such as in facial paralysis to more severe manifestations such as hemiplegia (one side of the body paralyzed) and encephalitis. The causes of the neurologic complications are not clear but fungal, viral agents and vasculitis may be responsible. Central nervous system involvement is responsible for a significant number of fatalities in this disorder.

Laboratory Findings of Hyper IgE Syndrome

Both STAT3 and DOCK8 deficiency impact the immune system and lead to immunological abnormalities. Increased serum IgE concentrations and eosinophil numbers are present in both forms of the disease. Total white blood cell counts are typically high in patients with AD-HIES and STAT3 mutations but may not increase appropriately during acute infection. Neutropenia (low blood numbers of white blood cells called neutrophils) has been reported but is uncommon. Serum IgG, IgA, and IgM typically are normal, although some individuals with AD-HIES have deficiencies in one or more of these immunoglobulin subtypes.

Patients with AR-HIES and DOCK8 deficiency typically exhibit very high eosinophil numbers in the peripheral blood in the face of severely low numbers of T-cells. They manifest low serum IgM levels and fail to sustain specific antibody responses upon vaccination.

Diagnosis of Hyper IgE Syndrome

The diagnosis of HIES can be made based on a combination of clinical and laboratory findings for both types of HIES. An elevated level of serum IgE is a virtually universal finding in these patients. However, it is not sufficient on its own to make the diagnosis as patients with other conditions such as severe eczema may exhibit IgE levels in the HIES range. Certain features, such as pneumatocele formation in the context of other findings of HIES, are strongly supportive of the diagnosis of type 1 HIES.

An HIES scoring system has been previously developed at the National Institutes of Health (NIH) that can help with the diagnosis of type 1 HIES. In this system, patients are evaluated for the existence and severity of the following clinical and laboratory features: newborn rash, eczema, skin abscesses, recurrent upper

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respiratory infections, pneumonia, lung changes (cavities), candidiasis, other severe infections, fatal infections, characteristic facial appearance, increased nasal width, high palate, retained primary dentition, joint hyperextensibility, fractures with minor trauma, scoliosis, midline anatomic abnormalities, lymphoma, high serum IgE level, and eosinophilia. The score correlates with the severity of the disease (scores of 0 to 15 unaffected, 16 to 39 possibly affected, 40 to 59 probably affected, and 60 or more definitively affected). The scoring system is a particularly useful tool for the diagnosis of AD-HIES but less so for AR-HIES. Definitive diagnosis can be established with genetic analysis of the STAT3 and/or DOCK8 genes.

Decreased serum IgM concentrations and peripheral blood T-cell counts are important laboratory findings of DOCK8 deficiency. Absent DOCK8 protein in blood cells is encountered in more than 95% of patients with DOCK8 deficiency and as such can be useful in confirming the diagnosis in suspected patients but not in excluding it if DOCK8 protein expression is normal. The diagnosis in the latter individuals would have to be established by DNA sequencing methods.

Inheritance of Hyper IgE Syndrome

Autosomal dominant HIES (with STAT3 mutations) - AD-HIES occurs in both males and females of all ethnic groups with apparently equal frequency. In families with more than one affected person, disease transmission is consistent with autosomal dominant inheritance. In most patients, the disease occurs sporadically. STAT3 mutations cause most, if not all, cases of autosomal dominant HIES. Mutational analysis of the STAT3 gene would enable definitive diagnosis and genetic counseling.

Autosomal recessive HIES (DOCK8 deficiency) - Most, but not all, of the patients with AR-HIES are from consanguineous families. Deletions and mutations in the DOCK8 gene on chromosome 9 account for most of the cases, although a few patients with AR-HIES have normal DOCK8 gene. Mutational analysis of the DOCK8 gene is important for diagnosis and genetic counseling.

Treatment of Hyper IgE Syndrome

Therapy of HIES remains largely supportive. Antibiotic prophylaxis with trimethoprim-sulfomethoxasole is a frequently used as prophylaxis against recurrent respiratory infections. Treatment for these infections, when they occur, should be started promptly. Given that patients with HIES suffer from significant eczema and skin infections and that the compromised skin offers a portal of entry to pathogens to cause deep seated infections, skin care and prompt treatment of skin infections is an important component of HIES management. When the eczema is severe, topical moisturizing creams and limited use of topical steroids can help achieve healing. Antiseptic treatments of the skin greatly reduce the bacterial burden in the skin

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without leading to emergence of antibiotic resistant bacteria.

Skin abscesses may require incision and drainage but can largely be prevented with prophylactic oral antibiotics. The role of prophylactic antibiotics has not been rigorously investigated, but there is general consensus in favor of use of antibiotics against *Staphylococcus aureus* in both HIES groups. Lung and other deep tissue abscesses may require drainage or resection. Following the resolution of acute pneumonias, pulmonary cysts or cavities form places for colonization with *Pseudomonas aeruginosa*, *Aspergillus* and other fungal species. These super infections can be a difficult aspect of HIES. Potential management strategies include continuous treatment with antifungal drugs and/or, aerosolized antibiotics.

Candidiasis of the fingernails, mouth or vagina in HIES rarely spreads to deeper tissues and responds well to oral antifungals. Although the over-use of antibiotics and antifungals is discouraged in general with "normal" patients due to concerns about selection for resistant organisms, the under-use of antibiotics in HIES patients leaves this group at risk for infections that are debilitating and dangerous.

A remarkable feature of HIES is how well the patients may feel (and appear) when they have an infection. For example, even with evidence of a significant infection on physical examination and x-ray corroboration of pneumonia, a HIES patient may deny feeling sick and may not see the need for invasive diagnostic testing or prolonged therapy. Moreover, doctors unfamiliar with HIES are hesitant to believe that patients who do not appear very ill and appear about the same as usual can really be quite ill.

Poor antibody responses to vaccination in both AD- and AR-HIES lend support to the use of immunoglobulin replacement therapy in those patients. The role of interferon-gamma, granulocyte-colony stimulating factor or other immune modulators in HIES is, however, unproven. Bone marrow transplantation is curative for AR-HIES with DOCK8 deficiency and is recommended given the severity of the disease and the life-long risk of developing fatal complications, including infections, autoimmunity and malignancies. In contrast, AD-HIES patients generally do well with intensive therapy and supportive care, and bone marrow transplantation is not recommended for those individuals.

Expectations for Patients with Hyper IgE Syndrome

Patients with both types of HIES require constant vigilance with regard to infections and development of chronic lung disease. With early diagnosis and treatment of infections, most patients with AD-HIES do fairly well. The more severe nature of AR-HIES should prompt early consideration of bone marrow transplantation, which is curative. Genetic counseling is advised for families with HIES children and is especially important for those families where consanguinity is involved.