



CHAPTER

# 12

## Hyper IgE Syndrome

*Hyper-IgE syndrome (HIES) is a complex primary immunodeficiency disorder characterized by a spectrum of abnormalities related to the immune system, bones, connective tissue and teeth.*

## Definition of Hyper IgE Syndrome

Hyper-IgE syndrome (HIES) is a complex primary immunodeficiency disorder characterized by a spectrum of abnormalities related to the immune system, bones, connective tissue and teeth. The cause of HIES is not known. The disease is also known as Job Syndrome because skin boils, a

hallmark of the syndrome, are reminiscent of the biblical character Job, who was smitten by Satan “with sore boils from the sole of his foot unto his crown.” HIES was initially defined as a triad of clinical problems involving skin boils, severe episodes of pneumonia and very high serum IgE levels.

## History of Hyper IgE Syndrome

Davis, Schaller and Wedgewood (1966) first reported two red-haired, fair-skinned girls with many episodes of pneumonia, eczema-like rashes and recurrent skin boils remarkable for their lack of surrounding warmth, redness, or tenderness. The syndrome was further defined and clarified by Buckley et al. (1972), who noted

similar infectious problems in two boys who also had distinctive facial appearances 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.

## Clinical Presentation of Hyper IgE Syndrome

Within the past decade, a large and comprehensive study of the clinical features of HIES revealed a more complete clinical picture of HIES involving the immune system, the skeleton and dentition (teeth). This study also showed that the severity of the different clinical findings varied with age and from individual to individual, even within the same family.

Fortunately, following institution of prophylactic anti-staphylococcal antibiotics, abscesses, or boils, occur less commonly and respiratory infections decrease.

A clinical hallmark of HIES is recurrent pneumonia. By early adulthood, more than 50% of patients have had three or more X-ray proven pneumonias. For reasons that are not understood, pneumonias in HIES cause destruction of lung tissue, resulting in cavities in the lung (pneumatocoles) or scarring and thickening of the lower air passages (bronchiectasis).

Another chronic infectious problem in HIES are chronic and recurrent candida fungal infections of mucus membranes (such as the mouth and throat) and the nail beds.

### Immune System

There are a number of clinical features of HIES that relate to underlying abnormalities in the immune system. These include eczema, abscesses, pneumonia, infections with a fungus called candida, IgE values in the blood serum that are extremely high and high numbers of a type of white blood cell known as eosinophils. In the first month of life, rashes are described in three quarters of HIES cases. Most often, the rashes occur in the creases behind the ears, the back, buttocks and scalp.

*Staphylococcus aureus* is the most common cause of the abscesses or boils. Unlike boils in people with normal immunity, those in HIES patients are often not “hot”, red, or painful. Consequently, they may not be recognized and treated promptly. Upper respiratory infections—sinusitis, otitis media, otitis externa and mastoiditis—are also frequent.

### Skeleton and Connective Tissue

Skeletal abnormalities and a characteristic facial appearance in HIES were recognized in the original reports, but the fair skin and red hair in the original cases turned out to be just a coincidence. Patients often resemble each other, having a prominent forehead and chin, broad nose and thickened facial skin; these features evolve during adolescence. Lax joints are also typical.

## Clinical Presentation of Hyper IgE Syndrome continued

Bone fractures occur with seemingly insignificant trauma, and bone density may be reduced. Curvature of the spine (scoliosis) is common and needs to be monitored as children with HIES grow so it can be treated if necessary. Fused skull bones (craniosynostosis), and extra or abnormally formed ribs or vertebrae are also found more often than in the general population.

### Teeth

Retention of primary (or baby) teeth in HIES patients appears to be quite a consistent finding. Reduced resorption of primary tooth roots

leads to failure to shed primary teeth, which in turn prevents the appropriate eruption of the permanent teeth. After an X-ray to make sure the permanent teeth are present, children who have had retained primary teeth extracted have had normal eruption of their permanent teeth.

### Other Clinical Findings

Patients with HIES are also at increased risk for malignancies, especially lymphoma. Systemic lupus erythematosus and other autoimmune diseases have also been associated with HIES.

## Diagnosis of Hyper IgE Syndrome

In the absence of a known gene or definitive test for HIES, the diagnosis must be made on a combination of clinical and laboratory findings. An elevated level of serum IgE alone is not sufficient to make the diagnosis since patients with certain conditions such as severe allergic skin rashes occasionally have IgE levels in the HIES range without having HIES. An IgE of over 2,000 IU/ml (normal adult value is less than 100 IU/ml) has been used as a cutoff level for HIES when other features including boils and pneumonia are present. In infants, in whom normal IgE levels are very low, an IgE of 10 times the age-appropriate level is a reasonable guide for HIES. It should be noted that

in some adults with HIES, IgE may decrease and even become normal. The presence of the other clinical features involving the skeleton and teeth can be very useful in supporting the clinical diagnosis.

Other than IgE level, laboratory tests are not helpful in diagnosing HIES, and even high IgE levels are not specific, since these can be found in other conditions. Many studies have focused on the immune aspects of HIES, such as the migration of neutrophils toward damaged or infected tissue. However, no specific immune defect has been found consistently in all patients with HIES.

## Inheritance of Hyper IgE Syndrome

### Autosomal dominant HIES

HIES is very rare, with only around 200 published cases. It occurs in males and females of all ethnic groups with apparently equal frequency. Most families with more than one affected person are consistent with autosomal dominant inheritance. In this form of inheritance, the presence of an abnormal gene on only one of the patient's two autosomes (non-sex chromosomes) causes the disease (see chapter titled *Inheritance*). The abnormal gene on one chromosome "dominates" the normal gene on the other chromosome and the disease occurs.

HIES in some, but not all of these families, have been linked to markers on chromosome 4, a region suggested by an abnormal chromosome in a single patient with a sporadic HIES.

### Autosomal recessive HIES

A small number of patients from consanguineous families with severe pneumonia, abscesses, eczema, high IgE and eosinophilia appear to have an autosomal recessive form of HIES. In addition to their bacterial infections, these patients

## Inheritance of Hyper IgE Syndrome continued

also have viral infections including Molluscum contagiosum, Herpes simplex and recurrent Varicella zoster. No lung cysts occurred in patients

with this form of HIES, although the incidence of pneumonia was the same, and many died in childhood with neurological complications.

## Treatment of Hyper IgE Syndrome

Skin care and prompt treatment of infections are the most important elements of HIES management. Skin colonization precedes infection. Topical antibacterials and oral antibiotic treatment are often effective preventive measures.

When eczema is severe, topical moisturizing creams and limited topical steroids can help achieve healing. Antiseptic treatments of the skin greatly reduce the bacterial burden in the skin without leading to emergence of antibiotic resistant bacteria.

Skin abscesses may require incision and drainage, but can largely be prevented with continuous 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 HIES.

Candidiasis of the fingernails, mouth or vagina in HIES rarely disseminates and responds to oral triazole antifungals, which have been of great benefit to patients with HIES. 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 in HIES leaves this group at risk for infections that are debilitating and dangerous.

A remarkable feature of HIES is how well the patient may feel (and appear) when they have an infection. For example, even with evidence of a significant infection on physical examination and X-ray evidence of pneumonia, an 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, are really quite ill.

Finding the organisms causing an infection cannot be overemphasized. Lung abscesses may require drainage or resection, but surgery is difficult in HIES because patients' remaining lung tissue often fails to expand to fill the chest cavity. Prolonged chest tube drainage and intensive IV antibiotic treatment may be needed. Therefore, pulmonary surgery in HIES should not be undertaken lightly, and ideally it should be performed at a medical center with experience with the disease.

Following the resolution of acute pneumonias, pulmonary cysts or cavities form what serve as a focus 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 aerosolised antibiotics.

Although individual case reports have suggested benefit from interferon, immunoglobulin replacement therapy, G-CSF or other treatments, a general role for immune reconstitution and/or immune modulators in HIES is unproven. It has been previously suggested that since immunodeficiency is a central part of HIES, bone marrow transplantation might be curative. However, in the two instances in which it has been performed, the results have not been encouraging enough to recommend bone marrow transplantation for most patients.

## Expectations for Hyper IgE Syndrome Patients

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.