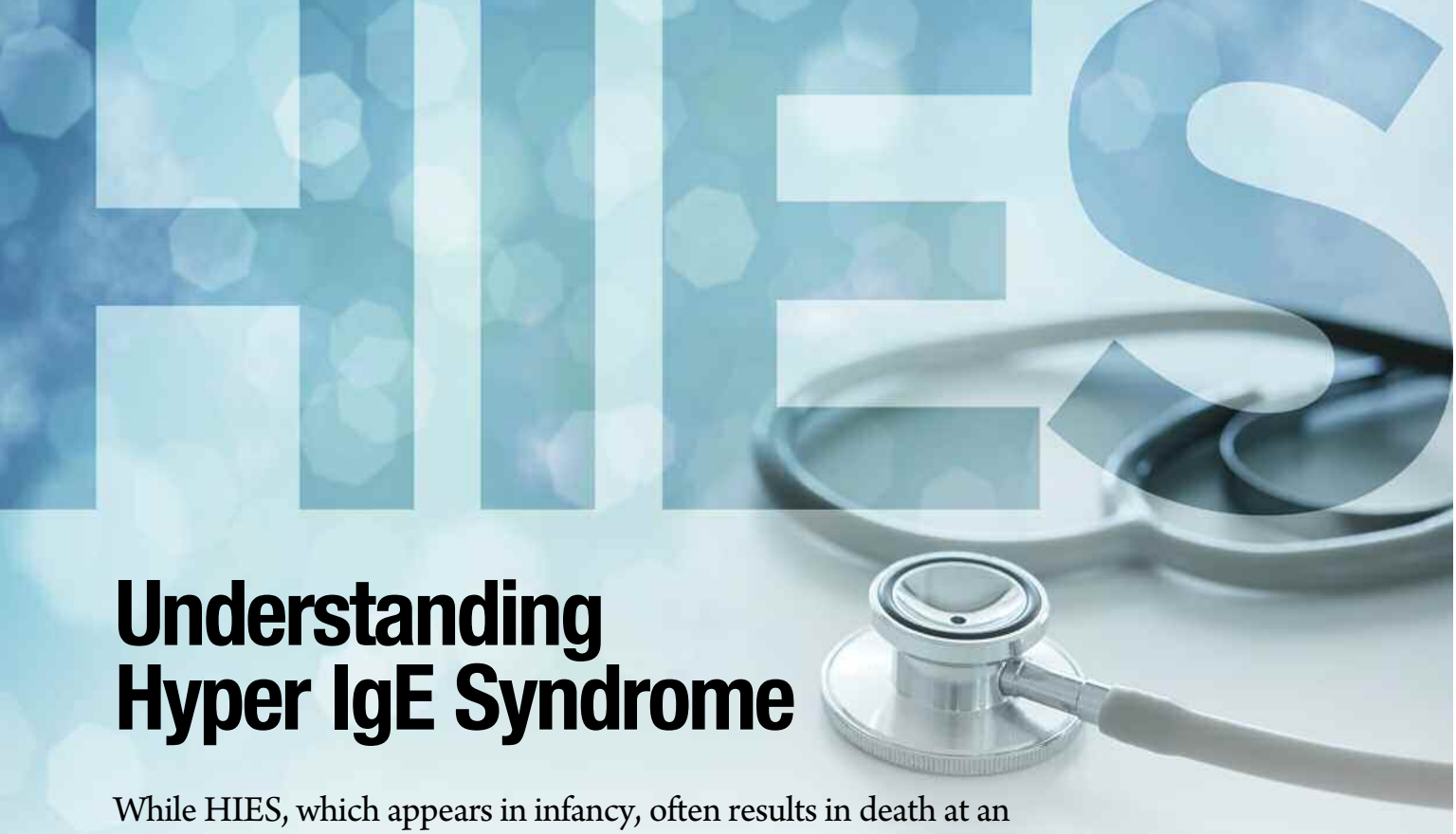

Understanding Hyper IgE Syndrome

While HIES, which appears in infancy, often results in death at an early age, more has been discovered about it over the years, and experimental treatments for this disease show promise.

By Ronale Tucker Rhodes, MS

HYPER IGE SYNDROME (HIES) was first called Job's syndrome in 1966, named after the biblical character Job whose entire body was covered in boils and sores. Later in 1972, when it was recognized those with the disease had extremely high serum IgE levels, it was renamed HIES. Until 2007, the syndrome remained the last of the major immune deficiencies without a known genetic etiology or a comprehensive understanding of the associated immune dysfunction.[1]

HIES is listed as a rare disease by the National Institutes of Health, meaning it affects fewer than 200,000 people in the U.S.[2] More than 200 cases of HIES have been described in the medical literature, affecting males and females in equal numbers and all ethnic groups. However, it often goes unrecognized or misdiagnosed, making its true frequency in the general population difficult to determine. Although HIES is present during infancy, diagnosis may not be made until adolescence and, in some cases, adulthood.[3]

What Is HIES?

HIES is a very rare primary immunodeficiency disorder characterized by the triad of highly elevated serum IgE, dermatitis and recurrent skin and lung infections. There are two forms of HIES: autosomal dominant (AD) (the more common form), some of which are caused by mutations in the STAT3 gene, and autosomal recessive (AR), with the majority of cases caused by mutations and deletions of the DOCK8 gene and the remaining for which a genetic cause is unclear.[1]

For years, researchers considered AD-HIES and AR-HIES different expressions of the same disorder; however, it is now known they are similar, yet distinct disorders.[4] In fact, each presents differently in courses and outcomes, and they share little in terms of pathogenesis other than elevated IgE serum. AD-HIES is characterized by nonimmunologic features, including skeletal, connective tissue and pulmonary abnormalities, as well as recurrent infections and eczema. Whereas, AR-HIES lacks the somatic features and has marked viral infections and neurologic complications.[1]

Causes of HIES?

Most cases of AD-HIES and AR-HIES are sporadic, but some genetic cases of HIES have been reported.[5]

As mentioned, some AD-HIES are caused by mutations in the STAT3 gene responsible for producing one of the signal transducer and activator of transcription (STAT) proteins involved in alerting the immune system to respond to

pathogens. While the mutations result in a normal amount of STAT3 protein, the function of the protein is affected making it unable to properly defend against pathogens. Only 60 percent of AD-HIES patients have mutations of the STAT3 protein, so it is believed other gene mutations may be associated with the disease. In dominant genetic disorders, only a single copy of an abnormal gene is necessary to cause the disease, and the gene can be inherited from either parent or it can mutate in the affected individual. The risk of passing the abnormal gene from an affected parent to an offspring is 50 percent for each pregnancy in both males and females.[6]

The majority of cases of AR-HIES are caused by mutations and deletions of the DOCK8 gene,[5] which helps maintain the structure and integrity of T cells and NK cells that recognize and attack pathogens. However, recessive genetic disorders occur when an individual inherits the same abnormal gene for the same trait from each parent. If the individual receives one normal gene and one abnormal gene, the person will be a carrier for the disease but will not usually exhibit symptoms. The risk for two carrier parents to both pass the defective gene onto the child is 25 percent with each pregnancy. The risk for the child to become a carrier like the parents is 50 percent with each pregnancy. And, the chance a child will receive two normal genes from both carrier parents is 25 percent. These percentages are true for both males and females.[4]

Symptoms of HIES

Symptoms for both types of HIES usually begin during infancy.

Common symptoms of AD-HIES include respiratory infections, newborn rash, eczema, recurrent skin abscesses, and ear, sinus and lung infections. A newborn rash is typically the first manifestation, with pustular and eczema-like rashes on the face and scalp beginning within the first month of life. Skin abscesses are typically caused by a susceptibility to infections with Staphylococcus aureas. Recurrent bacterial pneumonias usually start in childhood caused by Staphylococcus aureus, Streptococcus pneumoniae and Haemophilus influenzae. Fungal lung infections, especially with Aspergillus fumigatus, are common. Because the pneumonias often present with fewer symptoms than occur in persons with intact immunity, they often advance and cause significant tissue damage before treatment is begun. And, the severity of lung tissue damage and the subsequent emergency of chronic lung disease are higher in patients with AD-HIES, which may lead to large cavities in the lung (pneumatocele formation), a distinguishing feature of AD-HIES.

Other important features of AD-HIES patients include involvement of both skeletal and connective tissues, as well as abnormalities with teeth. Patients have an asymmetrical facial appearance with prominent forehead and chin, deep-set eyes, broad nose, thickened facial skin and a high arched palate, all of which evolve during childhood and become more established by adolescence. They also have hyperextensibility of the joints causing bone fractures from insignificant trauma, and bone density may be reduced. Scoliosis is also common, typically emerging during adolescence or later in life. And, fused skull bones and extra or abnormally formed ribs or vertebrae occur more often in AD-HIES patients than in the general population. Teeth abnormalities caused by reduced resorption of primary tooth roots include retention of primary (baby) teeth even after the permanent teeth have erupted.

AR-HIES symptoms are similar to AD-HIES with eczema, skin abscesses, recurrent respiratory infections, candidiasis and other fungal infections. Skin infections, however, usually start early in life but not during the newborn period. Unlike AD-HIES, AR-HIES exhibits severe recurrent or persistent skin viral infections and recurrent respiratory infections are usually caused by pathogens such as herpes simplex, herpes zoster and Molluscum contagiosum, possibly leading to chronic lung disease with damage to the airways and lung tissues. AR-HIES patients 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). A high frequency of neurologic complications, including encephalitis and vascular brain lesions, is also common in AR-HIES patients, which may be caused by viral infections of the

Symptoms for both types of HIES usually begin during infancy.

central nervous system and autoimmunity. In addition, they may experience neurologic manifestations such as facial paralysis and hemiplegia (one side of the body paralyzed). And, unlike AD-HIES patients, AR-HIES patients do not experience connective tissue or skeletal abnormalities.

Diseases/Conditions Sharing Some Symptoms of HIES

Immunologic Characteristics (% Frequency)

- Newborn rash (81%)
- Boils (87%)
- Recurrent pneumonias (87%)
- Pneumatoceles (77%)
- Eczema (100%)
- Mucocutaneous candidiasis (83%)
- Peak Serum IgE ≥ 2,000 IU/mL (97%)
- Eosinophilia (93%)
- Increased incidence of lymphoma

Nonimmunologic Characteristics (% Frequency)

- Characteristic face (83%)
- Retained primary teeth (72%)
- Minimal trauma fractures (71%)
- Scoliosis >10 degrees (63%)
- Hyperextensibility (68%)
- Focal brain hyperintensities (70%)
- Chiari 1 malformations (18%)
- Craniosynostosis (unknown)
- Arterial aneurysms (unknown)

Source: Freeman, AF, and Holland, SM. The Hyper IgE Syndromes. *Immunology and Allergy Clinics of North America*, 2008 May; 28(2): 277–viii. Accessed at www.ncbi.nlm.nih.gov/pmc/articles/PMC2683262.

Both AD-HIES and AR-HIES patients are at increased risk for malignancies, especially lymphomas. They are also more prone to other cancers such as leukemia, cancers of the vulva, liver and lung, and papilloma virus-induced squamous cell carcinoma. Autoimmune diseases are also associated with both types of HIES but most often in AR-HIES.[5]

Diagnosing HIES

Diagnosing HIES is made via a combination of clinical and laboratory findings, as well as a detailed patient history. For both types, blood tests will show elevated levels of IgE in the blood and elevated levels of blood cells known as eosinophils. Importantly, diagnosis of HIES cannot be made solely on elevated IgE since patients with other conditions such as severe eczema also present with elevated IgE levels. Also for both, X-ray studies such as computed tomography can detect lung infections, and in AD-HIES, the development of pneumatoceles (thin-walled, air-filled cysts) within the lungs. Serum IgG, IgA and IgM are typically normal; however, some individuals will have deficiencies in one or more of these.[4,5,6]

There are some important differences between AD-HIES and AR-HIES. In AD-HIES, IgE levels may drop to normal or near normal in adulthood, so that does not rule out an HIES diagnosis. In AR-HIES patients, IgM concentrations and peripheral blood T-cell counts are decreased. And, the DOCK8 protein is absent in more than 95 percent of AR-HIES patients, which can be useful in diagnosing the disease in suspected patients, but it also can't rule out a diagnosis if the protein expression is normal.[5,6]

After HIES was determined to be a multisystem disorder, the National Institutes of Health devised a clinical scoring system mainly useful for diagnosing AD-HIES that combines immunologic/infectious manifestations and skeletal/connective tissue abnormalities. Immunologic/infectious features include elevation of serum concentration of IgE, eosinophilia, recurrent skin abscesses, pneumonias, destructive parenchymal lung lesions following infection, other serious or fatal infections, newborn rash, eczema, sinusitis or otitis, and mucocutaneous candidiasis. Nonimmune features include three or more retained primary teeth, scoliosis, bone fractures following minimal trauma, hyperextensibility of joints, characteristic facial appearance, increased nasal width, high palate, congenital skeletal anomalies and lymphoma. Scores are weighted to reflect the severity of a finding and to emphasize findings specific for AD-HIES. Individuals with a high likelihood of AD-HIES have a combination of both types of features. A score of greater than 40 is suggestive of AD-HIES, a score of 20 to 40 is considered indeterminate, and a score of less than 20 is considered unlikely.[7] It should be noted that this scoring system can be used for diagnosing AR-HIES. However, a definitive diagnosis for either needs to be made with genetic analysis of the STAT3 and/or DOCK8 genes.[5]

Treating and Managing HIES

Treatment of HIES is directed at specific symptoms and is mostly supportive, and patients often require the coordinated efforts of a team of specialists, including pediatricians, dermatologists, pneumologists, immunologists and other healthcare specialists.

Most important for HIES is preventing bacterial infections with prophylactic antibiotic therapies. For AD-HIES, common antibiotics include dicloxacillin or cotrimoxazole. For severe infections, recombinant interferon-gamma may be given subcutaneously as adjuvant therapy. Common antibiotics to treat AR-HIES include dicloxacillin, trimethoprim-sulfamethooxazole, cephalosporin, cotrimoxazole and penicillin.

AD-HIES patients may require antifungal drugs such as fluconazole or itraconazole to treat mucocutaneous candidiasis. For both types of HIES, skin lesions may require surgical drainage followed by antibiotics. And, in some cases, topical steroids and moisturizing creams can be used.

Drug treatment for chronic lung infections that may lead to the formation of air cavities in AD-HIES patients is difficult, so management often requires surgically opening the chest to remove or drain infected pneumatoceles. AD-HIES patients may also need to have primary teeth removed, be regularly monitored for scoliosis and be evaluated for fractures following minor trauma.[4,6]

Most experimental therapies for HIES are for individuals who are unresponsive to other forms of treatment. These include cyclosporin-A (CSA), immune globulin (IG) supplementation and interferons for AD-HIES and AR-HIES, as well as antibodies directed against IgE for AD-HIES and bone marrow transplant for AR-HIES.

A recent study examined the effect of a small dose of CSA on the clinical course, and the excessive production of IgE and other immunologic parameters and infection in patients with HIES. Three patients, two females and one male (two were brother and sister) between 10 months and 3 years, were suffering from severe eczema, recurrent sinopulmonary infection, lung and skin abscesses, chronically draining ear and failure to thrive since the first few weeks of their lives. Their serum IgE was more than 10 times upper normal for age. Serum IgE, cytokine IL-4, and IFN-γ and serum immunoglobulins were measured before and after treatment, and skin score of dermatitis and the number of infections were evaluated before and after treatment with CSA. Following treatment with 2 mg/kg to 4 mg/kg per day of

CSA in two divided doses, after standard treatment failed, there was a dramatic and sustained clinical improvement, especially dermatitis associated with marked drop in serum IgE, IL-4 and IFN-γ. And, there was no significant change in serum levels of IgG, IgA and IgM, indicating immune imbalance in HIES can be modulated by CSA that leads to a marked drop on IgE and IL-4 synthesis and clinical remission. However, the researchers did recommend the treatment be repeated in a larger number of patients.[8]

While there is limited data suggesting improvement in some patients with high-dose IG therapy, researchers do suggest some form of controlled trial is probably warranted.

Bone marrow transplantation is curative for AR-HIES patients with DOCK8 deficiency, and it is recommended due to the severity of the disease and the lifelong risk of developing fatal complications, including infections, autoimmunity and malignancies.[5]

To date, bone marrow transplantation has also been tried in four patients with AD-HIES. The first patient was a 46-year-old man with recurrent pneumonias who received a peripheral stem cell transplant for B cell lymphoma. However, he died six months following transplant with interstitial pneumonitis. Subsequently, a 7-year-old girl was transplanted to treat her severe HIES, and her skin lesions improved. However, she developed recurrence of symptoms after four years. Her serum IgE also returned to pretransplant levels. Interestingly, this occurred despite full donor engraftment in all lineages, suggesting the reasons for recurrence may have been somatic or not just confined to the haematopoietic system.

More recently, two unrelated male children with sporadic STAT3 mutations were transplanted for high-grade non-Hodgkin's lymphoma. At 10 years and 14 years following transplantation, both patients were reported to be well with continued resolution of both immunological and nonimmunological features. Of particular note, both osteoporosis and the characteristic facies improved following transplant. According to the researchers, "the successful transplant in these two individuals is significant because this potentially represents a means of preventing the long-term complications of chronic lung disease, vascular aneurysms and brain lesions."[9]

It is recommended AD-HIES and AR-HIES patients and their families receive genetic counseling.[4,6]

Diseases/Conditions Sharing Some Symptoms of HIES

- Atopic dermatitis
- IPEX syndrome
- Wiskott-Aldrich syndrome
- Cornel-Netherton syndrome
- DiGeorge syndrome
- Chronic granulomatous disease
- Common variable immunodeficiency
- Chronic mucocutaneous candidiasis
- Parasitic disease
- HIV-AIDS
- Hematological malignancies – Sézary's syndrome
- Aspergillosis
- ABPA
- Churg-Stauss syndrome
- Omenn syndrome

Source: Mazer, B. Hyper IgE Syndromes. Accessed at www.cancertherapyadvisor.com/home/decision-support-in-medicine/hematology/hyper-ige-syndromes.

HIES Prognosis

The long-term outlook for HIES patients depends on whether it is the AD or AR form and its severity. Most individuals with AD-HIES survive into mid-adulthood, but a shortened life span is common. The oldest reported affected individual was approximately 60 years of age. Deaths in the second and third decades of life are mostly due to severe pulmonary disease and infection of pneumatoceles. Other reported complications include myocardial infarction (heart attack) related to coronary artery aneurysm and subarachnoid hemorrhage related to intracranial (brain) aneurysm. Lymphomas also occur more commonly, and other cancers have been reported.

Most individuals with AR-HIES do not reach adulthood if untreated. It has high mortality due to sepsis, central nervous system infections and early onset of malignancies. Those with mutations in the DOCK8 gene have frequent complications with cutaneous viral infections caused by varicella-zoster, herpes simplex viruses, HPV and molluscum contagiosum virus at a younger age. Individuals with AR-HIES are also known to develop severe chronic refractory molluscum contagiosum infections resistant to treatment.[10]

The Future of HIES?

While HIES was first described more than half a decade ago, it is now known the disease has two genetic defects

resulting in two separate syndromes: STAT3 mutations that cause AD-HIES and DOCK8 mutations and deletions that result in AR-HIES. While symptoms of both types of HIES are similar, there are some distinguishing features in each. And, although the disease is present in infants, it sometimes goes undiagnosed until adolescence and even adulthood. Treatment is mostly supportive, although a number of investigative therapies are being studied. Unfortunately, prognosis is often a shortened lifespan.

Currently, there are only five ongoing studies on ClinicalTrials.gov evaluating the genetics, symptoms and treatments for HIES. It's clear much more needs to be understood about the disease to enable researchers to create better therapies and prevent its morbidity and mortality. Perhaps the greatest help to researchers is for patients and their families to become involved in registries to examine the causes and characteristics of HIES. For more information about becoming involved, contact the United States Immunodeficiency Network, a research consortium established to advance scientific research in the field of primary immunodeficiency diseases, at usidnet.org.

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