Chapter 20

Hyper IgE Syndromes (HIES): STAT3 Loss of Function, DOCK8 Deficiency and Others

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Hyper IgE Syndromes (HIES) are rare forms of primary immunodeficiency diseases (PI) characterized by recurrent eczema, skin abscesses, lung infections, eosinophilia (high numbers of eosinophils in the blood), and high serum levels of immunoglobulin E (IgE). Although initially described as two forms, with autosomal dominant (AD) and autosomal recessive (AR) inheritance, we now recognize that these are two distinct diseases caused by different genetic causes, with the two most common being from harmful mutations in STAT3 causing loss of function (STAT3-LOF) and DOCK8. These diseases share overlapping clinical and laboratory features; however, they also exhibit distinct clinical symptoms, disease courses, and outcomes. In addition, several other genetic variants have since been described to present with similar symptoms.

History

STAT3-LOF was described first as Job Syndrome in 1966 in two girls with many episodes of pneumonia, eczema-like rashes, and recurrent skin boils. These boils were remarkable for their lack of surrounding warmth, redness or tenderness, and were so called cold abscesses. In 1972, the syndrome was refined and clarified upon. It found similar infectious problems in two boys who also had a 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-HIES. In 2009 mutations and deletions in the DOCK8 gene were found to underlie many patients with similar symptoms inherited in an AR fashion.

Clinical Presentation

STAT3 Deficiency

STAT3 Deficiency, is associated with heterozygous loss of function mutations in the transcription factor STAT3. This is the more common form of HIES in the U.S. It commonly presents with skin findings including newborn rash, eczema, and recurrent staphylococcal skin abscesses as well as ear, sinus, and lung infections. The lung infections often result in cavitary lesions in the lungs (pneumatoceles). Other common infections in STAT3 deficiency include mucocutaneous candidiasis (Candida fungus on mucous membranes and/or skin), manifesting typically as thrush, vaginal candidiasis or candidal nail infection (onychomycosis), and recurrent shingles outbreaks. Additional findings include connective tissue and skeletal abnormalities, such as a typical facial appearance, hyper-extensibility of joints, retained primary teeth, recurrent bone fractures with minimal trauma, and

Forms of HIES

Table 20:1

Syndrome	Causative Gene	Symptoms
"Autosomal dominant HIES" (Job's Syndrome)	STAT3 Deficiency	High IgE, High Eosinophils, Severe Eczema, Skin infections (boils). Mucocutaneous Candidiasis. Minimal Trauma Fractures, Retained Primary Teeth, Scoliosis
ZNF341 Deficiency	ZNF341	High IgE, High Eosinophils, Severe Eczema, Skin infections (boils). Mucocutaneous Candidiasis. Minimal Trauma Fractures, Retained Primary Teeth, Scoliosis
Autosomal recessive GP130 deficiency	IL6ST	High IgE, High Eosinophils, Severe Eczema, Skin infections (boils). Mucocutaneous Candidiasis. Minimal Trauma Fractures, Retained Primary Teeth, Scoliosis
Autosomal recessive IL-6 receptor deficiency	IL6R	High IgE, High Eosinophils, Severe Eczema, Skin infections (boils). Mucocutaneous Candidiasis. Minimal Trauma Fractures, Retained Primary Teeth, Scoliosis
Autosomal recessive HIES DOCK8 deficiency	DOCK8	High IgE, High Eosinophils, Severe Eczema, Skin infections (boils), Mucocutaneous Candidiasis, Warts, Herpes Viridae infections, Malignancy, Severe Food Allergies
Autosomal recessive PGM3 deficiency	PGM3	High IgE, Severe Eczema, Sinopulmonary Infections, Herpes Viridae infections, Malignancy, Severe Food Allergies, Asthma, Neurocognitive Delays, Scoliosis
Dominant negative CARD11 deficiency	CARD11	High IgE, High Eosinophils, Severe Eczema, Pulmonary Infections, Molluscum, Food allergies and Asthma
Comel-Netherton Syndrome	SPINK5	High IgE, High Eosinophils, Severe Eczema, "Bamboo Hair", Recurrent sinopulmonary infections, Enteropathy, Allergies (Food Allergy, asthma, allergic rhinitis)
CARMIL2 Deficiency	CARMIL2	High IgE, High Eosinophils, Severe Eczema, Warts (HPV and molluscum), Herpes Viridae infections, Eosinophilic GI Disease, Inflammatory Bowel Disease, Asthma/Bronchiectasis, EBV associated malignancy

a propensity to aneurysm formation of brain and cardiac blood vessels. Severe allergic diseases, such as food allergies, are not common in individuals with STAT3 Deficiency. However, they often have positive skin prick tests making it appear that they have significant allergies.

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 substantially decreased with prophylactic therapy with antibiotics against Staphylococcus aureus. Deep tissue abscesses, such as liver or bone infections, are much less common in AD-HIES.

Recurrent bacterial pneumonias are often encountered in individuals with AD-HIES. Pneumonias typically start in childhood and are most frequently caused by Staphylococcus aureus, Streptococcus pneumoniae, and Haemophilus influenzae. Similar to the occurrence of cold skin abscesses, these pneumonias may present with fewer symptoms than 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. 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 due to STAT3 deficiency. When pneumatoceles or bronchiectasis are present in the lungs, the individuals are more susceptible to lung infections with other bacteria such as Pseudomonas and molds such as Aspergillus.

Involvement of both the connective and skeletal tissues is an important feature of STAT3 deficiency. 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. Individuals with AD-HIES exhibit hyper-extensibility 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. Craniosynostosis, fused skull bones, and extra/abnormally formed ribs or vertebrae are also found more often in those with AD-HIES than in the general population. These skeletal abnormalities are not usually seen in individuals with DOCK8 deficiency.

Abnormalities affecting dentition are another common feature of AD-HIES with STAT3 mutations. Retention of primary teeth even after the permanent teeth have erupted is a consistent finding. 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 often necessary for healthy dentition. Children who have had their retained primary teeth extracted will have normal eruption of their permanent teeth.

DOCK8 Deficiency

Individuals with AR-HIES due to DOCK8 deficiency have characteristics similar to STAT3 deficiency in that they have eczema, skin abscesses caused by Staphylococcus aureus, recurrent respiratory infections, mucocutaneous candidiasis and other fungal infections. However, those with DOCK8 deficiency are distinguished from those with AD-HIES by the lack of joint, bone, and teeth changes. They tend to have frequent occurrence of severe, recurrent viral infections not seen in those individuals with STAT3-LOF. Individuals with DOCK8 deficiency often have frequent outbreaks from Herpes simplex (cold sores or other skin lesions) and Herpes zoster (shingles), and difficult to treat warts, like Human Papillomavirus (HPV), and Molluscum contagiosum a viral skin infection that causes round, firm, painless bumps that can occur on any part of the body.

Recurrent lung infections are common in DOCK8 deficiency, and they may also lead to chronic lung disease with damage to the airways (bronchiectasis) and lung tissues. However, cavitary lesions are not commonly seen in DOCK8 deficiency. DOCK8 deficiency is also associated with a higher incidence of pneumonia caused by the bacteria Pneumocystis jirovecii. Liver disease can result from chronic infection with the parasite Cryptosporidia.

Asthma and allergies can be more severe in DOCK8 deficiency, including food allergies manifesting with anaphylaxis.

Vasculitis, inflammation within blood vessels, may occur in the brain blood vessels and in the main body vessels, such as the aorta. This may lead to a stroke, resulting in neurologic impairments.

Risk of Cancer

Both individuals with STAT3-LOF and DOCK8 deficiency are at increased risk for malignancies, especially lymphomas. Individuals with DOCK8 deficiency are susceptible to papilloma virus-induced squamous cell carcinoma as well as lymphomas, particularly Epstein-Barr virus (EBV) induced lymphoma.

Laboratory Findings

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.

In those with STAT 3 Deficiency, total white blood cell counts are typically normal and may not increase appropriately during acute infection. Neutropenia, low blood numbers of white blood cells called neutrophils, are seen in some people, but is not severe. A special type of T cell called Th17 cells are very low. Antibody levels, including IgG, IgA and IgM levels, are usually normal, but the ability to respond to vaccines is sometimes abnormal. Some may require immunoglobulin (Ig) replacement therapy.

Individuals with DOCK8 deficiency typically have low numbers of T cells, which often decrease further with age. They also tend to have low serum IgM levels and the antibody responses to vaccines are often poor.

Diagnosis

The diagnosis of HIES can be made based on a combination of clinical and laboratory findings for both AD- and AR-HIES. An elevated level of serum IgE is a virtually universal finding in these individuals. However, it is not sufficient on its own to make the diagnosis as people with other conditions, such as severe eczema, may also have very high IgE levels.

An HIES scoring system has been previously developed at the National Institutes of Health (NIH) that can help with the diagnosis of STAT3-LOF. In this system, individuals are evaluated for the existence and severity of the following clinical and laboratory features: newborn rash, eczema, skin abscesses, recurrent upper respiratory infections, pneumonia, lung cavities, candidiasis, other severe infections, fatal infections, characteristic facial appearance, increased nasal width, high palate, retained primary dentition, joint hyper-extensibility, fractures with minor trauma, scoliosis, midline anatomic abnormalities, lymphoma, high serum IgE level, and eosinophilia. The score correlates with the presence of the disease and higher scores reflect a more severe presentation. In addition, a recent study demonstrated that scoring five features: eosinophilia, parenchymal lung disease, frequency of sinusitis/otitis, retained primary teeth and minimal trauma fractures allowed differentiation between defects in STAT3 versus DOCK8.

A definitive diagnosis can be established with genetic analysis of the STAT3 and/or DOCK8 genes.

Inheritance

STAT3 Deficiency

STAT3-LOF occurs in both males and females of all ethnic groups with apparently equal frequency. In many, the disease occurs sporadically but then can be passed down to children in an autosomal dominant manner with each child have a 50% chance of having the mutation. Mutational analysis of the STAT3 gene would enable definitive diagnosis and genetic counseling.

DOCK8 Deficiency

Some individuals with AR-HIES are from families that are consanguineous, where parents are related or descended from the same ancestor. Deletions and mutations occur in the DOCK8 gene on chromosome 9. Mutational analysis of the DOCK8 gene is important for diagnosis and genetic counseling.

Treatment

Antibiotic prophylaxis with trimethoprim-sulfamethoxasole is frequently used as prophylaxis against recurrent respiratory infections, and Staphylococcal abscesses. Treatment for these infections, when they occur, should be started promptly.

Given that most individuals with HIES suffer from significant eczema and skin infections that come from having open lesions on the skin, skin care and prompt treatment of skin infections is an important component of HIES management. When the eczema is severe, topical moisturizing creams, non-steroidal topical creams and limited use of topical steroids can

help achieve healing. Cleaning the skin by bathing with chlorhexidine or dilute bleach baths helps to reduce the amount of bacteria that are on the skin. Skin abscesses may require incision and drainage but can largely be prevented with prophylactic oral antibiotics.

A remarkable feature of STAT3 Deficiency is how well the individuals 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, the individual may deny feeling sick and may not feel the need for invasive diagnostic testing or prolonged therapy. Moreover, doctors unfamiliar with the diagnosis can be hesitant to believe that individuals who do not appear very ill can really be quite sick. Therefore, it is always important for individuals with this diagnosis to see their healthcare providers when there are even mild symptoms. Lung infections need to be diagnosed and treated promptly to prevent formation of pulmonary cavities. Once lung cavities are present, antifungal prophylaxis is often recommended to prevent mold infections. In those with structural lung disease, pulmonology consultation is recommended to assist with development of a regimen to improve airway clearance and decrease risk of further damage.

Frequent Candidiasis of the fingernails, mouth, or vagina may lead to consideration of antifungal prophylaxis. Also, individuals with this disease are more susceptible to some environmental fungi that are more common in certain part of the country, such as Histoplasmosis and Coccidiodes. Discussing with your healthcare provider any precautions based on location is important.

Those with DOCK8 deficiency with Herpes infections or shingles may benefit from prophylaxis with an antiviral agent such as acyclovir. Since those with DOCK8 deficiency have a higher incidence of Pneumocystis jirovecii, pneumonia prophylaxis for this disease is often recommended. These individuals are also more susceptible to the parasite Cryptosporidia that can be found in water. Depending on the water supply, bottled or filtered water may be recommended. Individuals with this diagnosis may be counseled to avoid water parks and swimming in fresh water lakes, ponds or rivers.

Hematopoietic stem cell transplantation (HSCT) is generally recommended for people with DOCK8 deficiency given the severity of the disease and the risk of developing fatal complications, including infections and malignancies early in life. In STAT3 deficiency, the role for HSCT is less clear, but it has been effective in select individuals with severe symptoms of the disease early in life.

In individuals with STAT3 deficiency who have demonstrated fractures, use of DEXA scan and consultation with an endocrinologist focused on bone health is recommended. Calcium and Vitamin D supplementation can also be considered. Collaboration with a dentist is essential in children to determine the optimal age to remove baby teeth. Adults should be monitored for high blood pressure as well as heart and brain aneurysms.

Expectations

Individuals 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 individuals with STAT3 deficiency do fairly well. DOCK8 deficiency is associated with much higher risk of death by age 30 without HSCT. The more severe nature of DOCK8 deficiency should prompt early consideration of HSCT.

Genetic counseling is advised for families with HIES children and is especially important for those families where consanguinity is involved.

Adapted from: Chapter 1 The Immune System and Primary Immunodeficiency Diseases. IDF Patient & Family Handbook for Primary Immunodeficiency Diseases 5th Edition. 2013.