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Hyper-IgE Syndrome

IDFA Immune Deficiencies Foundation Australia

IPOPI INTERNATIONAL PATIENT ORGANISATION FOR PRIMARY IMMUNODEFICIENCIES

ABBREVIATIONS

HIES	Hyper-IgE syndrome
IgE	Immunoglobulin E
IPOPI	International Patient Organisation for Primary Immunodeficiencies
PID	Primary immunodeficiency

Primary immunodeficiencies: Hyper-IgE syndrome (1st edition).

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INTRODUCTION

This booklet explains what hyper-immunoglobulin E (IgE) syndrome is, how it is diagnosed and how it is treated.

Hyper-IgE syndrome (HIES) is a human error of inborn immunity that affects around 1 in 1,000,000 people. The condition is characterised by eczema in the context of very high serum IgE levels and people with the condition experience characteristic bacterial and fungal infections, recurrent lung infections and high levels of eosinophils in the blood, amongst a variety of syndromal features.

Most cases of HIES are caused by a loss of function mutation in the *STAT3* encoding gene and usually arise sporadically. Some familial cases of HIES have been reported and the syndrome can be inherited either as an autosomal dominant disorder (meaning that just one copy of the mutated gene must be present for HIES to develop) or as an autosomal recessive disorder (meaning that two copies of the mutated gene must be present for it to develop). Autosomal dominant HIES is caused by loss of function mutations in the *STAT3, ERBB2IP, TGFBR1, TGFBR2, CARD11* and *IL6ST* genes, while the recessive form of the disease is caused by loss of function mutations in the *DOCK8, TYK2, ZNF341, IL6ST, IL6R, SPINK5* and *PGM3* genes.[1,2]

The following sections provide an overview of the symptoms and diagnosis of HIES, the genetic basis of the disease, how it is managed and how patients can live with the disease.

[1] Al-Shaikhly T, Ochs HD. Hyper IgE syndromes: clinical and molecular characteristics. Immunol Cell Biol 2019;97:368-379.

[2] Bergerson JRE, Freeman AF. An Update on Syndromes with a Hyper-IgE Phenotype. Immunol Allergy Clin North Am 2019;39:49-61.

WHAT IS HYPER-IGE SYNDROME

HIES is characterised by eczema in the context of very high serum IgE levels. Persons with this condition experience bacterial and fungal infections of the skin, nails and other soft tissues, recurrent sinus, ear and lung infections, high levels of eosinophils in the blood and often retain their baby teeth even after the adult teeth have come through.

Skeletal and connective tissue abnormalities such as hyper-extensive joints and recurrent bone fractures may also be present in patients with HIES. Patients have a characteristic asymmetrical facial appearance with a prominent forehead and chin, deep-set eyes, broad nose, thickened facial skin and a high arched palate. These features evolve during childhood and become more established by adolescence.

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, but they exhibit distinct clinical manifestations, courses and outcomes. Persons with autosomal recessive HIES do not have the skeletal or connective tissue abnormalities but experience other, more severe, manifestations that include:

- Severe, recurrent viral infections caused by pathogens such as *Herpes simplex, Herpes zoster* and *Molluscum contagiosum*
- Allergic characteristics such as food allergies
- Autoimmune and inflammatory complications such as haemolytic anaemia, vasculitis and Inflammation of the brain resulting in neurological complications.

GENES ASSOCIATED WITH HIES

HIES syndrome can be inherited either as an autosomal dominant disorder (meaning that just one copy of the mutated gene must be present for HIES to develop) or as an autosomal recessive disorder (meaning that two copies of the mutated gene must be present).

Most cases of autosomal dominant HIES are caused by a loss of function mutation in either the *STAT3, ERBB2IP, TGFBR1, TGFBR2, CARD11* and *IL6ST* encoding gene and usually arise sporadically.[1,2,3,4]The autosomal recessive form of the disease is caused by mutations in different genes, namely *DOCK8, TYK2 ZNF341, IL6ST, IL6R, SPINK5* and *PGM3* genes, and is less common than the autosomal dominant form.

[3] Freeman AF, Holland SM, Clinical manifestations of hyper IgE syndrome. Dis Markers 2010;29:123-30

[4] Zhang Q, et al. Human hyper-IgE syndrome: singular or plural? Mamm Genome 2018;29:603-17

[5] Grimbacher B, Schäffer AA, Holland SM, Davis J, Gallin JI, Malech HL, et al. Genetic linkage of hyper-IgE syndrome to chromosome 4. Am J Hum Genet 1999;65:735–744.

DIAGNOSIS OF HIES

The diagnosis of HIES can be made based on a combination of clinical and laboratory findings with an elevated level of serum IgE being a universal finding in these patients. However, this is not sufficient on its own to make the diagnosis as patients with other conditions such as severe eczema may exhibit elevated IgE levels that are in the HIES range. Certain features, such as pneumatocele (intrapulmonary air-filled cystic spaces) formation in the context of other findings of HIES, are strongly supportive of the diagnosis of autosomal dominant HIES.

A scoring system developed by the National Institutes of Health in the USA can be used to evaluate people and support a diagnosis of HIES caused by loss of function *STAT3* gene mutations as well as assess the severity of the condition. The system evaluates the presence of the following clinical and laboratory features:

- Presence of rash in newborn babies
- Eczema
- Skin abscesses
- Recurrent respiratory infections, including pneumonia
- Lung changes (cavities)
- Candidiasis and other severe infections
- Characteristic facial appearance (asymmetric appearance, increased nasal width, high palate) (see images)
- Retained primary dentition (milk teeth)
- Joint hyperextensibility
- Fractures with minor trauma
- Scoliosis
- Midline anatomic abnormalities
- Lymphoma
- High serum IgE level
- Eosinophilia (elevated blood eosinophil level).

The score correlates with the severity of the disease:

- 0–15: unaffected
- 16–39: possibly affected
- 40–59: probably affected
- ≥60: definitively affected

The scoring system is a particularly useful tool for the diagnosis of autosomal dominant HIES but less so for autosomal recessive HIES. Definitive diagnosis can be established with genetic analysis of the *STAT3* and/or *DOCK8* genes, among others.

WHAT TREATMENT IS SUGGESTED FOR HIES

Therapy of HIES remains largely supportive. There are currently no curative treatments for autosomal dominant HIES and treatment focuses on supporting the immune system often by prophylactic treatment against recurrent infections and skin care to reduce the risk of skin infections.

Constant vigilance for the emergence of infection is essential, particularly as people with HIES can already be very ill because of an underlying infection and yet appear, and report, feeling quite well.

PROPHYLACTIC ANTIBACTERIAL THERAPY

Skin abscesses may require incision and drainage but can largely be prevented with prophylactic oral antibacterial therapy. Lung and other deep tissue abscesses may require drainage or resection. Following the resolution of acute pneumonias, pulmonary cysts or cavities form places for bacterial colonisation and these super-infections can be a difficult aspect of HIES to treat. Potential management strategies include continuous treatment with antibacterial and/or antifungal drugs.

Candidiasis of the fingernails, mouth or vagina in HIES rarely spreads to deeper tissues and responds well to oral antifungal treatment.

SKIN CARE

Skin care is an important part of the management of HIES to reduce the risk of skin infections. When the eczema is severe, topical moisturising creams and limited use of topical steroids can help achieve healing. Antiseptic treatments of the skin greatly reduce the bacterial burden in the skin without leading to emergence of antimicrobial-resistant bacteria.

IMMUNOGLOBULIN REPLACEMENT THERAPY

Poor antibody response to vaccination lends support to the use of immunoglobulin replacement therapy in HIES patients. Bone marrow transplantation is curative for autosomal dominant HIES with *DOCK8* deficiency and is recommended given the severity of the disease and the life-long risk of developing fatal complications. In contrast, autosomal dominant HIES patients generally do well with intensive therapy and supportive care, and bone marrow transplantation is not recommended for those individuals.

This booklet has been produced by the International Patient Organisation for Primary Immunodeficiencies (IPOPI).

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