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Patient information sheet
HIES

Hyperimmunoglobulin E Syndromes

Summary

Hyperimmunoglobulin E syndromes (HIES) are very rare, inherited conditions that affect both males and females with symptoms usually beginning in childhood. Common features are severe eczema, increased susceptibility to infections and markedly raised levels of immunoglobulin E (IgE).

Currently, two distinct HIES have been defined. These are autosomal dominant HIES, also known as Job's syndrome, and autosomal recessive HIES. The majority of autosomal dominant HIES is caused by genetic changes (mutations) in the STAT3 gene and is associated with a cluster of facial, dental, skeletal, and connective tissue abnormalities that are not seen in the recessive type. Three different subgroups have been identified within the autosomal recessive form, distinguishable by different clinical symptoms. These are caused by mutations in the genes DOCK8, TYK2 and as yet undefined genetic causes.

Treatment is centred on preventing and treating infections using antibiotic, antifungal and antiviral medicines. Good skin care and hygiene to prevent infection is essential. Moisturising creams and steroid creams are used to treat the severe eczema associated with these conditions.

Recent reports document success in treating both the autosomal dominant and the autosomal recessive DOCK8 form of HIES using bone marrow transplantation. With early diagnosis and treatment of infections, most patients with HIES go on to lead full lives.

How did I get HIES?

Currently two distinct genetic types of HIES have been defined.

Autosomal dominant HIES (Job syndrome)

In the majority of patients this is caused by a genetic alteration (often referred to as a mutation by the medical profession) in the STAT3 gene, present on chromosome 17 that makes the STAT3 protein. This protein is involved in cell signalling pathways in the immune system; wound healing, cancer and blood vessel growth (angiogenesis). STAT3 mutations particularly affect the maturation of T cells.

As the name suggests, this disorder is inherited in an autosomal dominant manner meaning you need to inherit only one copy of the altered gene to be affected. It affects both males and females equally and all ethnic groups.

Some cases arise due to new genetic changes occurring at conception. These are sporadic and are referred to as "*de novo* mutations".

Autosomal recessive HIES

This type of HIES shows different clinical features and is currently classified into three different subgroups.

These subgroups are inherited in an autosomal recessive manner meaning you need to inherit two copies of the altered gene, one from each parent, to be affected.

- TYK2 deficiency is caused by changes in the TYK2 gene. TYK2 is important in relaying cell signals in response to chemical factors known as cytokines. Cytokines play an important role in the immune system and in inflammation. This condition is extremely rare.
- DOCK8 deficiency is caused by changes in the gene encoding DOCK8. DOCK8 interacts with other enzymes that work as signalling networks within cells. This condition is extremely rare.
- A third clinical subgroup characterised by problems with the central nervous system (CNS) and haemorrhaging in addition to susceptibility to fungal and viral infections. The genetic causes of this disorder are not yet known.

In the UK, gene testing is available at the Department of Immunology, University Hospital of Wales, Heath Park, Cardiff.

Family planning

Pre-implantation genetic diagnosis is available for HIES.

What are the symptoms of HIES?

The diagnosis of HIES is based on a combination of distinctive clinical symptoms and laboratory findings and not just on having raised levels of IgE and raised numbers of eosinophils (specialised white blood cells that help to combat parasites and infections). This is because other patients with severe allergy may also have these features without having HIES.

In HIES an IgE level of many thousands can be seen (normal adult value is less than 100 IU/ml). However, other conditions such as eczema can also lead to a significant rise in IgE. It is noteworthy that in some adults with HIES, IgE may decrease and even become normal. This is why the diagnosis should not be made on the basis of IgE levels alone. The presence of the distinctive clinical features described below helps to guide the diagnosis, and in some cases confirmation by genetic testing is possible.

Autosomal dominant HIES (Job Syndrome)

- Distinctive facial features – broad nose, deep set eyes, prominent forehead, facial asymmetry
- Eczema which can be severe, very itchy and can become infected
- Repeated bouts of ear and sinus infections – otitis and sinusitis
- Skin abscesses (boils) that are characteristically not red or inflamed. These are sometimes referred to as ‘cold’ abscesses
- Repeated bouts of pneumonia causing air-filled cysts in the lungs - pulmonary pneumatoceles

- Delay in losing baby teeth – known as retained primary teeth. Sometimes in adults, secondary teeth may be present at the same time as baby teeth
- Skin, mucous membrane (such as the mouth and throat) and nail infections, often caused by the fungus candida (the cause of thrush)
- Curving of the spine – scoliosis
- Bones that break easily due to osteoporosis
- Over flexible joints – hyperextensibility
- An abnormally shaped skull caused by fused skull bones – Craniosynostosis
- Dry eyes

Infections may be caused by:

- Bacteria
    - Staphylococcus aureus – affecting the lungs and skin
    - Streptococcus pneumoniae – affecting the lungs
    - Haemophilus influenzae – affecting the lungs
    - Pseudomonas aeruginosa – affecting the lungs
    - Nontuberculous mycobacterium – affecting the lungs
- Fungi
    - Candida albicans – infections of the skin and nails and causing thrush
    - Aspergillus species – affecting the lungs
    - Scedosporium species – affecting the lungs
    - Pneumocystis jirovecii – affecting the lungs
    - Histoplasma – affecting the gastrointestinal tract
    - Cryptococcus – affecting the brain and gastrointestinal tract

Autosomal recessive HIES

This type of HIES lacks the connective tissue and skeletal abnormalities of STAT3 deficiency. This means those affected lose their baby teeth normally, do not have the facial characteristics and their bones do not fracture easily.

Presenting features include:

- Repeated bouts of pneumonia but usually without the formation of air-filled cysts in the lungs called pulmonary pneumatoceles
- Susceptibility to infections caused by bacteria (particularly Mycobacteria and Salmonella); fungi and viruses (particularly Molluscum contagiosum, a viral infection of the skin; Herpes simplex, the cold sore virus and repeated infections with Varicella zoster, the virus that causes chicken pox and shingles).
- Infection of the blood – sepsis
- Symptoms affecting the CNS such as facial paralysis, paralysis of the arm, leg and trunk on the same side of the body (hemiplegia) and bleeding in the brain.

TYK2 deficiency

People with Tyk2 deficiency tend to show more severe clinical features. Those affected have extreme vulnerability to intracellular bacteria (bacteria that can grow within cells), as well as bacteria that grow on the outside of cells. These include Mycobacteria and Salmonella.

DOCK8 deficiency

This is also characterised by CNS symptoms caused by inflammation of blood vessel (vasculitis) within the CNS and susceptibility to fungal and viral infections. Viral infections caused by the JC

(John Cunningham) virus may lead to a serious condition involving inflammation of the white matter of the brain, known as progressive multifocal leukoencephalopathy.

Those affected are also known to be at high risk of malignancies including squamous cell carcinoma, a cancer of the skin; lymphoma, leukaemia, and Burkitt's lymphoma in late childhood and early adulthood.

The clinical differentiation of autosomal recessive from dominant forms of HIES in early childhood may be difficult since the distinctive facial features of autosomal dominant HIES may not be evident until many years later.

Making the diagnosis

Doctors will want to carry out a number of tests and scans after taking a clinical history and performing an examination looking for the clinical features. The investigations may include:

- Counting the number of eosinophils and types of other immune cells in your blood
- Examining the level of IgE in your blood
- Testing the responses of your T cells
- Identifying the organisms causing infections by taking samples of the infected site
- X-rays of the chest, bones and sinuses
- Genetic tests

Treatment

Treatment of Hyper IgE syndromes depends on preventing and management of infections to reduce the threat of overwhelming infection and limit damage to the lungs. It is important to find out which bug is causing the infection so that specific treatment can be given.

- Long-term treatment with antibiotics and antifungal therapy to prevent and treat infections. These are especially important to treat infections caused by Staphylococcus aureus, Haemophilus influenzae, Streptococcus pneumoniae and Candida albicans. The development of resistance in the course of long-term therapy outweighs the risk of severe infections and lung damage.
- Skin abscesses may need to be drained surgically, but these can largely be prevented with continuous oral antibiotics.
- Lung abscesses may require drainage or resection, but surgery is difficult in HIES patients because the remaining lung tissue often fails to expand to fill the chest cavity. Prolonged chest tube drainage and intensive intravenous antibiotic treatment is sometimes needed. Lung surgery requires specialist advice and should not be undertaken lightly, and ideally should be done at centres with experience with the disease.
- Infections caused by Pseudomonas aeruginosa, Aspergillus and other fungal species can follow the resolution of acute pneumonia. Treatment strategies include continuous treatment with antifungal drugs and/or aerosolised antibiotics.
- Immunoglobulin therapy may also help in situations where antibody deficiency is present.
- Infections caused by viruses are treated using anti-viral medicines, for example aciclovir to treat chicken pox.
- Good skin care and prompt treatment of skin infections is important. Topical and oral antibiotics are often effective at preventing infection. Attention to skin care is essential when plaster casts are used to treat fractures or scoliosis.

- Using moisturising creams helps treat the eczema and your doctor may occasionally give you steroid creams to use. Antiseptic treatments of the skin can help to reduce the bacterial burden in your skin without leading to emergence of antibiotic resistant bacteria. Your doctor may also recommend something to help relieve itching so that areas of eczema don't become infected.

Role of bone marrow transplantation

There has been success over the last few years in treating both the autosomal dominant and the autosomal recessive DOCK8 form of HIES using bone marrow transplantation (BMT).

Although the number of people treated by BMT remains small and the long-term outcomes are as yet unclear, clinical outcomes included the disappearance of skin problems and severe infections, improvement of lung function and a drop in IgE levels. The recommendation is that BMT should be considered early, before complications develop.

Are there any associated health problems with HIES?

Systemic lupus erythematosus (SLE) and other autoimmune diseases have been associated with HIES.

Immunisation

Killed or inactivated vaccines may be given but the use of live vaccines is however best avoided because of the risk of vaccine-induced disease, as seen in some patients with TYK2 deficiency.

This patient information was reviewed by the PID UK Medical Advisory Panel and Patient Representative Panel (November 2014; review date November 2015).

About Primary Immunodeficiency UK

Primary Immunodeficiency UK (PID UK) is a national organisation supporting individuals and families affected by primary immunodeficiency (PIDs).

Our website provides useful information on a range of conditions and topics and explains the work we do to ensure the voice of PID patients is heard.

If we can be of any help please contact us at hello@piduk.org or on 0800 987 8986 where you can leave a message. Visit www.piduk.org for further information.

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