

Hyperimmunoglobulin E syndromes (HIES)

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PID UK

Supporting families affected
by primary immunodeficiencies

About this booklet

This booklet provides information on hyperimmunoglobulin E syndromes (HIES). It has been produced by the PID UK Medical Advisory Panel and Patient Representative Panel to help answer the questions patients and their families may have about HIES but should not replace advice from a clinical immunologist.

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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 and 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?

Autosomal dominant HIES (Job's syndrome)

In the majority of patients autosomal dominant HIES is caused by a genetic alteration (often referred to as a mutation by the medical profession) in the STAT3 gene that is present on chromosome 17 and which 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:

- 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 is characterised by problems with the central nervous system and haemorrhaging in addition to susceptibility to fungal and viral infections. The genetic causes of this disorder are not yet known.

All three 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.

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. A genetic counsellor may help with specific aspects of understanding genetic disease, for example, family planning.

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 levels 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.

The symptoms of autosomal dominant HIES (Job's 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)
- Curvature 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*, causing infections of the skin and nails, and 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.

The symptoms of autosomal recessive HIES

This type of HIES lacks the connective tissue and skeletal abnormalities of the autosomal dominant form (STAT3 deficiency). This means that 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 central nervous system, 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 symptoms affecting the central nervous system (CNS), caused by inflammation of blood vessels (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 autosomal 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
- Taking X-rays of the chest, bones and sinuses
- Conducting genetic tests.

Treatment

Treatment of HIES depends on the prevention 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 is especially important to prevent and treat infections caused by *Staphylococcus aureus*, *Haemophilus influenzae*, *Streptococcus pneumoniae* and *Candida albicans*. The development of resistance in the course of long-term therapy is less than the risk of severe infections and lung damage.

- Skin abscesses may need to be drained surgically but can be largely 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. Ideally surgery 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 prevent recurrent infection, even when IgG levels are normal.
- Infections caused by viruses are treated using antiviral 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 have 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 best avoided due to the risk of vaccine-induced disease, as seen in some patients with TYK2 deficiency.

Glossary of terms

abscess – a collection of pus that has built up within a tissue of the body.

aerosolised – small particles of liquids or solids put into gas or air. This is a way of getting drugs into the body.

angiogenesis – the growth of new blood vessels in the body.

antibody – a type of protein (immunoglobulin) that is produced by certain types of white blood cells (plasma cells – a type of B-cell). The role of antibodies is to fight bacteria, viruses, toxins and other substances foreign to the body.

asymmetry – uneven distribution of features.

autoimmune/autoimmunity – when an individual's immune system attacks the body's own tissues or vessels.

autosomal dominant – a type of inheritance where just one faulty copy of a gene is all it takes to cause a genetic disorder. Somebody with a condition with this type of inheritance has a one in two chance, for each pregnancy, of passing it to each of his/her children.

autosomal recessive – a type of inheritance where a child inherits a faulty copy of a gene from both parents, which has a one in four chance for each pregnancy.

B-cell – a type of white blood cell (lymphocyte) that produces antibodies.

bone marrow transplantation (BMT) – transfer of bone marrow obtained usually from the hip bones from a healthy donor – either related or unrelated – to someone else; e.g. a patient with a primary immunodeficiency. The donor bone marrow replaces the patient's bone marrow and provides a new immune system, curing the immunodeficiency. Sometimes this is referred to as stem cell transplantation.

Burkitt's lymphoma – a cancer of B-cells.

central nervous system (CNS) – part of the nervous system consisting of the brain and spinal cord.

chromosome – a long threadlike strand of DNA that carries a set of genes. Normally humans have 23 pairs of chromosomes.

craniosynostosis – a problem of the skull which results in an abnormally shaped head.

cytokine – a protein that works as a messenger between cells and help instruct a cell to carry out a particular job.

deficiency – a lack or shortage.

de novo mutation (also called a 'sporadic mutation') – a 'new' alteration to a gene that is seen for the first time in a family. The new mutation is not inherited from a parent, but someone who has it can then pass it down to their children and so on. Conditions caused by sporadic mutations are due to an alteration to a gene that occurs out of the blue in either the egg or sperm near the time of conception or just afterwards.

eczema – an inflammatory condition affecting the skin. Symptoms may include dry, itchy skin.

enzyme – a protein that carries out biological reactions in the body.

eosinophil – a special type of white blood cell in the immune system.

gastrointestinal tract – the lining of body parts that run from the mouth to the bottom. It can also be referred to as the gut.

gene – the fundamental unit of inheritance that carries the instructions for how the body grows and develops.

genetic – something that relates to how your genes work and are inherited.

haemorrhage – bleeding.

hemiplegia – where one side of the body is paralysed.

immunoglobulins – proteins (globulins) in the body that act as antibodies. They work to fight off infections. They are produced by specialist white blood cells (plasma cells/B-cells) and are present in blood serum and other body fluids. There are several different types (IgA, IgE, IgG and IgM), and these have different functions.

immunoglobulin therapy – a plasma-based treatment. The immunoglobulin contains antibodies that help fight infection. This treatment can be given through a vein or through the skin.

inheritance/inherited – the passing down of genetic information from parents to children.

intravenous – inside or into a vein; e.g. antibiotics may be given directly into a vein.

leukaemia – a cancer of blood-forming cells.

lymph nodes – small bean-sized organs of the immune system distributed widely throughout the body. They are the home for the many types of cells that are important in fighting infections.

lymphocyte – a white blood cell that works to fight infection in the body. One type of lymphocyte is called a ‘B-cell’. This type of lymphocyte makes antibodies.

lymphoma – a group of blood cell cancers that develop from lymphocytes.

malignancy – a type of cancer.

mutation – a permanent alteration to a gene where part of the DNA within the gene is different from what it should be. There may be an extra or missing part, for example. Mutations may affect the proper growth or development of a person. They can have either positive or negative effects on an individual.

organism – a single-celled life form; e.g. a bacteria, virus or fungus. It can also mean an individual plant or animal.

osteoporosis – a condition that weakens bones, making them fragile and more likely to break.

otitis – a general term for inflammation or infection of the ear.

plasma – the liquid component of blood without the cells (but with all the proteins).

plasma cell – a specific subtype of B-cell that is found within the bone marrow or lymph nodes. Plasma cells are responsible for the majority of high-quality antibody production.

pre-implantation genetic diagnosis – a way to help couples with a known genetic disorder have children free from the disorder. It involves IVF.

progressive multifocal leukoencephalopathy – a rare infection that damages the material covering and protecting nerves in parts of the brain.

protein – one of the basic building blocks of life. Proteins make up the structure and determine the function of the cells that make up all the tissues of our bodies.

pulmonary pneumatoceles – a medical term for air-filled cysts in the lungs.

sepsis – a common and potentially life-threatening condition triggered by an infection.

sinuses – air-filled space within the bones of the face and around the nose. Infection of the sinuses is called sinusitis.

squamous cell carcinoma – a cancer of the skin.

systemic lupus erythematosus (SLE) – sometimes referred to as lupus. It is an autoimmune disease. Symptoms include joint pain and skin rashes.

T-cell – a type of white blood cell (lymphocyte) that helps the immune system work properly to fight infection.

thrush – an infection that is caused by a yeast fungus.

topical – used to describe a medication that is applied to body surfaces, such as the skin.

vasculitis – a group of disorders that destroy blood vessels by inflammation. This may cause narrowing or blockage that restricts blood flow.

About Primary Immunodeficiency UK

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

We are the UK national member of the International Patient Organisation for Primary Immunodeficiencies (IPOP), an association of national patient organisations dedicated to improving awareness, access to early diagnosis and optimal treatments for PID patients worldwide.

Our website at www.piduk.org 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.

Support us by becoming a member of PID UK. It's free and easy to do via our website at www.piduk.org/register or just get in touch with us. Members get monthly bulletins and newsletters twice a year.

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