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Patient information sheet
WAS

Wiskott-Aldrich Syndrome

Summary

Wiskott-Aldrich syndrome (WAS) covers a group of rare serious disorders affecting about 4 people in a million and usually affects only males. WAS affects the function of white blood cells making those affected susceptible to serious infections. There is also a significant reduction in the size and number of platelets (microthrombocytopenia), causing those affected to bleed easily.

WAS is caused by mutations or defects in the WAS gene that gives the instruction to make the Wiskott-Aldrich Syndrome Protein (WASP). The WAS gene defect and the severity of the condition varies widely between individuals. Severe cases may be present soon after birth or develop in the first year of life. Four clinical forms have been identified. Classic WAS is the most severe form of WAS. Its main symptoms are having repeated bouts of infection, prolonged and severe bleeding leading to bruising easily, severe eczema and a higher incidence of leukaemia and lymphoma and autoimmune disorders.

Milder forms of WAS are X-linked Thrombocytopenia, a condition with low platelet numbers but without many of the other symptoms of WAS; X-linked neutropenia, a condition with low amounts of white blood cells known as neutrophils but with normal levels of WASP and the mildest form called Intermittent Thrombocytopenia where the platelet abnormalities are sporadic and there is no immunodeficiency.

There have been enormous advances in the care of people with WAS due to improved control of infection, transfusion services and stem cell transplantation, for example bone marrow transplant, with those successfully transplanted leading relatively normal lives. Preventing and treating infections using antibiotics and immunoglobulin replacement therapy is used to manage the condition. Platelet and red blood cell infusions can be used to treat excessive bleeding. Skin care using moisturising and steroid creams are used to treat eczema. Stem cell transplant by a bone marrow or cord blood transplant offers the chance of a cure and is successful in 9 out of 10 cases. Gene therapy is also being developed as a potential alternative for people unable to find a suitably matched donor.

How did I/my child get WAS?

WAS is caused by mutations in the WAS gene, found on X chromosome Xp11.2.3, that provides instructions to make the protein called WASP (Wiskott-Aldrich Syndrome Protein). About one third of cases may arise due to a random new mutation occurring at the time of conception.

WASP is found in all blood cells and is involved in the communication of signals between the surface of blood cells to the actin cytoskeleton, a network of fibres that make up the blood cell's structural framework. WASP is needed for white blood cells to fight different kinds of infection from viruses, bacteria and fungi. White blood cells that lack WASP or have a WASP that doesn't work as well as it should are less able to fight infections. A lack of functional WASP in platelets also leads to their reduced size and early removal from the bloodstream resulting in low numbers.

How the genetic mutation affects the production of WASP determines how severe WAS is. If the mutation is severe and interferes almost completely with the gene's ability to produce WASP, those affected have the classic, more severe form of WAS. In contrast, if there is some production of mutated WAS protein, a milder form of the disorder may result.

Milder forms of WAS are caused by missense mutations in WASP. Missense mutations are point mutations where just one change in the genetic code occurs. This type of mutation preserves some level of WASP expression and activity and includes the conditions:

- **X-linked Thrombocytopenia**, a condition with low platelet numbers but without many of the other symptoms of WAS.
- **X-linked neutropenia**, a condition with low amounts of white blood cells known as neutrophils but with elevated levels of WASP activity.
- **Intermittent Thrombocytopenia**, here platelet abnormalities are intermittent and there is no immunodeficiency. It is the mildest form of WAS.

WAS is an inherited condition meaning it is passed down through the generations. It affects almost exclusively boys, although some carriers can occasionally show some signs of the disease. It follows what is called an X-linked recessive pattern of inheritance with transfer of a defective gene on one of the two X chromosomes of a mother to a son. This means that for every boy that is conceived to a carrier mother there is a 50/50 chance that they will have WAS. This has implications for family planning. Mothers, their maternal aunts and sisters may be carriers and should receive genetic counselling. Daughters that are born to carrier mothers should also be tested once they are old enough to give informed consent as there is a 50/50 chance they might carry the faulty gene.

Family planning and WAS

If the precise mutation of the gene WAS is known in a given family, it is possible to perform prenatal DNA diagnosis on cells obtained by amniocentesis or chorionic villus sampling.

Prenatal genetic diagnosis is available for families in which WAS is diagnosed.

What are the symptoms of WAS?

The initial symptoms of WAS may show soon after birth or develop in the first year of life.

Here are some common features that you may recognise and that may have led your clinician to a diagnosis of WAS:

- A tendency to bruise and bleed without injury. This can include unusual bruising,bleeding gums and prolonged nose bleeds. These are due to low platelet numbers. Haemorrhage into the brain is a dangerous complication.
- Presence of pin-head blueish type skin spots called petechiae. These are caused by low platelet numbers.
- Eczema, often very itchy, with bleeding in the rash and a tendency to become infected. In infants, the eczema may resemble "cradle cap", a severe nappy rash, or be more general covering large areas of the body such as the back. In older boys, eczema may be limited to the skin creases around the front of the elbow, around the wrist and neck and behind the knees or the eczema may involve much of the total skin area. Eczema may also be mild or absent in some patients.
- Bloody diarrhoea.
- Frequent and repeated infections caused by bacteria, viruses and sometimes fungi. Infections may involve the ear (otitis media), the sinuses (sinusitis) and the lungs causing pneumonia.

The skin may also become infected with various bacteria as a result of scratching of areas affected by eczema.

What are the common causes of infection in WAS?

Bacteria such as *Streptococcus pneumoniae* or *Haemophilus influenzae* may cause recurrent ear infections or infections of the blood stream (sepsis) and meningitis.

Viruses: the varicella-zoster virus causing chicken pox and Epstein Barr Virus (EBV) and Cytomegalovirus (CMV), which are causes of mononucleosis (glandular fever).

The *molluscum contagiosum* virus causes a viral skin infection and is characterized by red raised skin spots.

The fungus pneumocystis jiroveci (carinii) is a rare cause of severe pneumonia in WAS. Other fungal infections are caused by Aspergillus and Candida.

How is WAS diagnosed?

WAS will be considered in individuals presenting with repeated, severe or persistent infections. These individuals will usually be referred to a specialist for further assessment, following which an immunologist should be consulted.

Making the diagnosis

A clinical immunologist usually makes the diagnosis of WAS.

Diagnosis is confirmed by blood and skin tests. Tests may be intensive at the beginning of this investigative process.

The clinical immunologist will look at the number of platelets in your blood and their size. Lower numbers of and characteristically small sized platelets are almost always present in people with WAS.

They may also look at the presence of the WAS protein in your blood cells. Absent or decreased levels of WASP indicates Wiskott-Aldrich Syndrome.

Further tests will be done to determine the type of WAS. This can include the classical type of WAS; X-linked thrombocytopenia (XLT) or X-linked congenital neutropenia (XLN). These tests can include

- Measuring immunoglobulin levels of IgG, IgA, IgE and IgM. In WAS there is often decreased IgM and increases in IgA and IgE.
- Measuring levels of antibodies to blood group markers. People with WAS often have low levels of these antibodies.
- Measuring levels of antibodies to certain vaccines that contain polysaccharides or complex sugars such as the vaccine against streptococcus pneumoniae (Pneumovax). People with WAS do not produce the normal protective antibody response.
- Skin tests and blood tests to assess how many T cells are present and how well they are working. T-cells responses in WAS may be abnormal.

A definite diagnosis is made by looking for mutations in the WAS gene using molecular genetic testing. When a specific defect is found, the doctors will often test female members of the family

to diagnose those who carry the abnormal X-chromosomes.

Treatment

At present there is no cure for WAS but affected boys can grow up to lead normal productive lives if they keep to the treatments recommended and have regular check-ups with an immunologist.

Quick and aggressive treatment of infections and bleeding is needed in WAS before they develop into very serious health problems.

Treatment of infections may include antibiotics, antivirals, antifungals, immunoglobulins and corticosteroids. When there are symptoms of infection, doctors will try and identify what is causing the infection so that they can give the most appropriate treatment.

Preventing infections is very important and immunoglobulin replacement therapy containing antibodies that fight infection may be recommended. Immunoglobulin replacement therapy is particularly important if you have had a splenectomy (surgical removal of the spleen).

Eczema in WAS can be severe and requires constant care. It is best to avoid excessive bathing because these can dry out the skin and make the eczema worse. Bath oils, recommended by your doctor, can be added to the bath water to help relieve itching and a moisturising cream should be applied after bathing and several times daily to areas of dry skin/eczema. Steroid creams can sometimes help but they should be used in small amounts and their overuse should be avoided. It is not recommended to use steroid creams on your face.

Sometimes flares of eczema can be caused by food allergies. If certain foods make the eczema worse try and remove the offending food items from your diet.

Low platelet counts, known as thrombocytopenia, may be treated by platelet transfusions if there is active and dangerous bleeding. Haemorrhage into the brain is a dangerous complication and usually requires immediate platelet transfusions. Some doctors may recommend that toddlers with very low platelet counts wear a helmet to protect them from head injuries until treatment is able to raise their platelet count. Routine platelet transfusion because of a low platelet count is not advised because it can complicate future treatment by bone marrow transplantation.

It is important to be careful about taking over-the-counter medications as some may affect the how well your platelets work. Always ask for advice. Examples of some medicines that affect the function of platelets are aspirin, some medicines to treat headaches, and creams containing non-steroidal anti-inflammatory drugs (NSAIDs) used to treat sprains, aches and pains.

Your doctor may recommend iron supplements to treat symptoms of iron deficiency anemia caused by blood loss.

Splenectomy, the surgical removal of the spleen, is very effective at correcting the low platelet count in the absence of autoimmunity (see below) and results in considerable improvement in quality of life for the patient and family. This may be discussed if bleeding is a problem, and particularly in milder cases of WAS where the immunological problems are minimal.

Removal of the spleen can mean that people affected by WAS become more vulnerable to certain infections, especially infections of the blood stream and meningitis caused by bacteria like *Streptococcus pneumoniae* or *Haemophilus influenzae*. As a result your doctor will recommend daily doses of prophylactic antibiotics and will make sure that vaccinations are kept up to date.

Cure of WAS by stem cell transplantation
Stem cell transplantation such as a bone marrow transplant (BMT) is the only permanent cure for WAS and is the treatment of choice for those with severe clinical symptoms.

If BMT is successful, the blood cell and immune defects in WAS are corrected and eczema resolves. It is not without risk but significant advances in the last two decades have improved its success rate.

Stem cells from umbilical cord blood are now being used with good success.

The recommendation is to transplant early before infections take their toll on the body and before complications such as autoimmunity and malignancies occur.

Five-year survival rates for children transplanted under the age of 5 years with a perfect sibling match approaches 90%. In centres that specialise in BMT for WAS, success rates with matched unrelated donors are now as high.

Doctors will start the search for a good HLA tissue-matched donor as soon a diagnosis of WAS is made. If the affected boy has healthy brothers and sisters with the same parents the entire family will be tissue typed to see if there is a good match.

Chemotherapy is needed before transplant. This involves taking medication to destroy the patient's blood forming cells and to make place in the bone marrow for the donor cells. This process is sometimes referred to as conditioning.

Clinicians are constantly looking at ways to improve success rates by optimising the conditioning process using different combinations of drugs.

Currently 'reduced-intensity conditioning' treatments are being used for BMT to treat WAS.

Gene therapy for WAS
Gene therapy (GT) is an experimental therapy aimed at replacing the defective WAS gene with a healthy working copy of the normal gene. This allows cells to start producing the normal WASP protein, which may cure the disease.

To date two sets of clinical trials have taken place. The first trials took place in Hannover, Germany and succeeded in correcting WAS in 9 out of 10 children with one patient receiving insufficient number of cells. However, most of these patients went on to develop leukaemia related to the treatment.

Two trials using a different safer design of gene medicine are taking place in Milan, Great Ormond Street Hospital in London, Hopital Necker-Enfants Malades in Paris and the Children's Hospital, Boston, USA. Early reports show successful treatment of WAS with gene therapy and these new gene medicines seem to be safer with none of the children developing leukaemia.

Are there any other associated health problems with WAS and how will my/my child's health be monitored?

Yes some people with WAS, but not all, may have or may develop other health problems. These can occur in affected children, adolescents and adults. Monitoring is usually by clinical review (check-up) and infrequent blood tests.

Your clinical immunologist will be on the lookout for the complications and will work with other clinical specialists to offer you the most appropriate advice and treatments.

Complications associated with viral infections

These can be prevented by early treatment following exposure with antiviral drugs such as aciclovir and/or high dose immunoglobulin replacement therapy.

Complications associated with autoimmune disease

The symptoms of autoimmunity occur when the body starts to produce antibodies against itself, setting up an attack on the body tissues. In WAS the autoimmune complications include

Vasculitis - a type of blood vessel inflammation associated with fever and skin rash on the extremities—sometimes worsened following episodes of exercise. Occasionally vasculitis occurs in the muscles, heart, brain or other internal organs develops and causes a wide range of symptoms.

Haemolytic anaemia caused by antibodies that destroy the patient's own red blood cells.

Idiopathic thrombocytopenic purpura (ITP) where autoimmune antibodies attack the remaining platelets and further reduces platelet numbers.

A generalised disorder may affect some people, in which there may be high fevers in the absence of infection, associated with swollen joints, tender lymph glands, kidney inflammation, and gastrointestinal symptoms such as diarrhoea. These autoimmune or inflammatory episodes may last only a few days or may occur in waves over a period of many years and may be difficult to treat.

Autoimmune complications may need treatment with drugs that further suppress your immune system. Your doctor may recommend high dose immunoglobulin replacement therapy and steroids given by injection or in tablet form may help alleviate the problem. Doctors will ensure that the steroid dose is reduced to the lowest level needed to control symptoms as soon as possible.

Other problems

People with classical WAS have an increased risk of developing cancer. This can be lymphomas, cancers of the lymph nodes and leukaemia, cancers of the blood. Your doctors will check and monitor this carefully.

Immunisation

Some vaccines may be advised to prevent against infection but you should always seek medical advice. Live virus vaccines should be avoided in severe forms of WAS, as there is a possibility that a vaccine strain of the virus may cause disease.

This patient information was reviewed by the PID UK Medical Advisory Panel and Patient Representative Panel (August 2014; review date August 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 mailto:hello@piduk.org or on 0800 987 8986 where you can leave a message. Visit http://www.piduk.org for further information.

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