Wiskott-Aldrich syndrome (WAS)

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PID UK
Supporting families affected by primary immunodeficiencies

About this booklet

This booklet provides information on Wiskott-Aldrich syndrome (WAS). 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 this condition but should not replace advice from a clinical immunologist.

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Summary

Wiskott-Aldrich syndrome (WAS) covers a group of rare serious disorders that affect about four people in a million and usually only males. WAS affects the function of white blood cells, making people 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 WAS protein. 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. Its main symptoms are 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, and X-linked neutropenia, a condition with low amounts of white blood cells known as neutrophils but with normal levels of the WAS protein. The mildest form is 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 (e.g. bone marrow transplant), with those successfully transplanted leading relatively normal lives. Antibiotics are used to prevent and treat infections, and immunoglobulin replacement therapy is used to manage the condition. Platelet and red blood cell infusions can be used to treat excessive bleeding. Moisturising and steroid creams are used to treat eczema. Stem cell transplantation 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 WAS protein. About one third of cases may arise due to a random new mutation occurring at the time of conception.

The WAS protein 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. The WAS protein is needed for white blood cells to fight different kinds of infection from viruses, bacteria and fungi. White blood cells that lack the WAS protein or have WAS protein that doesn't work as well as it should are less able to fight infections. A lack of functional WAS protein 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 the WAS protein determines how severe WAS is. If the mutation is severe and interferes almost completely with the gene's ability to produce the WAS protein, 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 the WAS protein. Missense mutations are single changes in the genetic code for an amino acid (the building blocks of proteins), such that the protein formed no longer has an appropriate structure. This type of mutation preserves some level of WAS protein 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 WAS protein 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 who is conceived to a carrier mother there is a 50/50 chance that he will have WAS. This has implications for family planning. Mothers, their maternal aunts and

sisters may be carriers and should receive genetic counselling. Daughters who are born to carrier mothers should also be tested once they are old enough to give informed consent and decide if they wish to know whether or not they are a carrier, as there is a 50/50 chance they might carry the faulty gene.

Family planning and WAS

If the precise mutation of the WAS gene 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 which 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 the 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 bloodstream (sepsis) and meningitis.

Viruses such as the *Varicella zoster* virus (causing chickenpox), Epstein-Barr virus and Cytomegalovirus may cause mononucleosis (glandular fever).

The *Molluscum contagiosum* virus causes a viral skin infection and is characterised 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 and characteristically small platelets are almost always present in people with WAS.

The clinical immunologist may also look at the presence of the WAS protein in your blood cells. Absent or decreased levels of this protein indicate WAS.

Further tests will be done to determine the type of WAS (e.g. the classical type of WAS, X-linked thrombocytopenia or X-linked neutropenia). 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-cell 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 the definitive treatment for WAS is bone marrow transplant, however 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 to 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 it 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 to 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 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 anaemia 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 their 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 bloodstream and meningitis caused by bacteria such as *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 approach 90 per cent. 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 as 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 space 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 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 WAS 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 an 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 therapy are taking place in Milan, Great Ormond Street Hospital in London, Hôpital Necker-Enfants Malades in Paris and Boston Children's Hospital in the United States. 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?

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 acyclovir, 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 that is sometimes worsened following episodes of exercise. Occasionally vasculitis can affect the muscles, heart, brain or other internal organs, causing a wide range of symptoms.

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

- **Immune thrombocytopenic purpura**, where autoimmune antibodies attack the remaining platelets and further reduce 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 leukaemias (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.

Glossary of terms

amino acid – the building blocks of proteins.

amniocentesis – a type of diagnostic test carried out during pregnancy to assess whether the unborn baby could develop an abnormality or serious health condition. The test is usually performed after 15 weeks of pregnancy and takes cells from the amniotic fluid around the baby.

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.

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

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.

carrier – an individual who carries the abnormal gene for a specific condition, usually without showing symptoms.

chemotherapy – treatments that use medicines to target and remove cells. The cells may be cancerous or they may be immune cells, so chemotherapy may be used as part of conditioning for bone marrow transplantation.

chorionic villus sampling – a type of diagnostic test done during early pregnancy (10–15 weeks) that takes cells from the placenta and can help to identify problems with a developing baby.

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

conditioning – when applied to transplantation it is the process by which the recipient's body and immune system are 'made ready' to accept the transplant. This is usually by supressing or removing the patient's existing immune system to allow him/her to accommodate the new graft without rejection.

cord blood/umbilical cord blood – blood that normally circulates between the baby and the placenta via the umbilical cord and remains in the cord after childbirth. It can be used as a source of cells for transplant in the same way as bone marrow – see bone marrow transplantation.

deficiency – a lack or shortage.

DNA – the chemical part of chromosomes which provides the genetic information (code).

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

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

GCSF – a colony stimulating factor that promotes the growth and development of cells (mainly those that become neutrophils) in the bone marrow. It also causes cells from the bone marrow to be released into the circulation, including stem cells used for transplantation.

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

gene therapy – a way to help cure genetic diseases by placing a normal 'healthy' gene into cells that have a faulty version of that gene.

genetic counselling – a service that provides information and advice about genetic conditions to people and their families to help with family planning.

haemolytic anaemia – a condition where the red blood cells of the body are destroyed and removed from the bloodstream by the immune system. It can result in tiredness.

haemorrhage – bleeding.

hemizygous – describes an individual who has only one member of a chromosome pair or chromosome segment rather than the usual two; refers in particular to X-linked genes in males who under usual circumstances have only one X chromosome.

HLA tissue-matched donor – a donor whose cells carry the same immune markers (HLA) as the patient/recipient. This helps ensure that their cells are not rejected during transplantation.

immune thrombocytopenic purpura– low platelets (thrombocytopenia) due to immune destruction of platelets in the circulation.

immunoglobulin replacement 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.

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.

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

leukaemia – a cancer of blood-forming cells.

live virus vaccine – vaccine that uses a weakened (or attenuated) form of a virus. Examples are the chickenpox and MMR vaccines.

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.

microthrombocytopenia – a reduction in the number and size of blood cells called platelets that are involved in clotting.

missense mutation – a pinpoint change in DNA leading to an alteration in the structure and function of proteins in the body. If the protein is sufficiently altered by a missense mutation then it can cause disease.

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.

neutrophil – a type of white blood cell found in the blood and body tissues that can take in and destroy microbes, such as bacteria and fungi.

petechiae – pinpoint, round spots that appear on the skin as a result of bleeding under the skin.

placenta – the organ attached to the lining of the womb during pregnancy. It provides the nutrition and oxygen to the growing baby.

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.

platelet – a blood cell that works to prevent bleeding in the body by producing blood clots.

prenatal genetic diagnosis – diagnostic tests that will find out if a developing baby has a genetic condition.

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.

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

splenectomy – surgical removal of the spleen.

sporadic – something that happens at random, usually with low frequency.

stem cell transplantation – the transfer of healthy cells to help cure a condition. The cells may come from bone marrow, cord blood or by apheresis of a donor treated with GCSF.

steroid – sometimes known as a corticosteroid. A type of medicine used to reduce inflammation and which affects the way the immune system works.

thrombocytopenia – any condition with low platelets.

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

X chromosome – the chromosome that helps determine whether you are male or female. A female has two X chromosomes, whereas a male has one X chromosome and a Y chromosome.

X-linked neutropenia – a condition caused by a hemizygous change in the Wiskott-Aldrich syndrome gene.

X-linked recessive pattern of inheritance – a type of inheritance where a recessive gene on the X chromosome is passed down to children. Generally boys/men display full symptoms of the condition and girls/women do not have any symptoms. This is because females have two X chromosomes and only one of them has a faulty gene. The other, unaffected X chromosome can generally compensate for the faulty gene in the first X, masking any symptoms. Males display the full symptoms because they have one X and one Y chromosome – the Y chromosome can't compensate for the recessive genes that are carried on the X chromosome.

X-linked thrombocytopenia – a blood cell disorder that results in reduced numbers of cells (platelets) that are involved with blood clotting.

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 (IPOPI), 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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