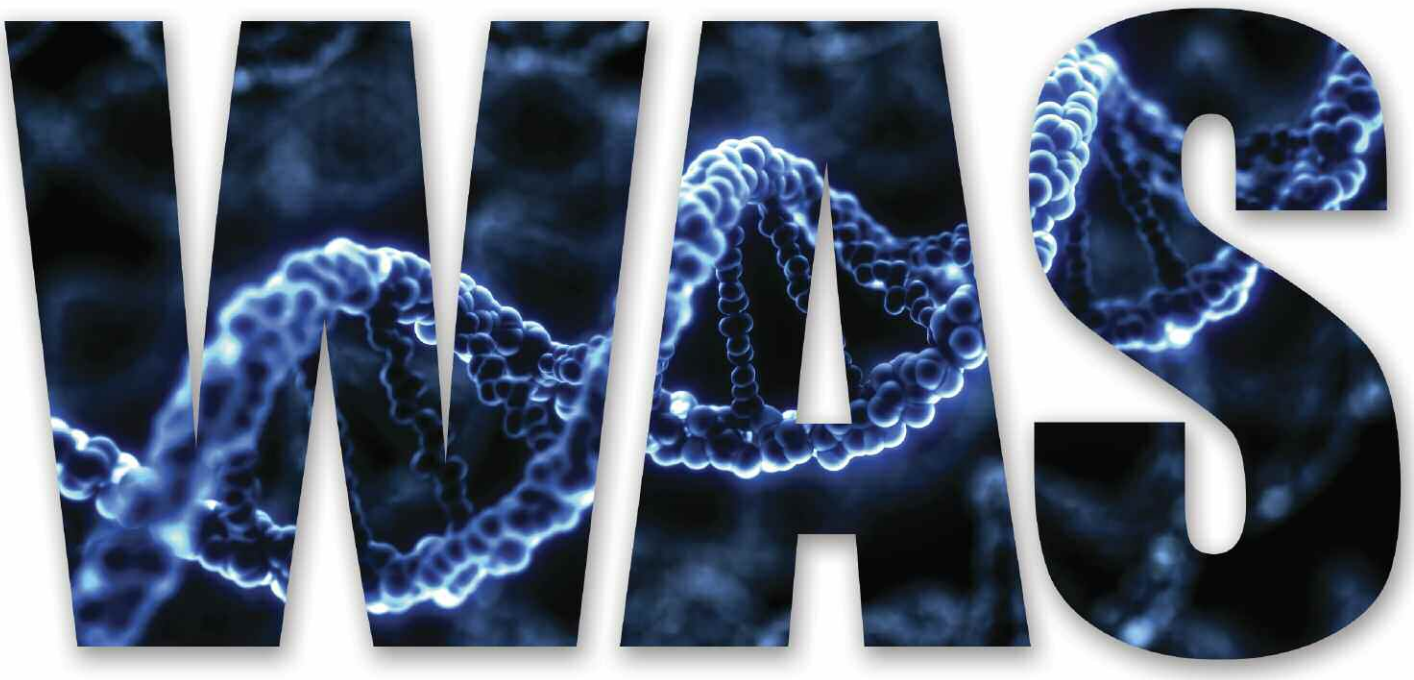
# Understanding Wiskott-Aldrich Syndrome




With advances in treatment, WAS patients gain longer life expectancy and more normal adult lives.

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**WISKOTT-ALDRICH SYNDROME** (WAS) is a rare hereditary disorder of the immune system. It is classified as a primary immunodeficiency and is present at birth, but it may be mild and go undiagnosed until childhood. It is characterized with a pattern of clinical problems that usually includes abnormal bleeding due to small size and low number of blood platelets (microthrombocytopenia), eczema of the skin, recurrent infections, a high incidence of autoimmune symptoms and cancers, particularly lymphoma.

The disorder was first described in 1937 by a German pediatrician, Dr. Alfred Wiskott. He reported a family with three brothers who all presented in infancy with symptoms of eczema, bloody diarrhea and thrombocytopenia with small platelets. The sisters of these boys had none of these conditions. Seventeen years later, an American pediatrician, Dr. Robert Aldrich, studied six generations of a family in which 16 out of 40 males all died in infancy of the symptoms described by Wiskott.[1]

## Clinical Features

Eczema, recurrent infections, bleeding tendency, autoimmunity and malignancy are the most common symptoms of WAS. Most individuals with WAS have recurrent ear, sinus and lung infections, as well as an increase in viral infections such as molluscum and warts. The WAS protein is important in the structure and function of white blood cells and their immune responses to infection. The two main types of white blood cells that are affected in WAS are T and B lymphocyte cells. T cells help defend against yeast and viral infections and some bacterial infections. T cells arise in the bone marrow and are "educated" in the thymus gland. B cells are formed in the bone marrow and work to fight infections caused by other viruses and bacteria. T cells help B cells make antibodies specific for infections. How severely the immune system is affected is variable as some boys have many more infections than others.

Individuals with WAS have frequent small purple spots on the skin (see Figure 1) from small bleeding sites under the skin called petechiae. They may also have nosebleeds, bloody bowel movements, bleeding gums and prolonged bleeding from cuts or at the time of circumcision. This occurs in WAS because the platelets are small and low in number. Platelets are blood cells that function to prevent and stop bleeding. A normal platelet count typically ranges from 150,000 to 300,000. In WAS, the platelet count is frequently much lower, around 15,000 to 50,000. The low platelet count may be the only feature or may be the dominant feature of WAS. The platelets are also extremely small in size. In a newborn or child with a low platelet count, examining the size of the platelets is important in making a diagnosis. Since aspirin may interfere with the ability of platelets to clump together in blood clotting, aspirin should be avoided in boys with severe thrombocytopenia. Serious hemorrhage into the brain is a very real danger in WAS boys and has caused deaths in boys with this syndrome. Therefore, "roughhousing" play should be restricted. To avoid being accused of child abuse, some parents always carry a letter from the doctor that identifies the child as having a bleeding disorder that causes bruises to last longer than in other children.

Typically, the skin is affected with eczema in WAS (see Figure 2). In infants, this can be seen as a "cradle cap" that is prolonged beyond infancy or as severe diaper rash. The folds of the neck, the front of the elbow and behind the knees are also areas that are frequently affected. It can also be generalized over the skin in an itchy rash. Sometimes, the itching is so intense and miserable that the boys will scratch until their skin bleeds, even when asleep. This rash can then become infected with bacteria such as Staphylococcus aureus (staph infection). As a preventative, dermatologists recommend heavy moisturizing after bathing. Steroid creams used sparingly on the skin can help inflammation, as can baths containing household bleach as an antiseptic measure. These "swimming pool" baths can be created by mixing in one-half cup of ordinary liquid bleach in a full bathtub of water, in which the patient can soak for 10 to 15 minutes followed by patting the skin dry and applying prescribed medications or moisturizers.[2]

With advances in treatment, WAS-affected boys are living longer into adulthood, and later, onset manifestations — such as autoimmunity — are being recognized. Autoimmune disorders are conditions that result from the immune system reacting against part of the patient's own body. A variety of symptoms can result such as joint swelling, new rashes, lower blood counts and kidney and bowel disease. Joint pains are mostly in the ankles, knees or hip, and sometimes are associated with swelling and/or fever. New skin rashes unrelated to eczema may appear, often associated with painful joints that can be severe enough to prevent walking. Sometimes the platelet count can decrease further because of autoimmune platelet disorder. Kidney involvement can cause nephropathy of varying severity, including renal failure, and inflammatory bowel disease can cause colitis and bloody diarrhea. Occasionally, inflammation of the arteries (vasculitis) can occur in the skin, heart, brain or elsewhere. Non-steroidal anti-inflammatory medications can help with the inflammation. These painful episodes, which may require

**Figure 1. Petechiae, small purple spots on the skin from small bleeding sites under the skin, is a symptom of WAS.**

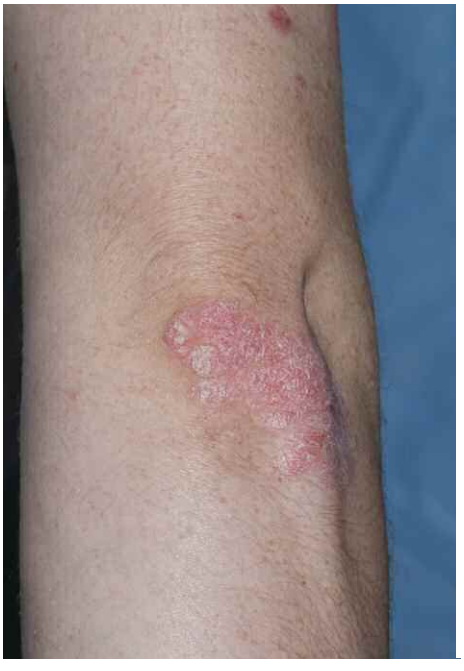

**Figure 2. Eczema, an itchy rash, can be localized in certain areas, or it can be generalized over the skin.**

hospitalization and treatment with high doses of steroids and several days of intravenous immune globulin (IVIG), can occur at any age and may last only a few days or come in waves that recur over many years.

A cancer that usually affects cells of the immune system (lymphoma) has also been seen at an increased incidence in boys and men with WAS. It has been shown that lymphoma is more likely to occur in those WAS patients who also have significant autoimmunity and less likely in those who do not have this complication.

There is a range of severity in WAS, from very mild to severe. The term for the milder presentations is "XLT," or X-linked thrombocytopenia, which is the major issue in these boys. Patients on the more severe end of the scale have extremely low platelet counts, high incidence and frequency of infection, more complications of autoimmunity and more extensive skin involvement.[3]

## Inheritance and Diagnosis

The WAS gene, identified in the early 1990s,[4] carries the information to make the protein WASp (Wiskott-Aldrich syndrome protein). Pinpointing the precise gene now allows genetic testing to look for a mutation in the WAS gene. Genetic testing, which can be done at special laboratories, should be conducted in children who have recurrent infections and small and/or low platelets. The platelet size (extremely small) is one of the best tests to confirm the diagnosis of WAS.

Gene therapy for WAS has also been used since 2006 for those severely affected by WAS, although results of these trials have been mixed.

WAS affects males almost exclusively and follows an X-linked inheritance pattern. X-linked disorders are caused by mutations (defects) in genes on the X chromosome. Families with an X-linked recessive disorder often have affected males, but rarely affected females, in each generation. A characteristic of X-linked inheritance is that affected fathers cannot pass X-linked traits to their sons (no male-to-male transmission), but their daughters will be obligate carriers. There is a one-in-four chance of a pregnancy of a carrier female resulting in a boy affected with WAS. It is possible to have two or more pregnancies in a row that result in affected boys, or for entire generations to be skipped even though the gene is present.[5] WAS is most easily diagnosed with a known family history. Frequently, there are brothers or maternal uncles or grandfathers with the family bleeding disorder.

WAS has similarities to other diseases that manifest with low platelets or recurrent infections. For example, idiopathic thrombocytopenic purpura (ITP) can be mistaken for WAS. However, the size of the platelets in ITP is normal, while WAS platelets are very small, and ITP is not associated with increased infections. Likewise, hyper IgE syndromes such as DOCK8 deficiency and Job's syndrome manifest with the similar clinical features of eczema and recurrent infections, but the platelet size and count are normal for these primary immunodeficiencies.

The presence of WAS within a family can be challenging, but many advancements in treatment have been made over the last several decades, and boys are living well into adulthood, marrying and having families of their own. There is no right or wrong decision about having children in a family affected with WAS. Parents should seek genetic counseling so they are fully aware of their options, including the possibility of pre-implantation genetic testing. The decisions about having children are highly personal and dependent upon many factors, including the basic philosophy and religious beliefs of the parents, their concept of the impact of a child's illness on their lives and the lives of the other family members, and other issues that are different for each family.

## Treatment Options

For all individuals with WAS, supportive and preventive treatment includes avoiding aggressive physical activity and sports, attention to infection prevention and skin care, and monitoring for bleeding. Bone marrow transplantation using a human leukocyte antigen (HLA)-identical matched sibling donor provides a definite cure. If no matched sibling is available, finding HLA-matched unrelated donors identified through the National Marrow Donor Program is a possibility.

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## WAS Sources

- Genetics Home Reference: ghr.nlm.nih.gov
- Genetic and Rare Diseases Information Center: rarediseases.info.nih.gov
- Immune Deficiency Foundation: www.primaryimmune.org

gene therapy, including improvements in the vectors (molecular vehicles) to carry the corrected gene into the cells to correct genetic mutation, have led to more success for more boys. The main benefit of gene therapy compared with bone marrow transplantation is that the treatment uses the boys' own cells and no rejection occurs. However, previous trials did have the serious complication of developing leukemia in some boys, who later had to undergo bone marrow transplantation.[6]

For those with less serious symptoms from WAS, preventive strategies are used to keep these children and adults as healthy as possible. Primary care doctors should establish a low threshold when looking for infections in individuals with WAS. In addition, for those with recurrent trouble with infections, prophylactic (preventive) antibiotics may be used long-term, including the use of IVIG or subcutaneous IG on a monthly or weekly basis, depending on the frequency of infections and antibody responses. Special precautions should be taken in boys with WAS to avoid receiving routine immunizations with live vaccines such as measles, mumps, rubella, chickenpox and flu nasal spray vaccine. The killed vaccine in an annual flu shot is safe to receive and should be given to family members with WAS, as well as the other household members. Similarly, healthy members of a WAS family household should receive all the standard immunizations to help prevent sharing a potentially dangerous infection to the WAS patient in the home.

Splenectomy was a treatment option used more frequently in the past to control bleeding and hemorrhage. Splenectomy results in immediate correction of thrombocytopenia, as the spleen acts as a filter of the bloodstream. The small size of platelets allows them to be trapped in the spleen during normal circulation, reducing the circulating platelets available for blood clotting. Splenectomy can also allow for a more normal active life because it reduces the risk of hemorrhage. The disadvantage of removing the spleen is that it greatly increases risk for infection and, therefore, requires lifelong prophylaxis with antibiotics and IVIG or SCIG. Splenectomy may also affect the success of subsequent bone marrow transplantation.[7]

Playing individual and team sports is a fun part of life, but individuals with WAS need to take special precautions to prevent injury. Some sports that are safe for everyone, with or without a bleeding disorder, are walking, swimming, biking, golf, fishing, frisbee and tennis. Some sports that are particularly dangerous for those with a bleeding disorder are tackle football, skiing, wrestling, soccer, hockey, basketball and baseball. WAS families should check with their hematologists for parameters of a safe range of platelet counts before joining a sport, and the WAS patient should always use protective equipment (helmet, padding, elbow and wrist guards) to lessen the chance of injury. Babies and young boys can benefit from wearing soft helmets to protect their heads from trauma. Some sources for this protective helmet are www.softtop4toddlers.com, www.danmarproducts.com and www.thudguard.com.

## A Unique Disease

As with other primary immunodeficiencies, WAS patients are at risk of infection, but the disease is distinct because it presents with low platelet count and small platelets. For the best treatment, it is important to have a multidisciplinary team that is aware of all the issues those with WAS may face. It is also essential to assemble a medical team that is aware of the latest advances in the immunology field as lifesaving therapies such as gene therapy and bone marrow transplantation are improved. ■

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