

## Chapter 11

# Wiskott-Aldrich Syndrome

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*Wiskott-Aldrich Syndrome (WAS) is unique among primary immunodeficiency diseases (PI) because, in addition to being susceptible to infections, individuals may have a bleeding problem, develop eczema, and have an increased incidence of autoimmunity and malignancies.*

*The bleeding tendency is the result of markedly reduced numbers of unusually small, dysfunctional platelets (blood cell fragments that play an important role in the formation of blood clots). These additional complications lead to unique health challenges for individuals with WAS that are not typically seen in other forms of PI. WAS is a rare X-linked genetic disorder with an estimated incidence of approximately 1 in 100,000 male live births. Milder forms of the disease that have some, but not all of the usual WAS symptoms, also exist, which can sometimes cause delays in making a correct diagnosis.*

### Clinical Presentation

WAS was first described in 1937 by Dr. Alfred Wiskott, a German pediatrician who identified three brothers with low platelet counts (thrombocytopenia) and small platelets, bloody diarrhea, skin rash (eczema), and recurrent ear infections. All three died at an early age from complications of bleeding or infection. Notably, their sisters did not have symptoms. Seventeen years later, by studying a large six-generation Dutch family with boys who had similar symptoms to the individuals described by Wiskott, Dr. Robert Aldrich, an American pediatrician, was able to clarify that the disease was passed down from generation to generation in an X-linked recessive manner. (See Inheritance Chapter.) In 1994, the gene that is defective in individuals with WAS was identified, and this discovery led to the understanding that milder forms of this disease, such as X-linked thrombocytopenia (XLT), exist and that individuals with XLT have mutations in the same gene.

In its classic form, WAS is characterized by three basic clinical features:

1. Increased tendency to bleed, caused by a significantly reduced number of very small platelets
2. Recurrent bacterial, viral, and fungal infections
3. Eczema affecting various regions of the skin

In addition to this basic triad of symptoms, individuals with WAS also have an increased risk of developing severe autoimmune diseases and have an increased incidence of malignancy (cancer), particularly lymphoma or leukemia. (See Autoimmunity in Primary Immunodeficiency Chapter.)

### Bleeding Tendency

Thrombocytopenia is a common feature of individuals with WAS. In addition to being decreased in number, the platelets themselves are small, less than half the size of normal platelets and dysfunctional. As a result, individuals with WAS may bleed easily, even if they have not had an injury. Bleeding into the skin may cause pinhead sized bluish-red spots, called petechiae, or they

may be larger and resemble bruises. Affected boys may also have bloody bowel movements (especially during infancy), bleeding gums, and prolonged nose bleeds. Hemorrhage into the brain is a dangerous complication, and some clinicians recommend that toddlers with WAS/XLT wear a helmet to protect them from head injuries. Since WAS is the only disorder where small (micro-) platelets are found, their presence is a useful diagnostic test for the disease.

## Infections

The combined immunodeficiency associated with WAS affects the function of both B and T cells. As a result, infections are common in the classic form of WAS and include bacteria, viruses and fungi. The most common infections consist of upper and lower respiratory infections, such as ear infections, sinus infections, and pneumonia. More severe bacterial infections, such as sepsis (bloodstream infection or “blood poisoning”) and meningitis (infection of the brain and spinal cord tissues), or severe viral infections, are less frequent but can occur. Occasionally, individuals with the classic form of WAS may develop pneumonia caused by the fungus *Pneumocystis jirovecii*. The skin may become infected with bacteria such as *Staphylococcus* in areas where individuals have scratched their eczema. In addition, a viral skin infection called molluscum contagiosum is commonly seen in WAS. Vaccination to prevent infections is often not effective in WAS since individuals do not make normal amounts of protective antibody responses to certain vaccines.

## Eczema

An eczema rash is common in individuals with classic WAS. In infants, the eczema may occur on the face or scalp and can resemble cradle cap. The rash can also have the appearance of a severe diaper rash, or it can be more generalized, involving the arms and legs. In older boys, eczema is often limited to the skin creases around the front of the elbows or behind the knees, behind the ears, or to the wrist. Since eczema can be extremely itchy, individuals often scratch themselves until they bleed, even while asleep. When the skin barrier is broken, the lesions serve as entry points for bacteria that can cause skin and blood stream infections.

## Autoimmune Manifestations

The term autoimmunity describes a situation in which one’s own immune system turns against itself and attacks specific cells or organs of the body. Clinical problems caused by autoimmunity are common in WAS, affecting almost half of all individuals. Among the most frequently observed autoimmune manifestations is the destruction of red blood cells by auto-reactive antibodies generated inappropriately by the dysregulated immune system. Red blood cell destruction is called autoimmune hemolytic anemia. Antibody-related platelet destruction in WAS is rare and is called idiopathic thrombocytopenic purpura (ITP). ITP, if it occurs, decreases further the platelet count and makes platelet transfusions difficult or ineffective. Another common autoimmune disorder in WAS is a type of blood vessel inflammation (vasculitis) that typically causes fever and skin rash on the extremities. Occasionally, vasculitis may affect the kidneys, muscles, heart, brain or other internal organs, which can cause a range of symptoms. Some individuals have a more generalized autoimmune disorder 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 diarrhea or colitis. Each of these autoimmune features may last only a few days or may occur in waves over a period of many years, and each may be difficult to treat.

## Malignancies

Individuals with WAS have an increased risk of malignancies (cancer) compared to unaffected individuals. Overall, it has been estimated that 15 to 20% of individuals with WAS eventually develop malignancies. Lymphomas or leukemias that arise from B cells are the most common, with Non-Hodgkin lymphoma making up the majority of cases. Malignancies can occur in young children but are more common as individuals age.

## Milder Forms of Disease

The clinical presentation of WAS varies from person to person. Some individuals have all three classic manifestations, including low platelet counts, immunodeficiency, and eczema while others have only low platelet counts and bleeding. Initially, the latter disorder was called X-linked thrombocytopenia (XLT). It was not until the gene that causes WAS was identified that it became evident that both disorders are caused by mutations in the same gene. Typically, individuals with XLT do not have

significant immunodeficiency and only few episodes of infections, but they do have an increased risk of autoimmunity and malignancy, although the risk is not as high as in classic WAS. Another very rare disorder associated with a mutation in the WAS gene causes a form of congenital neutropenia called X-linked neutropenia (XLN).

## Diagnosis

A diagnosis of Wiskott-Aldrich syndrome (WAS) should be considered in any boy who has unusual bleeding and bruises at an early age associated with thrombocytopenia. The characteristic platelet abnormalities including low numbers and small size are almost always present, even in the cord blood of newborns. The simplest and most rapid test to determine if an individual may have WAS is to obtain a platelet count and to determine the platelet size.

The immune problems typically begin to manifest themselves in toddlers and older children when individuals begin to develop frequent infections. Evaluation of the immune system typically shows that individuals are not able to make good antibody responses to certain types of vaccines, particularly those that contain polysaccharides or complex sugars, such as the vaccine against *streptococcus pneumoniae* (Pneumovax). IgE levels are usually elevated and B and T cell function is often abnormal.

A definitive diagnosis of WAS can be made by sequencing the WAS gene to identify a mutation and by studying the individual's blood cells to determine if the Wiskott-Aldrich Syndrome protein (WASp) is expressed at normal levels. These tests are done in a few specialized laboratories, and they require blood or other tissue.

## Inheritance

WAS is caused by mutations (variations) in the WASp. The WAS gene is located on the short arm of the X chromosome, so the disease is inherited in an X-linked recessive manner. (See Inheritance Chapter.) This means that boys develop the disease, but their mothers or sisters, who may carry one copy of the disease gene, do not generally have symptoms. Because of the X-linked recessive inheritance, boys with WAS may also have brothers or maternal uncles (mother's brothers) who have the disease. It is estimated that approximately 1/3 of newly diagnosed individuals with WAS have no identifiable family history and, instead, are the result of new gene mutations. Identification of the precise

gene mutation of an individual with WAS can help immunologists predict how severe their symptoms may be. In general, if the mutation is severe and interferes almost completely with the gene's ability to produce the WAS protein, the individual has 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. Identification of the mutation that causes WAS in a particular family not only allows the diagnosis of WAS in a specific individual but also makes it possible to identify females in the family who carry a mutant copy of the gene, and to perform prenatal DNA diagnosis for male pregnancies using cells obtained by amniocentesis or chorionic villus sampling.

## Treatments

### Vaccines

Because individuals with WAS have abnormal B and T cell function, they should not receive live virus vaccines since there is a possibility that a vaccine strain of the virus may cause disease. Complications of chicken pox infection occur occasionally and may be helped by early treatment following exposure with antiviral drugs, high dose immunoglobulin (Ig) replacement therapy or Varicella Zoster Immune Globulin (VZIG). Other non-live vaccinations can be given safely to individuals with WAS but may not generate protective levels of antibody.

### Infections

Since individuals with WAS have abnormal antibody responses to vaccines and to invading microorganisms, most are treated with Ig replacement therapy to prevent infections. Because of the bleeding tendency in WAS, subcutaneous immunoglobulin replacement therapy (SCIG) is used with caution, but most individuals tolerate SCIG very well. Individuals who have had a splenectomy are particularly susceptible to rapidly progressing severe bacterial blood stream infections, so Ig replacement therapy combined with prophylactic antibiotics is particularly important in these individuals. When there are symptoms of infection, a thorough search for bacterial, viral, and fungal infections is necessary to determine the most effective antimicrobial treatment.

### Bleeding Problems

Because the benefit is short-lived, preventative platelet transfusions are not recommended in WAS to increase the platelet count in an attempt to prevent bleeding episodes. In cases of active bleeding or injury especially if affecting the brain

or the gut, it may be necessary to stabilize the individual and prevent organ damage. For example, if serious bleeding cannot be stopped by usual measures, platelet transfusions are indicated. Due to constant increased blood loss, iron deficiency anemia is common among individuals with WAS, and iron supplementation is often necessary.

The spleen is an organ in the abdomen that serves as a sort of “filter” for the blood. Abnormal platelets or platelets that have been coated with autoantibodies are often trapped by the spleen where they are destroyed. For individuals with WAS, this may become a significant problem. Surgical removal of the spleen (splenectomy) has been performed in selected individuals with WAS/XLT in an attempt to correct thrombocytopenia, and in many cases, did increase platelet counts. Since the spleen also filters bacteria out of the blood stream, splenectomy significantly increases the susceptibility of individuals with WAS to blood stream infections (sepsis) and meningitis caused by encapsulated bacteria like *Streptococcus pneumoniae*, *Hemophilus influenzae*, and others. In the absence of a spleen, these infections can be rapidly fatal, so it is imperative that splenectomized individuals receive prophylactic antibiotics on a daily basis for the remainder of their lives. Splenectomy does not prevent the other features of WAS and should only be used to control particularly severe thrombocytopenia and potential lethal bleeding.

### **Eczema**

The eczema in WAS can be severe and persistent, requiring constant care. Consultation with an allergist or dermatologist is often helpful for these individuals. At a minimum, regular application of a thick moisturizing ointment, not a lotion, at least twice a day is recommended. Excessive bathing may dry the skin further and worsen the eczema. Steroid ointments should be used to control inflammation in areas that are more significantly affected, but they may thin the skin with chronic use so should be used sparingly and in consultation with an allergist or dermatologist.

### **Allergic Disease**

IgE mediated food allergy manifesting with anaphylaxis is common in WAS. Consultation with an allergist to assist in diagnosis and management of food allergies, including potential food challenges is recommended. Epinephrine should be prescribed to those with IgE mediated food allergy.

### **Autoimmune Disease**

Autoimmune complications may require treatment with drugs that further suppress the individual’s immune system. Systemic steroids (such as prednisone) are often the first immunosuppressant medication used to treat autoimmune disease and are often helpful in individuals with WAS. Since long-term use of high-dose steroid is associated with many undesired side effects, the dose should be reduced to the lowest level required to control symptoms and stopped if no longer needed. High dose Ig replacement therapy may also be beneficial in treating autoimmune disease in some cases. Rituximab, a B cell specific immunosuppressant, is effective in antibody mediated autoimmune diseases, such as autoimmune hemolytic anemia.

### **Hematopoietic Stem Cell Transplantation (HSCT)**

Until recently, before gene therapy was introduced, the only long-lasting treatment for WAS was transplantation of hematopoietic stem cells present in bone marrow, peripheral blood, or cord blood. (See Immunoglobulin Replacement Therapy and Hematopoietic Stem Cell Transplantation Chapter.) Individuals with WAS have some residual T cell and NK cell function despite having an immune deficiency, and this has the potential to cause rejection of transplanted donor cells. To prevent this, individuals must undergo conditioning, or treatment with chemotherapy drugs, to destroy their own immune cells before the donor stem cells are infused. There are four potential donor types for any transplant:

1. Matched sibling donor
2. Matched unrelated donor
3. Haploidentical donor (half-matched, typically a parent)
4. Cord blood donor

In general, the risks of transplant rejection and Graft Versus Host Disease (GVHD) are decreased when the HLA-types match between the donor and recipient are closest. In WAS, the outcomes using an HLA-identical sibling donor bone marrow are excellent with an overall success rate approaching 90%-100% in most centers. With improvements in conditioning regimens and supportive care, the outcome using cells from an HLA-matched unrelated donor approach those obtained with matched sibling donors. Transplants using fully or partially

matched cord blood stem cells have also been quite successful. Before the year 2000, transplantation with cells from a haploidentical (half-matched) donor was successful in only approximately 50% of cases. However, in more recent clinical trials, the success rate of haploidentical transplantation increased to 90% following the introduction of novel techniques to prevent graft versus host disease. There remains a slight, but significant survival advantage if transplantation is performed in individuals less than age 5. After transplant, most individuals remain on immunosuppressant medications for a short period of time in order to decrease the risk of GVHD.

### Gene Therapy

Gene therapy is an approach whereby a normal copy of the WAS gene is delivered into the individual's own bone marrow stem cells using a virus so the blood cells derived from the individual's bone marrow are then able to make normal WASp protein. (See Gene Therapy Chapter.) Since the individual's own cells are being modified, there is no risk for graft versus host disease like that observed after HSCT. The major risk of gene therapy is that the virus may insert a copy of the WAS gene randomly into one of the individual's chromosomes and cause increased production of one or more proteins that can cause cancer. Several years ago, gene therapy was used to successfully treat a small number of individuals with WAS, correcting their bleeding problems and immune deficiency. Unfortunately, most individuals participating in this trial developed leukemia as a result of the gene therapy virus inserting its DNA into a sensitive region of the individual's chromosomes. Subsequent clinical trials used new viral vectors demonstrating excellent long-term outcomes without resulting in leukemia. The success of more recent gene therapy trials for WAS is very encouraging, but a number of problems remain to be solved before it becomes more broadly applicable.

### Expectations

Thirty years ago, WAS was considered to be a fatal disorder with a life expectancy of only two to three years. Even though WAS remains a serious disease with potentially life-threatening bleeding and infectious complications, advances in Ig supplementation, antimicrobials, and other supportive care have improved quality of life and significantly prolonged the survival of individuals. In addition, improvements in HSCT protocols and the development of additional drugs to treat infectious complications have substantially improved the outcomes of HSCT to an overall survival of close to

100%. The recent success of gene therapy for WAS holds promise for being the treatment of choice for this disease in the future.

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