

Wiskott-Aldrich Syndrome



Chapter 10

Wiskott-Aldrich syndrome (WAS) is unique among primary immunodeficiency diseases because, in addition to being susceptible to infections, patients have problems with abnormal bleeding. The bleeding problems are the result of unusually small, dysfunctional platelets (blood cells that play an important role in the formation of blood clots). For patients with WAS, this leads to unique health challenges that are not typically seen in other immunodeficiency disorders. 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 of Wiskott-Aldrich Syndrome

Wiskott-Aldrich syndrome was first described in 1937 by Dr. Alfred Wiskott, a German pediatrician who identified three brothers with low platelet counts (thrombocytopenia), bloody diarrhea, skin rash (eczema) and recurrent ear infections. All three subsequently 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 patients 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 chapter titled “Inheritance.”) In 1994, the gene that is defective in patients with WAS was discovered and this subsequently led to the understanding that milder forms of disease exist that have mutations in the same gene.

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

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

In addition to this basic triad of symptoms, patients with WAS also have an increased risk of developing severe autoimmune disease and have an increased incidence of malignancy (cancer), particularly lymphoma or leukemia. (See chapter titled “Autoimmunity in Primary Immunodeficiency.”)

Bleeding Tendency

Thrombocytopenia (a reduced number of platelets) is a common feature of patients with WAS. In addition to being decreased in number, the platelets themselves are small and dysfunctional, less than half the size of normal platelets. As a result, patients 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 physicians recommend that toddlers with very low platelet counts (<15,000) wear a helmet to protect them from head injuries until treatment is able to raise their platelet count. Since WAS is the only disorder where small platelets are found, their presence is a useful diagnostic test for the disease.

(Clinical Presentation of Wiskott-Aldrich Syndrome continued)

Infections

The immunodeficiency associated with WAS causes the function of both B- and T-lymphocytes to be significantly abnormal. As a result, infections are common in the classic form of WAS and may involve all classes of microorganisms. These infections may include upper and lower respiratory infections such as ear infections, sinus infections and pneumonia. More severe infections such as sepsis (bloodstream infection or “blood poisoning”), meningitis and severe viral infections are less frequent but can occur. Occasionally, patients with the classic form of WAS may develop pneumonia caused by the fungus (*pneumocystis jiroveci carinii*). The skin may become infected with bacteria such as Staphylococcus in areas where patients have scratched their eczema. In addition, a viral skin infection called molluscum contagiosum is also commonly seen in WAS. Vaccination to prevent infections is often not effective in WAS since patients do not make normal protective antibody responses to vaccines.

Eczema

An eczema rash is common in patients with classic WAS. In infants, the eczema may occur on the face or scalp and can resemble “cradle cap.” It can also have the appearance of a severe diaper rash, or 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 around the wrist. Since eczema is extremely itchy, patients often scratch themselves until they bleed, even while asleep. These areas where the skin barrier is broken can then 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 and attacks specific cells or organs of the body. Clinical problems caused by autoimmunity are commonplace in WAS, affecting almost half of all patients. Among the most

common autoimmune manifestations observed is the destruction of red blood cells or platelets by auto-reactive antibodies generated inappropriately by the immune system. Red blood cell destruction is called hemolytic anemia and platelet destruction is called idiopathic thrombocytopenic purpura (ITP). ITP can worsen an already low platelet count.

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 muscles, heart, brain or other internal organs, which can cause a range of symptoms. Some patients have a more generalized 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. Each of these autoimmune features may last only a few days or may occur in waves over a period of many years and may be difficult to treat.

Malignancies

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

Milder Forms of Disease

The clinical presentation of WAS varies from patient to patient. Some patients have all three classic manifestations, including low platelets, 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, patients with XLT

(Clinical Presentation of Wiskott-Aldrich Syndrome continued)

do not have significant immunodeficiency but they do have an increased risk of malignancy although the risk is not as high as in WAS. Another very rare disorder

associated with a mutation in the WAS gene causes a form of neutropenia called XLN.

Diagnosis of Wiskott-Aldrich Syndrome

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

The immune problems typically begin to manifest themselves in toddlers and older children when patients begin to develop frequent infections. Evaluation of the

immune system typically shows that patients 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 T-lymphocyte function is often abnormal.

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

Inheritance of Wiskott-Aldrich Syndrome

WAS is caused by mutations (or alterations) in the WAS gene which produces the Wiskott-Aldrich Syndrome Protein (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 chapter titled "Inheritance."*) This means that boys develop the disease, but their mothers or sisters who may carry one copy of the disease gene, do not have symptoms. Because of the X-linked recessive inheritance, boys with WAS may also have brothers or maternal uncles (mom's brothers) who have the disease. It is estimated that

approximately one-third of newly diagnosed patients with WAS have no identifiable family history and instead, are the result of new gene mutations that occur at the time of conception. Identification of the precise gene mutation of a patient 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 patient 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.

(Inheritance of Wiskott-Aldrich Syndrome continued)

Identification of the mutation that causes WAS in a particular family not only allows the diagnosis of WAS in a specific patient but also makes it possible to identify females in the family that may carry a mutant copy of

the gene and to perform prenatal DNA diagnosis for any male pregnancies using cells obtained by amniocentesis or chorionic villus sampling.

Treatment of Wiskott-Aldrich Syndrome

Vaccines

Because patients with WAS have abnormal T- and B-lymphocyte 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 prevented by early treatment following exposure with antiviral drugs, high dose immunoglobulin replacement therapy or Varicella Zoster Immune Globulin (VZIG). Other “non-live” vaccinations can be given safely to patients with WAS but may not generate protective levels of antibody.

Infections

Since patients with WAS have abnormal antibody responses to vaccines and to invading microorganisms, most are treated prophylactically with immunoglobulin infusions to prevent infections. Because of the bleeding tendency in WAS, most physicians prescribe intravenous immunoglobulin (IVIG) therapy instead of subcutaneous immunoglobulin (SCIG) injections because of concern that SCIG injections may cause bleeding. Patients who have had a splenectomy are particularly susceptible to rapid, severe bacterial blood stream infections, so immunoglobulin 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

Platelet transfusions are typically not used prophylactically in WAS to increase the platelet count in an attempt to prevent bleeding episodes. In cases of active bleeding or injury however, they may be required to stabilize the patient and prevent organ damage. For example, if serious bleeding cannot be stopped by usual measures, platelet transfusions are indicated. Hemorrhages into the brain usually require immediate platelet transfusions to try and stop the bleeding. Due to increased blood loss, iron deficiency anemia is common among patients 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 in autoantibodies are often trapped by the spleen so they can be destroyed. For patients with WAS, this may become a significant problem. Surgical removal of the spleen (splenectomy) has been performed in these patients in an attempt to correct thrombocytopenia and in many cases, does improve platelet counts. It also improves the ability of high dose immunoglobulin replacement therapy to raise the platelet count. Since the spleen also filters bacteria out of the blood stream, splenectomy significantly increases the susceptibility of patients 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

(Treatment of Wiskott-Aldrich Syndrome continued)

spleen, these infections can be rapidly fatal so it is imperative that the patients receive regular prophylactic antibiotics and immunoglobulin replacement therapy for the remainder of their lives. Splenectomy does not cure the other features of WAS and should only be used to control particularly severe thrombocytopenia.

Eczema

The eczema in WAS can be severe and persistent, requiring constant care. If known food allergies exist and certain foods make the eczema worse, attempts should be made to remove these items from the diet. Excessive bathing may dry the skin further and worsen the eczema. Application of a good moisturizing cream after bathing and several times a day to areas of dry skin/eczema will make a significant difference. Lotions that contain alcohol should be avoided. Steroid ointments can be applied to control inflammation in areas that are more significantly affected, but they may thin the skin with chronic use so should be used sparingly. Stronger fluorinated steroid ointments should never be used on the face because of the risk of skin thinning.

Autoimmune Disease

Autoimmune complications may require treatment with drugs that further suppress the patient's immune system. Systemic steroids (such as prednisone) are often the first immunosuppressant medication used to treat autoimmune disease and are often helpful in patients 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. High dose immunoglobulin replacement therapy may also be beneficial in treating autoimmune disease in some cases.

Bone Marrow/Stem Cell Transplantation

Until recently, the only permanent cure for WAS was transplantation of stem cells from bone marrow, peripheral blood or cord blood. (*See chapter titled "Immunoglobulin Therapy and Other Medical Therapies for Antibody Deficiencies" and "Stem Cell Therapy and Gene Therapy."*) Patients with WAS have some residual T-lymphocyte and NK cell function despite having an immune deficiency and this has the potential to cause rejection of transplanted donor cells. To prevent this, patients must undergo some "conditioning," or treatment with chemotherapy drugs and/or total body irradiation to destroy their own immune cells, before the donor stem cells are infused. There are four potential donor types for any transplant: matched sibling donor, matched unrelated donor, haploidentical donor (half-matched, typically a parent), and cord blood donor. In general, the risks of transplant rejection and Graft Versus Host Disease (GVHD) are decreased, the more closely the HLA-types match between the donor and recipient. In WAS, the outcomes using an HLA-identical sibling donor bone marrow are excellent with an overall success (cure) rate approaching 90% 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. In contrast, transplant with cells from a haploidentical (half-matched) donor is successful in only approximately 50% of cases. After transplant, most patients remain on immunosuppressant medications for a period of time in order to decrease the risk of GVHD.

(Treatment of Wiskott-Aldrich Syndrome continued)

Gene Therapy

Gene therapy is an approach whereby a normal copy of the WAS gene is delivered into the patient's own bone marrow cells using a virus so the blood cells coming from the bone marrow are then able to make normal WASp protein. Since the patient's own cells are being modified, there is no risk for graft versus host disease like that observed after bone marrow transplantation. The major risk of gene therapy is that the virus may insert a copy of its DNA into one of the patient's chromosomes and cause abnormal production of one or more proteins that can cause cancer. Recently, gene

therapy was used to successfully treat a small number of patients with WAS, correcting their bleeding problems and immune deficiency. Unfortunately, at least one patient developed leukemia as a result of the gene therapy virus inserting its DNA into a sensitive region of the patient's chromosomes. Studies are currently underway to test new gene therapy viruses that are potentially safer and to develop alternative non-viral gene therapy methods. The initial success of gene therapy in WAS is very encouraging, but a number of problems remain to be solved before it becomes more broadly applicable.

Expectations for Patients with Wiskott-Aldrich Syndrome

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, improvements in immunoglobulin supplementation, antibiotics, and other supportive care have improved quality of life and significantly prolonged the survival of patients. In addition, improvements in bone marrow transplant protocols, the development of

additional drugs to treat infectious complications, and experience have substantially improved the outcomes of bone marrow transplantation. Indeed, follow-up of the earliest WAS bone marrow transplant recipients for more than 30 years has demonstrated that this therapy is curative. The recent success of gene therapy for WAS holds promise for being the treatment of choice for this disease in the future if the serious side effects observed in some patients can be prevented.