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Wiskott-Aldrich Syndrome

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WISKOTT-ALDRICH SYNDROME

Wiskott-Aldrich Syndrome is a primary immunodeficiency disease involving both T and B lymphocytes. In addition, the blood cells that help control bleeding, called platelets are also affected. The classic form of Wiskott-Aldrich Syndrome has a characteristic pattern of findings that include an increased tendency to bleed caused by a reduced number of platelets, recurrent bacterial, viral and fungal infections and eczema of the skin. With the identification of the gene responsible for this disorder, we now recognize that milder forms of the disease also occur that express some, but not all, of the above symptoms.

DEFINITION

In 1937, Dr. Wiskott described three brothers with low platelet counts (thrombocytopenia), bloody diarrhea, eczema and recurrent ear infections. Seventeen years later, in 1954, Dr. Aldrich demonstrated that this syndrome was inherited as an X-linked recessive trait. In the 1950s and 60s, the features of the underlying immunodeficiency were identified, and Wiskott-Aldrich syndrome joined the list of primary immunodeficiency diseases. Wiskott-Aldrich Syndrome (WAS) is a primary immunodeficiency disease involving both T and B lymphocytes. Blood cells responsible for controlling bleeding, the platelets, are also severely affected.

In its classic form, WAS has a characteristic pattern of findings that include:

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, long term observations of patients with WAS have revealed an increased incidence of malignancies, including lymphoma and leukemia, and an increased incidence of a variety of autoimmune diseases in many patients.

The WAS is caused by mutations (or mistakes) in the gene which produce a protein named in honor of the disorder, the Wiskott - Aldrich Syndrome Protein (WASP). The WASP gene is located on the short arm of the X chromosome. The majority of these mutations are "unique". This means that almost every family has its own characteristic mutation of the WASP gene. 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.

CLINICAL PRESENTATION

The clinical presentation of Wiskott-Aldrich Syndrome (WAS) varies from patient to patient. Some patients present with all three classic manifestations, including low platelets and bleeding, immunodeficiency and infection, and eczema. Other patients present just with low platelet counts (thrombocytopenia) and bleeding. In past years, the patients who presented with just low platelet counts were felt to have a different disease called X-linked thrombocytopenia (XLT). After the identification of the WAS gene, it was realized that both the WAS and X-linked thrombocytopenia are due to mutations of the same gene, and thus are different clinical forms of the same disorder. The initial clinical manifestations of WAS may be present soon after birth or develop in the first year of life. These early clinical signs are directly related to any or all of the classic clinical triad including bleeding because of the low platelet count, itchy and scaly skin rashes and eczema and/or infections because of the underlying immunodeficiency.

BLEEDING TENDENCY

A reduced number of platelets (thrombocytopenia) of small size is a characteristic hallmark of all patients with WAS. Since WAS is the only disorder where small platelets are found, their presence is a useful diagnostic test for the disease. Bleeding into the skin caused by the thrombocytopenia 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.

INFECTIONS

Due to a profound deficiency of T- and B-lymphocyte function, infections are common in classic WAS and may involve all classes of microorganisms. These infections may include upper and lower respiratory infections such as otitis media, sinusitis and pneumonia. More severe infections such as sepsis (blood stream infection or "blood poisoning"), meningitis and severe viral infections are less frequent. Infrequently, patients with classic WAS may develop pneumonia with pneumocystis jeruvesi (carinii). The skin may also become infected with various bacteria as a result of intense scratching of areas involved with eczema. A virus infection of the skin called molluscum contagiosum is also commonly seen in WAS.

ECZEMA

Eczema is commonly found in patients with classic WAS. In infants, the eczema may resemble "cradle cap", a severe diaper rash, or be generalized, occurring on the body and/or extremities. 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. Since eczema is extremely itchy (pruritic), affected boys often scratch themselves until they bleed, even while asleep. In extreme cases, the eczema may cause so much reddened skin inflammation that the boys "radiate" heat to the environment and have difficulty maintaining normal body temperature. Eczema may also be absent or mild in some patients.

AUTOIMMUNE MANIFESTATIONS

A problem observed frequently in infants, as well as adults with WAS is a high incidence of "autoimmune-like" symptoms. The word "autoimmune" describes conditions that appear to be the result of a dysregulated immune system reacting against part of the patient's own body. Among the most

common autoimmune manifestations observed in WAS patients is a type of blood vessel inflammation (vasculitis) associated with fever and skin rash on the extremities - sometimes worsened following episodes of exercise. Another autoimmune disorder is anemia caused by antibodies that destroy the patient's own red blood cells (hemolytic anemia). The low platelets can also be worsened by autoimmunity in which the patient makes antibodies to attack his remaining platelets (commonly called ITP or idiopathic thrombocytopenic purpura). 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. Occasionally, inflammation of arteries (vasculitis) occurring primarily in the muscles, heart, brain or other internal organs develops and causes a wide range of symptoms. These autoimmune episodes may last only a few days or may occur in waves over a period of many years and may be difficult to treat.

MALIGNANCIES

Malignancies can occur in young children, in adolescents and adults with WAS. Most of these malignancies involve the B lymphocytes resulting in lymphoma or leukemia.

DIAGNOSIS

Due to the wide spectrum of findings, the diagnosis of Wiskott - Aldrich Syndrome (WAS) should be considered in any boy presenting with unusual bleeding and bruises, congenital or early onset thrombocytopenia and small platelets. The characteristic platelet abnormalities, low numbers and small size, are almost always already present in the cord blood of newborns. The simplest and most useful test to diagnose WAS is to obtain a platelet count and to carefully determine the platelet size. WAS platelets are significantly smaller than normal platelets. In older children, over the age of two years, a variety of immunologic abnormalities can also be identified and used to support the diagnosis. Certain types of serum antibodies are characteristically low or absent in boys with WAS. They often have low levels of antibodies to blood group antigens (isohemagglutinins; e.g. antibodies against type A or B

red cells) and fail to produce antibodies against certain vaccines that contain polysaccharides or complex sugars such as the vaccine against streptococcus pneumonae (pneumovax). Skin tests to assess T-lymphocyte function may show a negative response and laboratory tests of T-lymphocytes function may be abnormal. The diagnosis is confirmed by demonstrating a decrease or absence of the WAS protein in blood cells or by the presence of a mutation within the WASP gene. These tests are done in a few specialized laboratories and require blood or other tissue.

INHERITANCE

WAS is inherited as an X-linked recessive disorder. Only boys are affected with this disease. Since this is an inherited disease transmitted as an X-linked recessive trait, there may be brothers or maternal uncles (the patient's mother's brother) with similar findings. It is possible that the family history may be entirely negative because of small family size or because of the occurrence of a new mutation. It is felt that about 1/3 of newly diagnosed WAS patients result from a new mutation occurring at the time of conception. If the precise mutation of WASP is known in a given family, it is possible to perform prenatal DNA diagnosis on cells obtained by amniocentesis or chorionic villus sampling.

TREATMENT

All children with serious chronic illness need the support of the parents and family. The demands on the parents of boys with WAS and the decisions they have to make may be overwhelming. Progress in nutrition and antimicrobial therapy, prophylactic use of immunoglobulin replacement therapy and bone marrow transplantation have significantly improved the life expectancy of patients with WAS. Due to increased blood loss, iron deficiency anemia is common and iron supplementation is often necessary.

When there are symptoms of infection, a thorough search for bacterial, viral and fungal infections is necessary to determine the most effective antimicrobial treatment. Since patients with WAS have abnormal antibody responses to vaccines and to invading microorganisms, the prophylactic

administration of immunoglobulin replacement therapy may be indicated for those patients who suffer from frequent bacterial infections. It should be noted that if the patient has low platelet counts, most physicians would prescribe intravenous immunoglobulin therapy because the injection of subcutaneous immunoglobulin may cause bleeding into the skin and under the skin. Immunoglobulin replacement therapy is particularly important if the patient has been treated with splenectomy.

The eczema can be severe and persistent, requiring constant care. Excessive bathing should be avoided because frequent baths can cause drying of the skin and make the eczema worse. Bath oils should be used during the bath and a moisturizing cream should be applied after bathing, and several times daily to areas of dry skin/eczema. Steroid creams applied sparingly to areas of chronic inflammation are often helpful but their overuse should be avoided. Do not use strong steroid creams, e.g. fluorinated steroids, on the face. If certain foods make the eczema worse and if known food allergies exist, attempts should be made to remove the offending food items.

Platelet transfusions may be used in some situations to treat the low platelet count and bleeding. For example, if serious bleeding cannot be stopped by conservative measures, platelet transfusions are indicated. Hemorrhages into the brain usually require immediate platelet transfusions. Surgical removal of the spleen (a lymphoid organ in the abdomen that "filters the blood") has been performed in WAS patients and has been shown to correct the low platelet count, or thrombocytopenia, in over 90% of the cases. Splenectomy does not cure the other features of WAS and should only be used to control thrombocytopenia in patients with particularly low platelet counts. The ability of high dose immunoglobulin replacement therapy to raise the platelet count in WAS boys has been shown to improve considerably once the spleen has been removed. Removal of the spleen increases the susceptibility of WAS patients to certain infections, especially infections of the blood stream and meningitis caused by encapsulated bacteria like S pneumonae or H influenzae. If splenectomy is used, it is imperative that the child be placed on prophylactic antibiotics and possibly immunoglobulin replacement therapy, potentially, for the rest of their lives to prevent these serious infections.

The symptoms of autoimmune diseases may require treatment with drugs that further suppress the patient's immune system. High dose immunoglobulin replacement therapy and systemic steroids may correct the problem and it is important that the steroid dose be reduced to the lowest level that will control symptoms as soon as possible.

As with all children with primary immunodeficiency diseases involving T-lymphocytes and/or B-lymphocytes, boys with WAS 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 Herpes Zoster Hyper Immune Serum.

The only "permanent cure" for WAS is bone marrow transplantation or cord blood stem cell transplantation and the search for an HLA-matched donor should be undertaken as soon as the diagnosis of WAS has been established. Because patients with WAS have some residual T-lymphocyte function in spite of their immunodeficiency, immunosuppressive drugs and/or total body irradiation are required to "condition" the patient before transplantation. If the affected boy has healthy siblings with the same parents, the entire family should be tissue typed to determine whether there is an HLA-identical sibling (a good tissue match) who could serve as bone marrow transplant donor. The results with HLA-identical sibling donor bone marrow transplantation in WAS are excellent with an overall success (cure) rate of 80-90%. This procedure is the treatment of choice for boys with significant clinical findings of the WAS. The decision to perform an HLA-matched sibling bone marrow transplant in patients with milder clinical forms, such as isolated thrombocytopenia, is more difficult and should be discussed with an experienced immunologist. Success with matched-unrelated donor (MUD) transplants has improved substantially over the past two decades. Fully matched-unrelated donor transplants are now almost as successful as matched sibling transplants if they are performed while the patient is under 5-6 years of age and before they have acquired a significant complication such as severe viral infections or cancer. The success rate of fully matched-unrelated donor transplants decreases with age

making the decision to transplant teenagers or adults with WAS difficult. Cord blood stem cells, fully or partially matched, have successfully been used for immune reconstitution and the correction of platelet abnormalities in a few WAS patients and may be considered if a matched sibling or fully matched unrelated donor is not available. In contrast to the excellent outcome of HLA-matched transplants, haploidentical bone marrow transplantation (the use of a parent as a donor) has been much less successful than are HLA-matched transplants.

EXPECTATIONS

Three decades ago, the classic Wiskott-Aldrich Syndrome was one of the most severe primary immunodeficiency disorders with a life expectancy of only 2-3 years. Although it remains a serious disease in which life threatening complications may occur, many affected males go through puberty and enter adulthood, live productive lives and have families of their own. The oldest bone marrow transplanted patients are now in their twenties and thirties and seem to be cured, without developing malignancies or autoimmune diseases.

NOTES

This booklet has been produced by the International Patient Organisation for Primary Immunodeficiencies (IPOPI).

Other booklets are available in this series.

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