Wiskott-Aldrich syndrome

Synonym: Wiskott-Aldrich-Huntley syndrome

This is an X-linked recessive condition with immunodeficiency as an underlying problem. An autosomal dominant form has also been described.[1] It is characterised by:[2]

- Recurrent bacterial infections of the sinuses and lungs.
- Eczema that resembles an atopic dermatitis.
- A bleeding tendency due to thrombocytopenia and platelet dysfunction.

Wiskott-Aldrich syndrome (WAS) was first described by Wiskott in Germany in 1937[3] and later by Aldrich in the USA in 1954.[4] However, descriptions of the condition go back to the 19th century.[5]

Pathophysiology

- The underlying mutation is in the gene for the Wiskott-Aldrich syndrome protein (WASP) on the X-chromosome at Xp11.22-23.[6]
- WASP is needed for normal antibody function, T-cell responses and platelet production.

Epidemiology

- The incidence of the classic syndrome is estimated to be between one and ten in one million individuals, although it is likely to be higher.[7]
- Being X-linked and potentially lethal, it would be expected almost invariably to affect males and more than 90% of affected patients are male. However, affected females have been reported.

- Affected females usually have no family history and some have been shown to have nonrandom inactivation of the X chromosome bearing the functional Wiskott-Aldrich syndrome (WAS) allele.

Presentation[6]

Presentation can be any time from birth to 25 years but most cases present in the first 2 years of life. Less than one third of affected individuals have the full triad at presentation but almost 90% present with features of thrombocytopenia. Around 5% present only with infection and 20% only with haematological problems.[8]

- Bleeding problems:
    - Petechiae and ecchymoses can occur.These may be around the oral mucosa.
    - Bloody diarrhoea is quite common.
    - There may be bleeding from the umbilical stump or after circumcision.
    - In fewer than 2% there is intracranial haemorrhage. This may happen at birth, possibly from the trauma of delivery.
- Infections:
    - These usually begin after maternal IgG declines in the first 3 months of life.
    - Pneumonia, meningitis and sinusitis are often due to *Streptococcus pneumoniae*, *Haemophilus influenzae* type b (Hib), and *Staphylococcus aureus*.
    - Opportunistic, fungal and viral infections can occur.
    - Otitis media is also very common.

- Eczema:
    - This tends to develop during the first year of life and it is clinically similar to atopic eczema.
    - However, it presents earlier than usual and may be worse during infection.
    - There may be other atopic conditions such as allergic rhinitis.
- Autoimmune disease:
    - This can occur at any age and is most often autoimmune haemolytic anaemia.
    - Renal failure can result from glomerulonephritis.
    - In a series of 55 patients from France, 40 individuals (72%) had at least 1 autoimmune or inflammatory complication. 20 cases (36%) had autoimmune haemolytic anaemia, always starting before 5 years old. Other problems were neutropenia (25%), arthritis (29%), skin vasculitis (22%), cerebral vasculitis (7%), inflammatory bowel disease (9%), and renal disease (3%).[9]
- Malignancy:
    - This may occur in children but is more common in adults.
    - Around a quarter of those over 20 years develop lymphoma.
    - Leukaemia may also occur but the most common malignancy is non-Hodgkin's lymphoma.

Differential diagnosis[2]

- Bruton's agammaglobulinaemia.
- Neonatal alloimmune thrombocytopenia.
- Atopic eczema.
- Di George's syndrome.
- Histiocytosis.

- X-linked severe combined immunodeficiency.

Investigations

- Low platelet count (≤70 x 10^9/L).[2]
- Low mean platelet volume (<5fL).
- Low IgG and IgM levels with elevated IgA and IgE (values need to be interpreted for age).
- Testing may show impairment of cell-mediated immunity.
- Autoantibodies may be detected if autoimmune disease is present, especially in autoimmune haemolytic anaemia and immune thrombocytopenia and neutropenia.
- Consider the diagnosis in boys with thrombocytopenia. Detection of the Wiskott-Aldrich syndrome protein (WASP) can facilitate the diagnosis.[10]
- Bacteriology is required to help treat infection.
- Chest X-ray may be indicated depending on infective symptoms.
- Renal and liver function should be monitored.
- Tissue typing of the patient and close family members may be indicated if stem cell transplantation is considered.
- Carrier females may have low platelet counts.[11]

Management

General

- All immunisations should be given as usual. Hib is especially important.
- Encourage normal work and school but avoid contact sports.

Medical management

- Infections will need appropriate antibiotics. Infusion of immunoglobulin may also be required.

- Bleeding may require transfusion of packed red cells and platelets. Blood should be low in white cells to reduce the risk of isoimmunisation, as a stem cell transplant may be required in the future.
- Skin disease should be treated, including treating eczema with moisturising creams and topical steroid preparations as indicated.
- If there is exposure to chickenpox, immunoglobulin or antivirals such as aciclovir are indicated. Varicella vaccine may be protective.
- In severe thrombocytopenia, splenectomy may be indicated but this also increases the risk of infection. Prophylactic antibiotics and immunisation (pneumococcal, Hib and meningococcal) are needed. [2]
- Autoimmune diseases are managed in the normal way.

Potential cure

- Stem cell transplant can offer the chance of cure. It may be successful in over 90% of cases. [2] [12]
- In the future, gene therapy may also be an option. [13]

Complications

- Recurrent infections as outlined above.
- Bleeding can be difficult to control and intracranial bleeding may occur.
- Chronic renal disease may be associated with autoimmune disease.
- Haematological malignancy, especially non-Hodgkin's lymphoma.
- Graft-versus-host disease and other complications from stem cell-transplantation.

Prognosis

- The prognosis has improved enormously over the years due to improved control of infection, transfusion services and stem cell transplantation.

- If stem cell transplantation is not carried out, individuals usually survive until their second or third decade and die from bleeding, malignancy or infection.[2]
- Successful stem cell transplantation can mean reversal to normal immune function and the potential for a normal life span.[2]
- A recent multicentre study looked at long-term outcome following stem cell transplantation in Wiskott-Aldrich syndrome (WAS). Amongst 96 patients, three patients died 2.1 to 21 years following transplantation. Overall 7-year event-free survival rate was 75%.[14]

Prenatal diagnosis

- This can detect mutations in the Wiskott-Aldrich syndrome protein (WASP) gene in those with a family history of Wiskott-Aldrich syndrome (WAS).
- It may allow planning for Caesarean section to reduce the risk of intracranial bleeding due to birth trauma.
- It may also allow planning for early stem cell transplantation, as this can improve prognosis.

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