Cancer Prone Disease Section
Short Communication

Wiskott-Aldrich Syndrome (WAS)

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Identity

Other names
Eczema-thrombocytopenia-immunodeficiency syndrome

Note
The clinical spectrum of disease also includes chronic or intermittent X-linked thrombocytopenia (XLT), a milder clinical variant; and X-linked neutropaenia (XLN) due to an arrest of myelopoiesis.

Inheritance
X-linked recessive; overall incidence is estimated to be 4.0 per million live male births, with no known ethnic or geographical predominance.

Clinics

Note
WAS is characterized by low numbers of small platelets, easy bruising and prolonged bleeding, eczema and recurrent infections. It can be complicated by autoimmunity and haematopoietic cell malignancies.

Phenotype and clinics
Clinical manifestations suggesting WAS/XLT are often present at birth and consist of petechiae, bruising, and bloody diarrhoea. Excessive haemorrhage after circumcision is an early diagnostic clue.
Infections, including purulent otitis media, pneumonia and skin infections, are common during the first 6 months of life. Infections are most often caused by bacteria and viruses such as CMV, rarely by Pneumocystis carinii. Patients with XLT have fewer problems with eczema and infections and are often misdiagnosed as having idiopathic thrombocytopenia (ITP).

Thrombocytopenia associated with small platelet volume is a consistent finding in both classical WAS and XLT and is a key diagnostic indicator. In most patients the mean platelet volume is half that of normal control subjects. Life-threatening bleeding, including severe oral bleeding, gastrointestinal bleeding, and intracranian haemorrhage, has been reported in up to 30% of patients.

Compromised humoral and cellular adaptive immunity is a hallmark of classical WAS. Common findings include mild to moderate lymphopaenia, defective T cell proliferation in response to TCR stimulation, low levels of IgM and high levels of IgA and IgE. Antigen-specific T and B cell responses, particularly to polysaccharides, are also impaired in patients with WAS. Patients with XLT by definition have minimal immunological disturbances.

Autoimmune diseases are frequent, the most common being haemolytic anaemia, thrombocytopenia, neutropaenia followed by vasculitis, renal disease, Henoch-Schonlein-like purpura, and inflammatory bowel disease. Incidence of autoimmune disease is less in XLT but has been reported to occur.

Prominent features of XLN include chronic neutropaenia and monocytopenia, although some cases have values that fall within the low-normal range. Low-normal IgA levels, low to low-normal platelet counts (normal mean platelet volume) and reduced natural killer (NK)-cell counts have been reported.

Neoplastic risk
Malignancies are more frequent in adolescents and young adults with the classic WAS phenotype. Most frequent malignancies reported are B cell lymphoma (often Epstein-Barr virus-positive) and leukaemia. Some younger patients may also present with marrow
dysplasia. In XLN there is experimental evidence of genomic instability that may predispose patients to myeloid malignancy.

**Treatment**

Classic WAS has a poor prognosis, but early treatment with haematopoietic stem cell transplant is curative in most patients. More recently, gene-modified stem cell therapy using retroviral or lentiviral vectors has become available as an alternative.

XLT and XLN, with a better prognosis, may be treated more conservatively with antibiotic prophylaxis. In XLN G-CSF should be used with caution as long term G-CSF usage may predispose to CSF3R mutations, and this is highly predictive for malignant transformation.

Intravenous immunoglobulin (IVIG) therapy is indicated in patients with a significant antibody deficiency.

Autoimmune manifestations may require immunosuppressant. Autoimmune cytopenia often responds to a monoclonal antibody targeting the CD20 antigen (rituximab).

**Prognosis**

Reported median survival in patients with WAS is age 20 years. Death results from infections, bleeding complications, autoimmune diseases, and malignancies. WAS-associated malignancies have a poor prognosis.

**Genes involved and proteins**

**WAS**

- **Location**: Xp11.23
- **DNA/RNA**: 12 exons spanning 9 kb of genomic DNA.
- **Protein**: 502 amino acids; 54 kDa; consists of an N-terminal Ena-VASP homology domain 1 (EVH1), a basic domain, a GTPase binding domain (GBD), polyproline domain and the C-terminal domain comprising of a cluster of verprolin homology (V), central (C) and acidic regions (A) (the VCA domain).
- **Expression**: WASp protein (WASp) is constitutively expressed in all haematopoietic stem-cell-derived lineages, except in mature red blood cells.

![Schematic representation of regulation of WASp activity](image)

(A) Cytosolic WASp adopts an auto-inhibited conformation in which the VCA domain is associated with the proximal GTPase binding domain (GBD). (B) Binding of the GTPase Cdc42 via a complex with Toca-1 results in disruption of the autoinhibited conformation, which releases the VCA domain and allows Arp2/3 and actin monomer binding. WASp-bound Arp2/3 complex is then able to mediate new actin polymerization, driving the assembly of a branched network of actin filaments and providing the mechanical propulsion for membrane protrusion, cell motility and cell shape changes (Bouma et al., 2009).
Schematic representation of the WASP gene, which encodes a protein with 12 exons (a) and 5 major functional domains (c). Six mutational hot spots, defined as occurring in 7 or more unrelated families (>2.5%), were identified in a cohort of 270 unrelated families with patients with WAS-XLT. Three of these mutations (168C>T;290 C=N291 G=N, and IVS6+5g>a) were consistently found in WASP-positive patients with a mild phenotype (XLT), whereas the other 3 mutations (665C>T, IVS8+1 g=n, and IVS8+1 to +6 del gtga) were predominantly WASP negative correlating with the more severe phenotype of WAS (Ochs and Thrasher, 2006).

**Localisation**
WASp is located in the cytoplasmic compartment with highest density along the cell membrane.

**Function**
WASp acts as an adaptor to bring together downstream mediators that facilitate Arp2/3-mediated actin polymerization. A lack of WASp results in cytoskeletal defects that compromise multiple aspects of normal cellular activity including proliferation, phagocytosis, immune synapse formation, adhesion and directed migration.

**Mutations**

**Geriminal**
More than 295 unique mutations have been identified. 158 unique WASP gene mutations had been identified in a cohort of 270 unrelated WAS/XLT families. The most common are missense mutations, followed by splice-site mutations, short deletions, and nonsense mutations.
Insertions, complex mutations, and large deletions are less frequent. Most deletions and insertions involve fewer than 10 nucleotides and result in frame shifting and early termination of transcription.
Amino acid substitutions are typically located in exons 1-4. Splice-site mutations occur predominantly in the downstream half of the WAS gene (introns 6-12).
Mutations affecting invariant splice sites may result in multiple splicing products, which often include small amounts of normal WASP cDNA.
Six mutational hotspots, defined as occurring in > 2.5% of the population, have been identified. Three of these hotspots represent point mutations within the coding regions, whereas the other 3 involve splice sites.

Patients who have missense or splice-site mutations may have residual protein expression and have a less severe clinical phenotype.
X-linked neutropaenia result from missense mutations in the Cdc42-binding site.

**References**


This article should be referenced as such: