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The Wiskott-Aldrich syndrome

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The Wiskott-Aldrich syndrome (WAS) is a rare X-linked disorder with variable clinical phenotypes that correlate with the type of mutations in the *WAS protein* (*WASP*) gene. WASP, a key regulator of actin polymerization in hematopoietic cells, has 5 well-defined domains that are involved in signaling, cell locomotion, and immune synapse formation. WASP facilitates the nuclear translocation of nuclear factor κB and was shown to play an important role in lymphoid development and in the maturation and function of myeloid monocytic cells. Mutations of *WASP* are located throughout the gene and either inhibit or dysregulate normal WASP function. Analysis of a large patient population demonstrates a phenotype-genotype correlation: classic WAS occurs when WASP is absent, X-linked thrombocytopenia when mutated WASP is expressed, and X-linked neutropenia when missense mutations occur in the Cdc42-binding site. The progress made in dissecting the function of WASP has provided new diagnostic possibilities and has propelled our therapeutic strategies from conservative symptomatic treatment to curative hematopoietic stem cell transplantation and toward gene therapy. (J Allergy Clin Immunol 2006;117:725-38.)

Key words: *Wiskott-Aldrich syndrome, X-linked thrombocytopenia, X-linked neutropenia, function of WASP, immune defects, scoring system, mutation analysis, mutational hotspots, genotype-phenotype correlation, hematopoietic stem cell transplantation, gene therapy*

Abbreviations used

Arp2/3:	Actin-related protein 2/3
CRIB:	Cdc42-and Rac-interactive binding
DC:	Dendritic cell
GTP:	Guanosine triphosphate
HSC:	Hematopoietic stem cell
IS:	Immune synapse
ITP:	Idiopathic thrombocytopenia
IVIG:	Intravenous immunoglobulin
NK:	Natural killer
N-WASP:	Neuronal Wiskott-Aldrich syndrome protein
PIP_2:	Phosphatidylinositol (4,5) biphosphate
WAS:	Wiskott-Aldrich syndrome
Toca-1:	Transducer of Cdc42-dependent actin assembly
WASP:	Wiskott-Aldrich syndrome protein
WIP:	Wiskott-Aldrich syndrome protein–interacting protein
XLT:	X-linked thrombocytopenia

The Wiskott-Aldrich syndrome (WAS) is an X-linked immunodeficiency disease with a characteristic clinical phenotype that includes thrombocytopenia with small platelets, eczema, recurrent infections caused by immunodeficiency, and an increased incidence of autoimmune manifestations and malignancies.[1-3] The identification of the molecular defect in 1994[4] has broadened the clinical spectrum of the syndrome to include chronic or intermittent X-linked thrombocytopenia (XLT), a relatively mild form of WAS,[5,6] and X-lined neutropenia caused by an arrest of myelopoiesis.[7] In this review we will describe the clinical presentations associated with mutations of the *WAS protein* (*WASP*) gene, the laboratory abnormalities, the known functions of WASP, and evidence for a strong genotype-phenotype correlation.

CLINICAL AND PATHOLOGIC MANIFESTATIONS

The incidence of the classic WAS phenotype has been estimated to be between 1 and 10 in 1 million individuals.[8,9] With broader awareness of the different clinical phenotypes, along with the availability of reliable diagnostic tools, the incidence might be much higher. Clinical manifestations suggesting WAS-XLT are often present at birth and consist of petechiae, bruising, and bloody diarrhea.[1] Excessive hemorrhage after circumcision is an early diagnostic sign. Eczema is a frequent

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TABLE I. Clinical phenotypes associated with mutations of the *WASP* gene

	WAS	XLT	IXLT	XLN
Phenotype				
Thrombocytopenia	+	+	(+)	−
Small platelets	+	+	+	−
Eczema	+/++/+++	−/+	−	−
Immune deficiency	+/++	−/(+)	−	−
Infections	+/++	−/(+)	−	+*
Autoimmunity and/or malignancies	Frequent	Possible	−	−
Congenital neutropenia	−	−	−	+
Disease scores	3, 4, or 5	1, 2, or (5)†	<1	0
WASP mutations	Nonsense; frame shift caused by deletions, insertions; splicing defects	Missense (exons 1-3); inframe deletions or insertions	Missense	Missense in Cdc42-binding site
WASP expression	Absent or truncated	Present, reduced quantity	Present, normal quantitiy	Present
Treatment				
IVIG	Yes	No (with exceptions)	No	No
HSCT	Yes at an early age	Might be considered if there is a sibling donor	No	?
Splenectomy	No	Might be considered‡	No	No

IXLT, Intermittent XLT; *HSCT*, hematopoietic stem cell transplantation; *XLN*, X-linked neutropenia.
*Infections typical for neutropenia.
†Patients with XLT with a score of 1 or 2 might progress to a score of 5. Incidence of autoimmunity and malignancies are less in XLT than in WAS.
‡Splenectomy results in increased platelet numbers and reduced bleeding but causes a marked increase in sepsis, requiring continuous antibiotic prophylaxis.

manifestation of classic WAS during infancy and childhood. The most consistent finding at diagnosis of both classic WAS and XLT is thrombocytopenia and small platelets. Infections, including otitis media with drainage of mucoid purulent material, pneumonia most often caused by bacteria and rarely by *Pneumocystis carinii*, and skin infections, are frequent complaints during the first 6 months of life. Patients with XLT have less problems with eczema and infections and often receive misdiagnoses of idiopathic thrombocytopenia (ITP), considerably increasing the actual age of diagnosis. X-linked neutropenia caused by missense mutations in the Cdc42-binding domain does not resemble classic WAS or XLT. To delineate these strikingly different clinical phenotypes (Table I), we have generated a simple scoring system.[10]

Defects of the immune system

The severity of the immune deficiency can vary from family to family, depending largely on the mutation and its effect on protein expression.[11,12] Both T- and B-lymphocyte functions are affected. During infancy, the number of circulating lymphocytes might be normal or moderately decreased.[13,14] By 6 years of age, lymphopenia caused by reduced T-lymphocyte numbers is a common finding in patients with classic WAS and might be due to accelerated cell death observed in patients with classic WAS, although not in those with XLT.[15,16]

The number of B cells might be normal or moderately decreased.[17] Serum IgG levels are generally within normal range, IgM levels are moderately decreased but can be normal or increased, and IgA and IgE levels are frequently increased. Antibody responses are adequate to some antigens and insufficient to others.[3,13,18] Consistent findings are low isohemagglutinin titers, markedly decreased responses to polysaccharide antigens, and low antibody titers associated with defective class-switch recombination after immunization with the T cell–dependent neoantigen bacteriophage ΦX174.[13] In a multicenter retrospective review, antibody responses to a variety of protein antigens, including diphtheria and tetanus toxoid, and conjugated *Haemophilus influenzae* B vaccine were reported to be abnormal in the majority of patients with WAS; in contrast, antibody responses to live virus vaccines were mostly normal.[3] As expected, patients with XLT were found to have a more robust response to bacteriophage ΦX174, with amplification and isotope switching that is often comparable with that seen in healthy control subjects.[19] Abnormal T-cell function is suggested by diminished but not absent lymphocyte responses to mitogens,[18] decreased proliferative responses to allogeneic cells,[13] and immobilized anti-CD3 mAb.[20] Skin test results for delayed-type hypersensitivity were abnormal in 90% of patients studied.[3] An increased incidence of *Pneumocystis carinii* pneumonia also points to a significant T-cell defect in classic WAS. Recent studies suggest that B-cell function is equally affected. EBV-transformed B lymphoblasts derived from patients with WAS have reduced levels of F-actin and defective actin polymerization,[21] and B cells from patients lacking WASP have defective cell motility (as discussed later).

WASP is also involved in innate immunity. In normal natural killer (NK) cells, WASP can easily be detected in the immunologic synapse, together with F-actin. In contrast, NK cells derived from patients with WAS lack WASP and show a markedly reduced accumulation of