Autoimmunity in Wiskott–Aldrich Syndrome: Updated Perspectives

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Abstract: Wiskott–Aldrich syndrome (WAS) is an uncommon X-linked combined-immunodeficiency disorder characterized by a triad of thrombocytopenia, eczema, and immunodeficiency. Patients with WAS are also predisposed to autoimmunity and malignancy. Autoimmune manifestations have been reported in 26%–72% of patients with WAS. Autoimmunity is an independent predictor of poor prognosis and predisposes to malignancy. Development of autoimmunity is also an early pointer of the need for hematopoietic stem-cell transplantation. In this manuscript, we have collated the published data and present a narrative review on autoimmune manifestations in WAS. A summary of currently proposed immunopathogenic mechanisms and genetic variants associated with development of autoimmunity in WAS is also included.

Keywords: thrombocytopenia, vasculitis, genetics, hematopoietic stem–cell transplant, bleeding, malignancy

Introduction

Wiskott–Aldrich syndrome (WAS) is an uncommon X-linked combined immunodeficiency disorder that has a heterogeneous clinical spectrum.1–3 Manifestations vary from a relatively milder form of the disease (intermittent X-linked thrombocytopenia [XLT]) characterized by thrombocytopenia with little or no immunodeficiency to severe WAS, with profound immunodeficiency, bleeding episodes, autoimmunity, and increased risk of malignancy.3–5 Many patients with WAS have intermediate grades of severity. It is this heterogeneity in the clinical spectrum that makes the initial diagnosis of WAS so challenging.

In a US study, WAS incidence was reported to be 3.3–5.2 per million live male births.6 National registry data on primary immunodeficiency diseases from Sweden and Switzerland estimated WAS incidence to be 3.7 and 4.1 per million live births, respectively.7,8

In 1994, almost six decades after the initial description of the condition, Derry et al identified the gene responsible for the defect:9 WAS, which comprises 12 exons and is located on the short arm of the X chromosome (Xp11.23).10 It encodes for WAS protein (WASp), a 502–amino acid cytosolic protein and a key molecule for actin-cytoskeleton polymerization.11–14 WASp is ubiquitously expressed in all nonerythroid hematopoietic cells.15 It consists of a pleckstrin homology (PH) domain and an enabledvasodilator-stimulated phosphoprotein homology (EVH1, also known as WH1) domain at the amino terminal, a short basic domain (B), a Cdc42- and Rac-interactive binding (CRIB) domain, a large proline-rich region...
WAS mutations affect actin cytoskeleton–dependent cellular processes, immunological synapse formation,16–20 cell migration, and signaling,21,22 and result in impaired functioning of WASp, causing XLT/WAS. Gain-of-function mutations WAS gene manifest as severe congenital X-linked neutropenia, which is characterized by recurrent bacterial infections, neutropenia, and monocytopenia without thrombocytopenia.23,24

The clinical course of WAS is complicated by frequent bleeding episodes, eczema, and recurrent infections. Patients with WAS are also predisposed to autoimmune manifestations and malignancies.3,4 Autoimmunity is an independent independent predictor of poor prognosis and predisposes to malignancy.25 As such, development of autoimmunity is an early indicator of the need for hematopoietic stem–cell transplantation (HSCT) in patients with XLT/WAS. Though HSCT is curative, it does not completely ameliorate the risk of later development of autoimmunity in WAS. Recent reports on the emergence of post-HSCT autoimmunity in these patients have rekindled interest in this field, and suggest the need for a better understanding of autoimmunity.26–30 Despite being one of the earliest immunodeficiency syndromes described in the literature, pathophysiological mechanisms of underlying autoimmunity in WAS are still unclear.31 This review focuses on putative pathogenetic mechanisms, genetic predisposition, and clinical manifestations of XLT/WAS with autoimmunity.

**Methods**

We carried out a literature search on PubMed, Scopus, Web of Knowledge, Google, and Google Scholar using the keywords “Wiskott Aldrich syndrome,” “autoimmunity,” “eczema,” “anemia,” “nephritis,” “arthritis,” “neutropenia,” “vasculitis,” “Wiskott Aldrich syndrome protein,” and “malignancy.” A supplementary manual search to identify additional primary studies was conducted and papers published up to December 2020 collated. Data on autoimmune manifestations were extracted from all single/multicenter cohorts and clinical case reports.

Demographic details, clinical and genetic profiles, WAS clinical scores, WASp expression, and outcomes were tabulated.

**Incidence of Autoimmune Manifestations**

One of the earliest reports of autoimmunity in WAS was published in 1976 by Gershwin et al, who evaluated patients with primary immunodeficiency diseases for the presence of autoantibodies.32 Three of eleven children with WAS had autoantibodies against nucleic acids. However, a US multicentre study of a cohort of patients with WAS made no mention of autoimmunity.6
In 1994, Sullivan et al reported autoimmune manifestations in 40% of patients with WAS. The study highlighted autoimmunity to be a risk factor of the development of malignancy. Since then, autoimmunity has been a well-recognized entity in patients with WAS and an important indicator in predicting clinical outcomes and prognoses. Subsequently, several studies from different centers have reported variable figures (26%–72%) for the occurrence of autoimmune manifestations in patients with WAS (Table 1).

Proposed Mechanisms of Autoimmunity

WASp is involved in cytoskeleton remodeling, and absence of or residual WASp-expression defects cause functional defects in all immune-system cells. Formation of immunological synapses in T cells and T-cell receptor (TCR)-dependent activation is impaired in WAS. Reduced cytotoxic activity of T cells, natural killer cells, and naturally occurring regulatory T (nTreg) cells contributes to poor pathogen clearance. Motility, adhesion, and migration of B cells is also defective. However, underlying mechanisms for occurrence of autoimmune manifestations are still not completely understood. Some hypotheses currently proposed for development of autoimmunity in WAS are summarized in the following sections.

Role of T Cells in Autoimmunity in WAS

Autoimmunity is caused by failure in self-tolerance mechanisms. Treg cells play a pivotal role in immunotolerance and prevent autoimmunity. They prevent autoimmunity by maintaining tolerance to self-antigens and suppression of excessive immune response. Development and function of Treg cells requires effective TCR signaling with involvement of the CD28 costimulator, expression of master regulator FOXP3, and growth maintenance by IL2. Although peripheral blood Treg-cell numbers have been found to be comparable in patients with WAS and healthy controls, WASp-deficient Treg cells demonstrated impaired ability to suppress proliferation of activated T-effector cells. Distribution and phenotype of nTreg cells have also been found to be normal in the thymi and spleens of WASp-deficient mice. nTreg cells, however, have been found to be reduced in inflamed peripheral tissue and lymph nodes. Reduction in nTreg cells correlates with lack of tissue-homing markers like integrin αβ7, chemokine receptor CCR4, and P- and E-selectin ligands.

A mouse model of autoimmunity has failed to control aberrant T-cell activation by WASp-deficient nTreg cells. WASp-deficient nTreg cells fail to suppress B-cell activation and proliferation. Defective granzyme-mediated B-cell killing by nTreg cells has been demonstrated in some studies.

Role of B Cells in Autoimmunity in WAS

The role of B cells and autoantibodies in the pathogenesis of autoimmune diseases like lupus is well recognized. B-cell dysfunction in patients with WAS is evident from the variable distribution of serum immunoglobulins and demonstration of autoantibodies. Classically, WAS is associated with low serum IgM, normal IgG, and elevated IgE and IgA levels. Patients have impaired response to polysaccharides and other T-cell-independent antigens.

Elevated IgM levels correlate with development of autoimmunity. Around 90% of patients with elevated IgM levels have been found to have developed AIHA in comparison to none with low IgM.

WASp deficiency affects adhesion, motility, and homing of B cells. Defective B-cell function results in insufficient pathogen clearance, chronic immunoactivation, and failure of peripheral B-cell tolerance. In addition, reduced surface expression of complement receptors CD21 (CR2) and CD35 (CR1) results in impaired opsonization and negative selection of self-reactive B cells, thereby breaking peripheral tolerance and helping in autoantibody production.

Murine WASp-deficient B cells demonstrate increased proliferation with autoantibody production and differentiation into plasmablasts. Enhanced proliferation of transitional B cells in response to stimulation by antigen or MYD88 has been seen in both humans and mice.

Breg cells influence the balance and recruitment of Treg cells and Th17 cells during inflammation. Recent studies have suggested that WASp is required for normal Breg-cell numbers and functions. Murine studies have also revealed reduced levels of IL10 secreting Breg cells (B10) in patients with WAS.

Bouma et al found reduced numbers of IL10-producing Breg cells, reduced Treg cells, and increased Th17 cells in arthritic WAS-knockout mice. Adoptive transfer of wild-type Breg cells ameliorated arthritis and restored the balance between Treg and Th17 cells.

Role of Invariant NKT Cells in Autoimmunity in WAS

Invariant NKT cells possess properties of both T and NK cells. They prevent autoimmunity by limiting development of Th17 cells, anti-DNA antibody production, and
Table 1 Frequency of autoimmune manifestations reported in large cohorts of XLT/WAS

| Study                  | Patients, n | Patients with autoimmunity, n (%) | AIHA, n (%) | Autoimmune thrombocytopenia, n (%) | Neutropenia, n (%) | Vasculitis, n (%) | Arthritis, n (%) | Renal disease, n (%) | IBD, n (%) | Alopecia, n (%) | Other, n (%) |
|------------------------|-------------|-----------------------------------|-------------|------------------------------------|--------------------|-------------------|-------------------|---------------------|------------|----------------|---------------|
| Sullivan et al25        | 154         | 61 (40)                           | 22 (14)     | –                                  | 4 (2.5)            | 30 (19.4)         | 32 (21)           | Renal disease 18 (12), IgAN 5, CRF 2 | 5 (3)     | 1 (10.6)       |               |
| Dupuis-Girod et al13    | 55          | 40 (72)                           | 20 (36)     | 18 (32.7)                          | 14 (25)            | 16 (29)           | 16 (29)           | –                   | 5 (9)       | –              |               |
| Imai et al24            | 50          | 12 (24)                           | 3 (6)       | –                                  | –                   | 4 (8)             | 3 (6)             | IgAN 5 (10), CRF 2 (4) | 2 (4)       | 1 (1.8)        |               |
| Lee et al25             | 35          | 12 (34.2)                         | 6 (17.1)    | –                                  | –                   | –                 | –                 | –                   | –          | –              |               |
| Albert et al16          | 173 (XLT)   | 21 (12), 26 events                | 6/26 events (23) | ITP: 4/26 events (15) | –                   | 3/26 events (11.5) | 3/26 events, 11.5 | Nephropathy 9/26 (35) | 1 (3.8)     | 1 (3.8)        |               |
| Shin et al28            | 47          | 15 (32)                           | –           | –                                  | –                   | –                 | –                 | –                   | –          | –              |               |
| Chen et al29            | 53          | 14 (26.4)                         | 12 (22.6), DCT* 12 (22.6), ICT* 6 (11.3) | 1 (1.8)           | 1 (1.8)           | –                 | 1 (1.8)           | Probable IgAN 1 (1.8) | –          | –              | ANA* 3 (5.6), antplatelet IgG 1 (1.8) |
| Elfeky et al27          | 34          | 15 (44)                           | 9 (26.4)    | 4 (11.7)                           | –                   | 2 (5.8)           | –                 | –                   | –          | –              |               |
| Jin et al28             | 42          | 15 (32)                           | –           | –                                  | –                   | –                 | –                 | –                   | –          | –              |               |
| Burroughs et al30       | 129         | 32 (25)                           | 10 (8)      | 19 (15)                            | 7 (5)              | 2 (2)             | 1 (1)             | Nephritis 1 (1) | 2 (2)       | 1 (1)          |               |
| Haskologlu et al39      | 23          | 3 (9)                             | –           | –                                  | –                   | –                 | –                 | –                   | –          | –              |               |
| Suri et al40            | 95          | 38 (40)                           | AIHA 9 (9.5), DCT* 9 (9.5) | –                   | –                  | –                 | Skin vasculitis 9 (9.5), Takayasu arteritis 1 (1) | –          | –              | –              | ANA* 9 (9.5), GBS 1 (1.1), ALPS-like 1 (1.1) |

Notes: *Recurrent angioedema 2 (1.2%); uveitis 3 (1.9%); dermatomyositis 1 (0.6%); autoimmune hepatitis1 (0.6%); pyoderma gangrenosum 1 (0.6%); erythema nodosum 1 (0.6%); cardiac vasculitis 1 (0.6%).

Abbreviations: AIHA, autoimmune hemolytic anemia; IBD, inflammatory bowel disease; CRF, chronic renal failure; ITP, immune thrombocytopenic purpura; IgAN, IgA nephropathy; MPGN, membranoproliferative glomerulonephritis; DCT, direct Coombs test; ICT, indirect Coombs test; ANA, antinuclear antibody; GBS, Guillain–Barré syndrome; ALPS, autoimmune lymphoproliferative syndrome.
autoreactive B-cell production. Reduced numbers, defective invariant NKT cells, and increased IFNγ production have been reported in WASp-deficient mice.

Role of IFN1 in Autoimmunity in WAS

Plasmacytoid dendritic cells (pDCs) are specific subsets that produce IFN1 in response to foreign nucleic acids. Viral infections and certain self-nucleic acids serve as stimulants of TLR7 and TLR9 and keep them persistently activated. Susceptibility to viral infections, impaired clearance, and exposure of self-antigens following cell death activate the IFN1 pathway. This pathogenic mechanism is associated with several autoimmune diseases, such as lupus, Sjögren’s syndrome, and psoriasis.

WASp deficiency leads to exaggerated activation of TLR9 by its ligand and subsequent increased IFN1 signature. WASp-deficient mice show persistent activation of pDCs and elevated IFN1 levels. Ablation of IFN1 in WASp-deficient mice results in blockade of chronic activation of pDCs. This is accompanied by remission of colitis and reduction in spleen size.

Defects in Apoptosis Pathway and Development of Autoimmunity in WAS

Restimulation-induced cell death is a process that augments Fas-mediated apoptosis of activated T cells. It helps eliminate T cells that are activated against chronically expressed antigens like autoantigens. Nikolov et al demonstrated defective FasL in WASp-deficient mice leading to defective elimination of activated T cells and predisposition to autoimmunity. Defective Fas has also been hypothesized to be a pathophysiological mechanism for lymphoproliferative lupus–like syndrome in Fas/FasL-negative mice.

Role of Inflammasomes in Autoimmunity in WAS

Excessive inflammasome activation has been shown in human monocytes and mouse DCs. Some autoimmune manifestations (especially rash and arthralgias) are related to excessive NLRP3-inflammasome activation.

Correlation of Genetic Variants with Autoimmunity

We compiled details of genetic variants reported in the literature in patients with WAS and autoimmune manifestations. In sum, 166 variants were associated with autoimmunity in 197 WAS patients (Table 2, Figure 2). These included 143 exonic (136 well-defined) and 23 intronic variants. Exonic variants were located at 83 amino acid positions. Most variants were found in the PH and EVH1 domains (n=84, 50.6%) followed by the PRR domain (n=20, 12.2%), VCA domain (n=9, 5.5%), and B and CRIB domains (n=4, 2.4%). The variants described included missense (56), deletions (50, 41 exonic and nine intronic), nonsense (27), splice-site (25), insertions (7), unknown frameshift (five), and complex (four).

Deletions are spread across the gene, while most missense variants are seen in the PH and EVH1 domains. Missense variants (p.T45M and p.T45K) at position 45 in PH and EVH1 have been found to be associated with autoimmunity. Normal/absent WASp expression was found such patients. Twelve patients with missense variants at position 86 (R86G, R86C, R86H and R86A) developed autoimmunity. Both p.E31K and p.E133K were reported in five patients each that developed autoimmunity.

Patients with XLT can progress to autoimmune WAS. The XLT phenotype with missense variants in PH and EVH1 is most associated with development of autoimmune WAS. Albert et al identified 13 positions associated with XLT to autoimmune WAS progressions, 9 of which lie in PH and EVH1 domain.

Patients with XLT can also develop autoimmunity. Albert et al identified 13 amino acid positions that were prone to progress to autoimmune WAS.

We identified 18 variants in 25 patients reported to demonstrate progression of XLT to autoimmune WAS. Of these, 13 (all missense) were located in PH and EVH1.

Clinical Manifestations

Autoimmune Hemolytic Anemia (AIHA)

AIHA is the commonest autoimmune manifestation seen in patients with WAS, accounting for 30%–85% of all autoimmune manifestations. The reported frequency of AIHA is 8%–36%. The mean age of development of AIHA was 13.7–17.5 (1–58) months in two studies (Table 3). All patients had AIHA onset aged <5 years. The commonest clinical presentations of AIHA include anemia, jaundice, and hepatosplenomegaly. Positive antinuclear antibodies have been demonstrated in 5%–9% of patients with AIHA, while Coombs tests were positive in some patients.
| Sr number | Amino acid position | Domain | Type of variant | Variant | Patients, n | WASp expression | WAS clinical score | Autoimmune manifestations | Study |
|-----------|---------------------|--------|-----------------|---------|-------------|-----------------|---------------------|---------------------------|-------|
| 1         | 8                   | PH     | Deletion G      | Exon 1, p.G8fs44* | 1           | Absent         | 5                   |                           | Jin et al⁶⁸         |
| 2         | 13                  |        | Nonsense        | Exon 1, p.R13*    | 1           | Absent         | 5                   | Leukocytodlastic vasculitis | Jin et al⁶⁸         |
|           |                     |        |                 |                      | 1           | Absent         | 5                   | Gastroesophageal reflux with food and drug allergy; developmental delay | Suri et al⁶⁹     |
| 3         | 16                  |        | Deletion ACCA   | Exon 1, p. P16Rfs44* | 1           | Absent         | 5                   | EBV-associated lymphoproliferative disorder | Lee et al⁷⁰      |
| 4         | 24                  |        | Missense        | Exon 1, p.S24F     | 1           | Reduced        | 2 to 5A             |                           | Albert et al³⁶      |
|           |                     |        |                 |                      | 1           | Normal         | 5A                   |                           | Imai et al³⁴       |
|           |                     |        |                 | Exon 1, p.S24P     | 1           |                | 5                   |                           | Jin et al³⁸        |
| 5         | 28                  |        | Deletion C      | Exon 1, p.H30del   | 1           | Absent         | 5                   | Colitis; vasculitis; arthritis; lymphadenitis | Braun et al⁷¹     |
| 6         | 30                  |        | Deletion 3nt    | Exon 1, p.F36fs4*  | 1           |                | 5                   |                           |                   |
|           | (inframe)            |        |                 | Exon 1, p.E31K     | 1           | Absent         | 2 to 5A             |                           | Albert et al³⁶      |
| 7         | 31                  |        | Missense        | Exon 1, p.E31K     | 1           |                | 5A                  |                           | Braun et al³⁷      |
|           |                     |        |                 |                      |              |                |                     | Colitis                   |                   |
|           |                     |        |                 |                      |              |                |                     | 2 nd; reduced             | Suri et al⁶⁵       |
|           |                     |        |                 |                      |              |                |                     | Leukocytodlastic vasculitis; Lupus band test positive; AIHA |                   |
|           |                     |        |                 |                      |              |                |                     |                           |                   |
| 8         | 34                  |        | Nonsense        | Exon 1, p.R34*     | 1           | ND             | 5A                  | Vasculitis                | Mahlaoui et al⁶⁶   |
|           |                     |        |                 |                      |              |                |                     |                           | Jin et al³⁸        |
|           |                     |        |                 |                      |              |                |                     | Hypothyroidism            | Suri et al⁶⁵       |
|           |                     |        |                 |                      |              |                |                     | Posttransplant autoimmunity | Bouma et al³⁷     |
|           |                     |        |                 |                      |              |                |                     |                           |                   |
| 9         | 36                  |        | Deletion TT     | Exon 1, p.F36fs36* | 3           | Absent         | 5                   | IBD                       | Jin et al³⁸        |
| No. | 39 | PH and EVH1 | Missense | Exon | Mutation | Severity | Associated Features | Authors |
|-----|----|------------|---------|-----|----------|----------|---------------------|---------|
| 10  | PH and EVH1 | Missense | Exon 1, p.L39P | 1 | Reduced | 1 to 5A/M | 1/2 to 5A Vascitis; arthritis; anti-smooth muscle and other autoantibody-positive | Albert et al |
|    |     |       |         |     |         | 1        |                      | Crestani et al |
|    |     |       |         |     |         | 1        |                      | Suri et al |
| 12  | Nonsense | Exon 1, p.R41* | 1 | Reduced | 5A | AIHA; leukocytoclastic vasculitis; primary sclerosing cholangitis | Crestani et al |
|    |     |       |         |     |         | 1        |                      | Suri et al |
|    |     |       |         |     |         | 1        |                      | Vignesh et al |
| 13  | Missense | Exon 2, p.T45M | 3 | Reduced (2) and absent (1) | 1 to 5A, 2 to 5A (2) | 1/2 to 5A Vascitis; ANA, ANCA, anti-smooth muscle and other autoantibody-positive | Albert et al |
|    |     |       |         |     |         | 1        |                      | Imai et al |
|    |     |       |         |     |         | 1        |                      | Wu et al |
|    |     |       |         |     |         | 1        |                      | Liu et al |
|    |     |       |         |     |         | 1        |                      | Lee et al |
| 14  | Missense | Exon 2, p.T481 | 5 | 5A | AIHA, neutropenia | 1/2 to 5A Vascitis; ANA, ANCA, anti-smooth muscle and other autoantibody-positive | Crestani et al |
|    |     |       |         |     |         | 1        |                      | Haskoloğlu et al |
| 15  | Missense | Exon 2, p.A56V | 1 | Reduced | 1 to 5A | HSP; ulcerative colitis; leukocytoclastic vasculitis; amyloidosis; AIT; HSP with IgA nephropathy (2) | Albert et al |
|    |     |       |         |     |         | 1        |                      | Albert et al |
| 16  | Missense | Exon 2, p.S58A | 1 | Reduced | 2 to 5A | AIHA; Coombs-positive; IBD; vasculitis, ANA-positive, multiple autoantibody-positive | Albert et al |
|    |     |       |         |     |         | 1        |                      | Jin et al |
| 17  | Deletion C | Exon 2, p.S58fs75* | 1 | ND | 5 |          |                  |                          |
| 18  | Deletion T | Exon 2, p.W64R | 1 | 5 | AIHA; Coombs-positive; IBD; vasculitis, ANA-positive, multiple autoantibody-positive | Crestani et al |

(Continued)
| Sr number | Amino acid position | Domain                  | Type of variant                          | Variant                          | Patients, n | WASp expression | WAS clinical score | Autoimmune manifestations                                      | Study                  |
|-----------|---------------------|-------------------------|------------------------------------------|-----------------------------------|-------------|-----------------|-------------------|---------------------------------------------------------------|------------------------|
| 19        | 67                  | Frameshift              | Exon 2, p.E67Efs_\*                     | 1                                 | ND          | 5A              | IBD               |                                                               | Crestani et al\textsuperscript{119} |
| 20        | 68                  | Deletion of 4aa and frameshift | Exon 2, p. H68fs72\*                  | 1                                 | Absent      | 5               |                   |                                                               | Jin et al\textsuperscript{68} |
| 21        | 70                  | Deletion of 6nt inframe | Exon 2, p.70_71GAdel                     | 1                                 | Absent      | 5A              | AIHA              |                                                               | Mahlaoui et al\textsuperscript{96} |
| 22        | 73                  | Missense                | Exon 2, p.C73Y                          | 1                                 | ND          | 5A              | AIHA              |                                                               | Mahlaoui et al\textsuperscript{96} |
|           |                     |                         | Exon 2, p.C73Y                          | 1                                 | Reduced     | 5A              | AIHA; DCT-positive |                                                               | Suri et al\textsuperscript{10} |
| 23        | 75                  | Missense                | Exon 2, p.V75M                          | 2                                 | Reduced; 5A | 1 to 5A, 2 to 5A | Renal failure     |                                                               | Albert et al\textsuperscript{26} |
| 24        | 76                  | Deletion A              | Exon 2, p. K76Rfs126\*                  | 1                                 | Absent      | 5A              |                   |                                                               | Imai et al\textsuperscript{14} |
| 25        | 82                  | Missense                | Exon 2, p.S82P                          | 1                                 | 5            |                  |                   | Renal failure                                               | Kolluri et al\textsuperscript{72} |
| 26        | 85                  | Missense                | Exon 2, p.I85H                          | 1                                 | 5A          |                  | Severe thrombocytopenia; severe eczema |                                                               | Boztug et al\textsuperscript{77} |
| 27        | 86                  | Missense                | Exon 2, p.R86G, p. R86C, p.R86H         | 1, 3                              | Reduced; 5A | 2 to 5A, 2 to 5A | AIHA; colitis; severe eczema; vasculitis |                                                               | Albert et al\textsuperscript{26} |
|           |                     |                         | Exon 2, p.R86H                          | 1                                 | 5A          |                  | AIHA; colitis; severe eczema; vasculitis |                                                               | Braun et al\textsuperscript{71} |
|           |                     |                         | 1                                      | Normal                            | 5A          |                  | AIT               |                                                               | Abina et al\textsuperscript{178} |
|           |                     |                         | 3                                      | ND (2) reduced                    | 5A; 5A      |                  | Leukocytodlastic vasculitis; AIHA; DCT-positive |                                                               | Suri et al\textsuperscript{49} |
|           |                     |                         | Exon 2, p.R86C                          | 1                                 | 5A          |                  | AIT               |                                                               | Buchbinder et al\textsuperscript{179} |
|           |                     |                         | 1                                      | 5A                                |             |                  |                  |                                                               | Pala et al\textsuperscript{80} |
|           |                     |                         | Exon 2, p.R86A                          | 1                                 | 5A          |                  |                  |                                                               | Amarinthukrowh et al\textsuperscript{81} |
| Exon | Missense                | Frame shift | Deletion C | Deletion T | Deletion TTC | Missense       | Missense       | Missense       | Missense       | Missense       |
|------|-------------------------|-------------|------------|------------|--------------|----------------|----------------|----------------|----------------|----------------|----------------|
| 28   | Exon 2, p.Y88C          | 1           | Absent     | Absent     | Reduced      | Exon 3, p.Y107S| Exon 3, p.Y107C| Exon 3, p.Y114I| Exon 4, p.Y114M| Exon 4, p.Y116P|
| 29   | Exon 3, p.Q91A          | 1           | Absent     | Absent     | Reduced      | Exon 3, p.Q91X| Exon 3, p.Q91X| Exon 3, p.Q91X| Exon 3, p.Q91X| Exon 3, p.Q91X|
| 30   | Exon 3, p.W97C          | 1           | Absent     | Absent     | Reduced      | Exon 3, p.W97C| Exon 3, p.W97C| Exon 3, p.W97C| Exon 3, p.W97C| Exon 3, p.W97C|
| 31   | Exon 3, p.Q99X          | 1           | Absent     | Absent     | Reduced      | Exon 3, p.V107S| Exon 3, p.V107C| Exon 3, p.V114I| Exon 4, p.V114M| Exon 4, p.V116P|
| 32   | Exon 3, p.Y107S         | 1           | Absent     | Absent     | Reduced      | Exon 3, p.Y107C| Exon 3, p.Y107C| Exon 3, p.Y114I| Exon 4, p.Y114M| Exon 4, p.Y116P|
| 33   | Exon 3, p.Y114I         | 1           | Absent     | Absent     | Reduced      | Exon 3, p.Y107C| Exon 3, p.Y107C| Exon 3, p.Y114I| Exon 4, p.Y114M| Exon 4, p.Y116P|
| 34   | Exon 3, p.V114I         | 1           | Absent     | Absent     | Reduced      | Exon 3, p.Y107C| Exon 3, p.Y107C| Exon 3, p.Y114I| Exon 4, p.Y114M| Exon 4, p.Y116P|
| 35   | Exon 4, p.Y114M         | 1           | Absent     | Absent     | Reduced      | Exon 3, p.Y107C| Exon 3, p.Y107C| Exon 3, p.Y114I| Exon 4, p.Y114M| Exon 4, p.Y116P|
| 36   | Exon 4, p.Y116P         | 1           | Absent     | Absent     | Reduced      | Exon 3, p.Y107C| Exon 3, p.Y107C| Exon 3, p.Y114I| Exon 4, p.Y114M| Exon 4, p.Y116P|
| 37   | Exon 4, p.Y126P         | 1           | Absent     | Absent     | Reduced      | Exon 3, p.Y107C| Exon 3, p.Y107C| Exon 3, p.Y114I| Exon 4, p.Y114M| Exon 4, p.Y116P|
| 38   | Exon 4, p.F128L         | 2           | Absent     | Absent     | Absent       | Exon 3, p.Y107C| Exon 3, p.Y107C| Exon 3, p.Y114I| Exon 4, p.Y114M| Exon 4, p.Y116P|
| 39   | Exon 4, p.F128L         | 2           | Absent     | Absent     | Absent       | Exon 3, p.Y107C| Exon 3, p.Y107C| Exon 3, p.Y114I| Exon 4, p.Y114M| Exon 4, p.Y116P|

(Continued)
Table 2 (Continued).

| Sr number | Amino acid position | Domain | Type of variant | Variant | Patients, n | WASp expression | WAS clinical score | Autoimmune manifestations | Study |
|-----------|---------------------|--------|----------------|---------|-------------|----------------|----------------------|--------------------------|-------|
| 40        | 131                 |        | Complex missense | Exon 4, p.E131K | 1           | Absent         | 5                    |                          | Jin et al<sup>66</sup> |
|           |                     |        | Missense        | Exon 4, p.E131K | 1           | 5A             |                      |                          | Derry et al<sup>9</sup> |
| 41        | 132                 |        | Deletion of 6nt | Exon 4, p.132_133DEdel | 1           | Absent         | 5A/M                | AIHA; malignancy         | Mahlaoui et al<sup>96</sup> |
| 42        | 133                 |        | Missense        | Exon 4, p.E133K | 1           | ND             | 5                    |                          | Jin et al<sup>66</sup> |
|           |                     |        |                 |                     | 1           | Absent         | 5A                   |                          | Liu et al<sup>76</sup>  |
|           |                     |        |                 |                     | 1           | 5A             | Colitis; vasculitis   |                          | Marangoni et al<sup>85</sup> |
|           |                     |        |                 |                     | 1           | 5A             | AIHA; Colitis         |                          | Braun et al<sup>71</sup> |
|           |                     |        |                 |                     | 1           | 5A             | AIHA; IBD; eosinophilic gastritis; multiple food allergies |                          | Glanzmann et al<sup>86</sup> |
| 43        | 134                 |        | Missense        | Exon 4, p.A134V   | 1           | Affected       | 5A                   | Recurrent arthritis; renal disease | Abina et al<sup>78</sup> |
|           |                     |        | Missense        | Exon 4, p.A134T   | 1           | 5A             | Colitis              |                          | Braun et al<sup>71</sup> |
| 44        | 151                 |        | Deletion AG     | Exon 4, p.R151fs167<sup>a</sup> | 1           | Absent         | 5                    |                          | Jin et al<sup>66</sup> |
|           |                     |        | Missense        | Exon 4, p.R151T   | 1           | 5A             | Colitis              |                          | Braun et al<sup>71</sup> |
| 45        | 162                 | SH3    | Insertion C     | Exon 5, p.P162Tfs<sup>a</sup>168 | 3           | Absent (1)     | 5 (3)                |                          | Jin et al<sup>66</sup> |
| 46        | 179                 |        | Deletion T      | Exon 6, p.L179fs260<sup>a</sup> | 1           | 5               |                      |                          | Jin et al<sup>66</sup> |
|           |                     |        | Deletion T      | Exon 6, p.L179fs260<sup>a</sup> | 1           | 5A              | Vasculitis; arthritis; IgA nephropathy |                          | Marangoni et al<sup>85</sup> |
| 47        | 187                 |        | Missense        | Exon 7, p.G187C   | 1           | 5A             |                      |                          | Derry et al<sup>9</sup>  |
| 48 | 190 | Splice-site substitution IVS6 variant | c.559+5G>A | 2 | Reduced and absent | 2 to 5A (2) | Albert et al[36] |
|---|---|---|---|---|---|---|---|
| 49 | 210 | Splice-site substitution IVS6 Variant | c.559+5G>A | 1 | Normal | 5A | Imai et al[34] |
| 50 | 211 | Deletion T | Exon 7, p. S210fs260* | 1 | Normal | 5A | Pancytopenia | Abina et al[78] |
| 51 | 218 | Nonsense | Exon 7, p.R211* | 1 | ND | 5A | Leukocytoclastic vasculitis; Hypothyroidism | Suri et al[10] |
| 52 | 224 | Insertion CGCA | Exon 7, p. P218fs222* | 1 | Absent | 5 | | |
| 53 | 246 | Missense | Exon 7, p.D224G | 1 | Absent | 5A | AIHA | Mahlaoui et al[96] |
| 54 | 285 | Nonsense | Exon 9, p.E285* | 1 | Absent | 5A | | |
| 55 | 297 | Nonsense | Exon 9, p.Q297* | 1 | Absent | 5 | | |
| 56 | 303 | Frameshift | Exon 9, p. V303fs305* | 1 | Absent | 5A | Colitis; vasculitis; lymphadenitis; arthritis | Braun et al[71] |

(Continued)
| Sr number | Amino acid position | Domain       | Type of variant | Variant             | Patients, n | WASp expression | WAS clinical score | Autoimmune manifestations                                                                 | Study                      |
|-----------|---------------------|--------------|----------------|---------------------|-------------|----------------|-------------------|------------------------------------------------------------------------------------------|---------------------------|
| 57        | 321                 | PRR          | Nonsense       | Exon 10, p.R321*   | 3           | Absent         | 5 (3)             |                                                                                          | Jin et al۶۸               |
|           |                     |              |                |                     |             |                |                   | Allergy; developmental delay                                                              | Ferrua et al۷۰             |
| 58        | 332                 |              | Deletion G     | Exon 10, p. V332fs444* | 1           | Reduced        | 5                 |                                                                                          | Jin et al۶۸               |
| 59        | 334                 |              | Frameshift     | Exon 10, p. G334V6444* | 2           | ND             | 5A (2)            | AIHA (2)                                                                                   | Mahlaoui et al۹۶           |
| 60        | 336                 | PRR and motif 1 | Nonsense       | Exon 10, p.K336*   | 1           | 5A             | 5                 | Glomerulonephritis                                                                       | Shigemura et al۹۷          |
| 61        | 342                 |              | Insertion C    | Exon 10, p. L342fs494* | 1           | Reduced        | 2 to 5A          | IgA nephropathy                                                                           | Lee et al۹۹               |
| 62        | 353                 | PRR          | Deletion C     | Exon 10, p. P353fs444* | 1           | ND             | 5                 |                                                                                          | Jin et al۶۸               |
| 63        | 358                 |              | Insertion G    | Exon 10, p. G358fs494* | 1           | Absent         | 5                 | Relapsing polychondritis                                                                   | Adriani et al۱۸           |
| 64        | 360                 |              | Deletion C     | Exon 10, p. P360fs444* | 1           | Absent         | 5                 |                                                                                          | Jin et al۶۸               |
| 65        | 362                 |              | Deletion 5nt   | Exon 10, p.P362fs* | 1           | 5A             | 5                 | AIHA, hemorrhagic vasculitis, migratory joint pain                                         | Trifari et al۹۶           |
|           |                     |              | Deletion C     | Exon 10, p. P362fs444* | 1           |                | 5                 |                                                                                          | Jin et al۶۸               |
| 66        | 363                 |              | Frameshift     | Exon 10, p. G363Afs444* | 1           | Absent         | 5A                |                                                                                          | Mahlaoui et al۹۶           |
| 67        | 364                 |              | Nonsense       | Exon 10, p.R364*   | 1           | Reduced        | 5A                | DCT-positive; ALPS-like illness                                                           | Suri et al۴۰               |
|           |                     |              |                |                     |             |                |                   |                                                                                          | Jin et al۶۸               |
| 68        | 383                 | PRR and motif 2 | Deletion G     | Exon 10, p. P383Lfs444* | 1           | Absent         | 5A                |                                                                                          | Liu et al۷۶               |
| 69        | 384                 |              | Deletion C     | Exon 10, p. P384fs444* | 1           | Absent         | 5                 |                                                                                          | Jin et al۶۸               |
| 70 | 387 | PRR | Deletion T | Exon 10, p. G387fs444* | 1 | Absent | 5 | Jin et al68 |
|---|---|---|---|---|---|---|---|---|
| 71 | 389 | Complex mutation with inframe 18nt deletion and frameshift 49nt insertion | Exon 10, p. P397Rfs444* | 1 | Reduced | 5A | Liu et al76 |
| 72 | 397 | Deletion C | Exon 10, p. P397Rfs444* | 1 | Reduced | 5A | Guillain–Barré syndrome | Suri et al80 |
| 74 | 423 | Frameshift | Exon 10, p. G432Cfs496* | 1 | ND | Postransplant autoimmunity | Bouma et al77 |
| 75 | 424 | Missense | Exon 10, p.G424P | 1 | Reduced | 5A | Skin vasculitis | Abina et al78 |
| 76 | 425 | Insertion G | Exon 10, p. L425fs494* | 2 | Truncated (2) | 5 (2) | Jin et al68 |
| 77 | 432 | V or WH2 | Deletion G | Exon 10, p. G432Efs444* | 1 | Normal | Skin vasculitis | Abina et al78 |
| | | Deletion A | Exon 10, p. G432Gfs444* | 1 | Absent | 5A | Du et al89 |
| 78 | 452 | Frameshift | Exon 11, E452fs494* | 1 | ND | 5A | AIHA | Mahlaoui et al86 |
| 79 | 477 | C | Deletion of 5nt | Exon 11, p. R447Qfs492* | 1 | Absent | 5A | Mahlaoui et al86 |
| 80 | 485 | Insertion TC | Exon 11, p. Q490Efs* | 1 | 5 | 5 | Jin et al68 |
| | | Missense | Exon 11, p.D485N | 1 | Reduced | 2 to 5A | Albert et al76 |
| 81 | 490 | A | Insertion G | Exon 12, p. Q490Efs* | 1 | 5A | Kolluri et al73 |
| 82 | 495 | Deletion T | Exon 12, p. D495fs* | 1 | Absent | 5 | Jin et al68 |
| 83 | 503 | Missense | Exon 12, p.*503A | 1 | 5A | Amarnihukrowh et al81 |
| Sr number | Amino acid position | Domain | Type of variant | Variant | Patients, n | WASp expression | WAS clinical score | Autoimmune manifestations | Study |
|-----------|---------------------|--------|----------------|---------|-------------|----------------|-------------------|--------------------------|-------|
| 84        |                     |        | Substitution   | IVS1-1G>C | 1           | Absent         | 5A                | EBV-associated lymphoproliferative disorder | Lee et al\(^6^9\) |
| 85        |                     |        | Substitution   | IVS2+1G>A | 1           | ND             | 5A                | AIHA                     | Mahlaoui et al\(^9^6\) |
| 86        |                     |        | Substitution   | IVS2+1G>A | 1           | ND             | 5A                | AIHA                     | Mahlaoui et al\(^9^6\) |
| 87        |                     |        | Substitution   | IVS2+1G>A | 1           | Absent          | 5A                | AIHA; colitis; growth retardation | Jin et al\(^6^8\) |
| 88        |                     |        | Deletion       | IVS3+1G>T | 1           | Absent          | 5A                | AIHA                     | Braun et al\(^7^1\) |
| 89        |                     |        | Deletion       | IVS6+1G>T | 1           | Absent          | 5A                | AIHA; AIT; autoimmune neutropenia | Braun et al\(^7^1\) |
| 90        |                     |        | Splice site    | IVS6+1   | 1           | Absent          | 5A                | Membranoproliferative glomerulonephritis associated with antiliglomerular basement-membrane antibody | Boztug et al\(^7^7\) |
| 91        |                     |        | Deletion       | Exon 6, c.559 +1 del 12 | 1 | 5A | Leukocytoclastic vasculitis | Pellier et al\(^1^0^0\) |
| 92        |                     |        | Substitution   | IVS6+2T>G | 1           | Absent          | 5A                | AIHA                     | Jin et al\(^6^8\) |
| 93        |                     |        | Substitution   | IVS6+5G>A | 1           | Absent          | 5A                | AIHA                     | Jin et al\(^6^8\) |
| 94        |                     |        | Substitution   | IVS6+5G>A | 1           | Reduced         | 5A                | AIHA                     | Suri et al\(^9^7\) |
| 95        |                     |        | Deletion       | IVS7-1delG | 1 | Absent | 5A | AIHA | Pamela et al\(^3^5\) |
| 96        |                     |        | Substitution   | IVS7+1G>T | 1 | Absent | 5A | AIHA | Jin et al\(^6^8\) |
| 97        |                     |        | Substitution   | IVS7+5G>A | 1 | Absent | 5A | Leukocytoclastic vasculitis; hepatosplenomegaly; allergy | Albert et al\(^3^6\) |
| 98        |                     |        | Deletion       | IVS8+1_4 delGAGT | 1 | Absent | 5A | EBV-associated lymphoproliferative disease | Braun et al\(^7^1\) |
| 99        |                     |        | Substitution   | IVS8+1G>A | 1 | Absent | 5A | Severe lower-limb vasculitis; arthritis | Jin et al\(^6^8\) |
| 100       |                     |        | Deletion       | IVS8+1delG | 1 | Absent | 5A | Severe lower-limb vasculitis; arthritis | Jin et al\(^6^8\) |
| 101       |                     |        | Substitution   | IVS9+1G>C | 1 | Absent | 5A | Severe lower-limb vasculitis; arthritis | Jin et al\(^6^8\) |
| 102       |                     |        | Substitution   | IVS9+2T>G | 1 | Absent | 5A | Severe lower-limb vasculitis; arthritis | Jin et al\(^6^8\) |
|   |   |   |   |   |
|---|---|---|---|---|
| 103 | Deletion | 1337–1338 + 9del in cDNA | I | Ferrua et al\textsuperscript{70} |
| 104 | Substitution | IVS10+1G>A | I | Haskoloğlu et al\textsuperscript{79} |
| 105 | Deletion | c.1453+1 G>C | I | Absent | Abina et al\textsuperscript{78} |
| 106 | Insertion | IVS11c. 118Ins | 2 | 2 to 5A | Jin et al\textsuperscript{68} |

**Undefined variants**

|   |   |   |   |   |
|---|---|---|---|---|
| 107 | Deletion | 735–2A→G in cDNA | I | Food allergy | Ferrua et al\textsuperscript{70} |
| 108 | Deletion | nv(X) (5,721, 11,840) | I | Recurrent arthritis; vasculitis, Henoch–Schönlein purpura with nephritic-nephrotic syndrome; panuveitis; Crohn’s-like enterocolitis; perianal fistulae and abscesses; pyoderma gangrenosum | Ferrua et al\textsuperscript{70} |
| 109 | Deletion | c.1296delA | I | Absent | 5A | Du et al\textsuperscript{89} |
| 110 | Deletion | c.1177delG | I | Absent | 5A | Du et al\textsuperscript{89} |
| 111 | Deletion | c.709delC | I | Absent | 5A | AIHA | Fillat et al\textsuperscript{80} |
| 112 | Deletion | Exon12, 1509A→T in cDNA (rs1289921805) | I | Colitis or gastrointestinal bleeding, mucosal bleeding, suspected food allergy | Ferrua et al\textsuperscript{70} |
| 113 | Deletion | Exon 10, 1595del, proximal breakpoint (5247_6842del) in genomic DNA | I | Food allergy, hepatomegaly, splenomegaly, inflammatory lymphadenopathy; eosinophilia | Ferrua et al\textsuperscript{70} |

**Notes:** Transcript ENST00000376701.5 for protein positions. *Translational termination (stop) codon.

**Abbreviations:** AIHA, autoimmune hemolytic anemia; AIT, autoimmune thrombocytopenia; ALPS, autoimmune lymphoproliferative syndrome; ANA, antinuclear antibody; ANCA, antineutrophil cytoplasmic antibody; ASMA, anti-smooth muscle antibody; EBV, Epstein–Barr virus; DCT, direct Coombs test; IBD, inflammatory bowel disease; ND, not done.
Autoimmune Thrombocytopenia (AIT)

Microthrombocytopenia is a cardinal feature of WAS. Abnormality in WASp results in megakaryocyte dysfunction, leading to formation of small platelets. These abnormal microplatelets are recognized by self-antibodies and are prematurely cleared by the spleen.\(^91\)\(^-\)\(^93\) Immunomediating thrombocytopenia also plays a contributing role in 15%–32% of patients (Tables 1 and 2).\(^2\),\(^29\),\(^30\),\(^33\),\(^36\) Antiplatelet antibodies have been found in 40% of WASp-deficient mice.\(^94\) Assays for antiplatelet antibodies are difficult to standardize and may not be easily available, especially in developing countries. Moreover, these antibodies may have a poor correlation withAIT.\(^95\) AIT may evolve over and exacerbate the underlying thrombocytopenia that is characteristic of WAS. A sudden drop in baseline platelet counts (usually \( <10\times10^9/\text{L} \)) with or without overt clinical bleeding is an important clinical clue to emergence of AIT. Failure to demonstrate a significant rise or fall in platelet count after platelet transfusion may herald the development of AIT.\(^95\)

Most autoimmune manifestations evolve over time, but immunothrombocytopenia may have an early age of onset. In a cohort of patients with WAS aged <2 years with a clinical severity score of 5, ten of 26 (38.4%) had antiplatelet antibody–positive severe refractory thrombocytopenia.\(^96\) Intracranial hemorrhage is a major cause of mortality in patients with WAS.\(^25\)

Differentiating AIT from baseline thrombocytopenia in WAS is crucial, as management strategies vary. Institution of appropriate immunosuppressive therapy is needed to maintain platelet counts.

Autoimmune Neutropenia

Autoimmune neutropenia is found in 2%–25% of patients with WAS.\(^25\),\(^29\),\(^30\),\(^33\),\(^35\)

Vasculitides

Vasculitis is the second-commonest autoimmune manifestation, and has been found in 1.5%–29% of patients with WAS. It accounts for 6%–45% of all autoimmune manifestations.\(^25\),\(^30\),\(^33\),\(^34\),\(^36\),\(^39\),\(^40\) (Tables 1 and 2)

Two patterns of vasculitic abnormality have been reported in WAS: medium-sized and small-vessel vasculitis of skin, renal, coronary, cerebral, or hepatic arteries, and large-vessel vasculitis involving the aorta and its major branches.\(^40\),\(^5097\)--\(^101\) Involvement of small vessels, especially those of the skin,\(^25\),\(^33\),\(^39\),\(^102\),\(^103\) is the commonest vasculitic abnormality (75%).\(^33\) IgA vasculitis (previously termed Henoch–Schönlein purpura) has been reported in 28.5% of patients with vasculitis.\(^25\) Kawakami et al described Kawasaki disease in a patient with WAS.\(^104\) Involvement of small- and medium-sized arteries of the gastrointestinal tract,\(^97\),\(^105\),\(^106\) heart,\(^104\),\(^105\) liver,\(^98\),\(^104\) gallbladder,\(^105\) kidneys,\(^98\),\(^106\) stomach,\(^102\) and cerebral blood vessels,\(^98\),\(^107\) has also been reported. In a single-center study of 55 patients of WAS, Dupuis-Girod et al noted cutaneous vasculitis at a mean age of 52.5 (11–184) months.\(^33\) Lao et al reported large-vessel vasculitis involving the aorta and renal artery in a 5-year-old boy with WAS.\(^100\) Pellier et al described five children with WAS who developed aortic aneurysms predominantly involving the thoracic and abdominal aorta.\(^101\) Four of these five patients with vasculitis were asymptomatic, and aneurysms were discovered only on screening.

Predisposition to developing vasculitis has been ascribed to immunodysregulation in WAS. Patients with WAS typically have depressed levels of IgM and elevated levels of IgA and IgE. It has been suggested that immunodeposition within the vessel wall can lead to necrotizing vasculitis.\(^98\) Alternatively, vasculitis could result from an infectious insult due to the underlying immunodeficiency.
Table 3 Clinical profile, treatment, and outcomes of patients with autoimmunity in XLT/WAS

| Study               | Autoimmune manifestations                                      | Mean age at onset (months) | Investigations                                                                 | Treatment                  | Outcomes                                                                 |
|---------------------|---------------------------------------------------------------|----------------------------|--------------------------------------------------------------------------------|----------------------------|--------------------------------------------------------------------------|
| Sullivan et al.     | Total patients with autoimmunity 61/154, 39.6%               | –                          | Impaired antibody response Diphtheria (58%); tetanus (62%); polio (50%); measles (0); mumps (50%); rubella (33%); pneumococcus (69%) | –                          | Autoimmunity: Poor prognostic marker                                    |
|                     | AIHA: 22/154, 14.2%                                           |                            | Serum immunoglobulin Variable, no correlation of immunoglobulin levels with autoimmunity |                            | Poor predisposition to malignancy: More chance of developing malignancy, ~75% of reported malignancies occurred in patients with autoimmunity |
|                     | Vasculitis: 20/154, 12.9%                                     |                            |                                                                               |                            |                                                                          |
|                     | Renal disease: 18/154, 11.6%                                  |                            |                                                                               |                            |                                                                          |
|                     | Transient arthritis: 17/154, 11%                             |                            |                                                                               |                            |                                                                          |
|                     | Chronic arthritis: 15/154, 9.7%                               |                            |                                                                               |                            |                                                                          |
|                     | HSP: 8/154, 5.1%; IBD: 5/154, 3.2%; Dermatomyositis: 1/154, 0.6% Other*: 14/154, 9% |                            |                                                                               |                            |                                                                          |
| Dupuis-Girod et al. | Total patients with autoimmunity 40/55, 72.7%                | 13.7                       | AIHA: 13.7 Neutropenia: 23.8 Arthritis: 45.3 Skin vasculitis: 53 Cerebral vasculitis: 52 IBD: 39.2 Renal disease: 7 | AIHA Corticosteroids at 2 mg/kg/day: CR 2, PR 12, ineffective 6 Cyclophosphamide Effective in 1/3 cases used Azathioprine effective in 4/9 cases used HSCN n=19, retransplant in 1 | Median survival 14.5 years Three of the four (75%) patients with cerebral vasculitis died Overall survival at 16 years of age 38.2% Poor prognostic factors Maintaining platelet counts >20x10^9/L for <5 months after splenectomy (p=0.012) High IgM (14/15 patients, 93%) with high IgM had AIHA, whereas no patients with low IgM had autoimmunity (p=0.02) AIHA RR 2.38 (p<0.04) |
Table 3 (Continued).

| Study               | Autoimmune manifestations | Mean age at onset (months) | Investigations                                                                 | Treatment                                                                 | Outcomes                                                                                                                                 |
|---------------------|----------------------------|---------------------------|-------------------------------------------------------------------------------|---------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------|
| Imai et al<sup>24</sup> | Total patients with autoimmunity 12/50, 24% Vasculitis: 4/50, 8%; Arthritis: 3/50, 6%; IBD: 2/50, 4%; AIHA: 3/50, 6%; IgA nephropathy: 5/50, 10%; Chronic renal failure: 2/50, 4%; Other: Asthma: 4/50, 8%; Food allergy: 4/50, 8% | –                          | Comparison of WASp-positive and WASp-negative patients Severe eczema: more in WASp-negative patients ($p=0.003$). High serum IgE: more in WASp-negative patients ($p<0.05$). | –                                                                                                                                      | Comparison of WASp-positive and WASp-negative patients: Incidence of autoimmune manifestations comparable between groups ($p=0.31$) |
| Ozsahin et al<sup>26</sup> | Pre-HSCT autoimmunity 17/96 (17.7%) De novo post-HSCT autoimmunity total 19/96, 19.7% | –                          | –                                                                            | HSCT with matched sibling donor 7, matched unrelated donor 6, matched related donor 4 | Seven of 17 patients had relapse of autoimmune disease after transplant ($p=0.06$) 7-year EFS in patients who had autoimmunity was 45%, whereas it was 83% in patients with no autoimmunity ($p=0.005$) |
| Albert et al<sup>26</sup> | Total patients with autoimmunity 21/173, 12.1% Events: 26 Nephropathy: 9/26, 34.6%; AIHA: 6/26, 23%; Vasculitis: 3/26, 11.5%; ITP: 4/26, 15.3%; Arthritis: 3/26, 11.5%; Colitis: 1/26, 3.8% | Median age 12.2 (4.9–56) years | –                                                                            | Conservative management                                                                                                                 | No significant difference in EFS observed with respect to level of WASp expression, IVIg prophylaxis, or antibiotics prophylaxis |
| Chen et al. | Total patients with autoimmunity 14 (26.4%) | AIHA: 17.5 (4–98 months) | Positive DCT in all 12 cases with AIHA; DCT and ICT both positive in 7 cases; Anti-PAIgG (1); ANA (3); low IgM (5); high IgM (1) | AIHA Corticosteroids first-line agents (9 of 12 cases). Additional agents IVIg (8) Rituximab (3) Cyclosporine (2) Plasma exchange (2) Tacrolimus (1) Splenectomy (1) CS 5 (42%), PR 4 (33%), no remission in 2 cases (17%) relapse in 1 case (8%) HSCT: For 8 cases of AIHA

| Burroughs et al. | Pre-HSCT autoimmunity Total: n=32, 24.8%; Thrombocytopenia: n=19, 14.7%; Hemolytic anemia: n=10, 7.7%; Neutropenia: n=7, 5.4%; Vasculitis: n=3, 2.3%; IBD: n=2, 1.6%; Arthritis: n=3, 2.3% Nephritis: n=1, 0.8%; Alopecia: n=1, 0.8%. | – | – | Individuals managed conservatively (n=4): 2 died, 50%. Individuals managed with HSCT (n=8): 3 died, 37.5% Post-HSCT: 5 cases had relapses requiring multiple immunosuppressives

**Notes:** *Recurrent angioedema, neutropenia, cerebral vasculitis, uveitis myositis, autoimmune hepatitis, pyoderma gangrenosum, erythema nodosum, cardiac vasculitis.

**Abbreviations:** HSCT, hematopoietic stem–cell transplant; HSP, Henoch–Schönlein purpura; AIHA, autoimmune hemolytic anemia; CR, complete remission; PR, partial remission; MSD, matched sibling donor; MUD, matched unrelated donor; MRD, matched related donor; EFS, event-free survival; CB, cord blood; ITP, immunothrombocytopenic purpura; IBD, inflammatory bowel disease; DCT, direct Coombs test; ICT, indirect Coombs test; PAIgG, platelet-associated IgG.*
Pellier et al showed evidence of varicellazoster virus, Epstein–Barr virus, and human herpesvirus 6 in the aortic vessel wall on histopathology in a patient with WAS and aortic aneurysm.\textsuperscript{101}

**Arthritis**

Arthritis has been reported in 1%–29% of patients with WAS, and accounts for 3%–52% of all autoimmune manifestations (Table 1).\textsuperscript{25,29,30,33,35,36} Sullivan et al observed arthritis in 32 of 152 patients (21%). Of these, 17 had transient arthritis and 15 persistent arthritis.\textsuperscript{25} Median age at presentation of arthritis was 45.3 (13–180) months.\textsuperscript{33}

**Renal Disease**

Onset of renal disease in XLT/WAS occurs at a relatively later age: 7–20 years.\textsuperscript{36,37} Clinical manifestations include transient proteinuria,\textsuperscript{23} hematuria, azotemia, and nephritic–nephrotic syndrome.\textsuperscript{25,29,33,35–37,100} Reported histopathological patterns include IgA nephropathy, membranoproliferative glomerulonephritis, mesangial proliferation, and interstitial nephritis.\textsuperscript{108–111} IgA nephropathy is the commonest renal disease, described in 27%–41% of patients in various long-term cohorts.\textsuperscript{25,35,36} Prevalence appears to be higher in patients with residual WASp expression.\textsuperscript{35,36} Screening for renal involvement has been recommended in all patients with XLT/WAS.

Aberrant glycosylation of IgA is attributed as a cause for renal disease associated with WAS. Elevated levels of $\beta_1,6$-N-acetyl-glucosaminyl transferases have been documented in patients with WAS. This leads to aberrant O-glycosylation of sialophorin in patients with WAS.\textsuperscript{101,112}

**Inflammatory Bowel Disease (IBD)**

Bleeding from the gastrointestinal tract is a common symptom in WAS and often secondary to thrombocytopenia. In our cohort, 49.4% of children presented with blood-stained stools.\textsuperscript{40} Autoimmune colitis has also been reported in 1%–9% of patients.\textsuperscript{25,29,30,35,36} Both ulcerative colitis and Crohn’s disease have been observed. WAS-associated colitis is challenging to treat and often refractory to immunosuppressants.\textsuperscript{113} In our experience, IBD can be a presenting feature of WAS. Ohyya et al reported that 16.6% of patients with IBD had a \textit{WAS} mutation.\textsuperscript{113} Similarly, Cannioto et al showed that 25% of patients aged <2 years with IBD were later shown to have WAS.\textsuperscript{114}

WASp-deficient mice have been observed to have chronic colitis with mucosal thickening and lymphocytic and neutrophilic infiltrates in the lamina propria.\textsuperscript{115} Suggested pathogenic mechanisms for IBD in WAS include WASp deficiency-mediated dysfunction of $T_{reg}$ cells and anti-inflammatory macrophages, increased self-reactive B cells, and altered gut microbiota.\textsuperscript{113,116}

**Other Rheumatic Manifestations**

Monteferrante et al described lupus nephritis in a patient with WAS.\textsuperscript{117} Similarly, other connective-tissue disorders like dermatomyositis,\textsuperscript{27} uveitis,\textsuperscript{27} autoimmune hepatitis,\textsuperscript{27} primary sclerosing cholangitis,\textsuperscript{40} amyloidosis,\textsuperscript{39} and relapsing polychondritis\textsuperscript{118} have been reported in the context of WAS.\textsuperscript{27} Crestani et al reported positive antineutrophil cytoplasmic antibodies, and positive antiphospholipid antibodies in patients with WAS.\textsuperscript{119}

**Autoimmune Skin Diseases**

Eczematous dermatitis is a cardinal clinical manifestation of WAS. Eosinophilia and elevated levels of serum IgE are associated findings. DC dysfunction and skewed Th2 immunity may play a role in the development of eczema in this condition.\textsuperscript{120} Apart from atopy, other autoimmune skin manifestations have been reported in WAS. These include recurrent angioedema, pyoderma gangrenosum, and erythema nodosum.\textsuperscript{25} Alopecia has been reported in 1%–3% of patients with WAS.\textsuperscript{25,30,34,36}

**Posttransplant Autoimmune Manifestations**

Development of autoimmunity is considered a predictor of severe disease, and often warrants the need for early HSCT in patients with XLT/WAS. HSCT is curative and is associated with 5-year survival of 91%.\textsuperscript{30} However, occurrence of autoimmunity in the posttransplant period has been observed in 13%–20% of patients (Table 4).\textsuperscript{26–30} Autoimmune cytopenia is the commonest autoimmune manifestation seen after HSCT.\textsuperscript{30} Burroughs et al reported that 75% of patients with autoimmune manifestations responded to immunosuppressive therapy and attained remission within a year of transplant.\textsuperscript{30} Mixed or split donor chimerism is an important predictor of development of post-HSCT autoimmunity.\textsuperscript{26,27,30} Autoimmunity is most frequently encountered in patients who undergo matched unrelated donor transplants. However, it is also seen in matched related-donor and matched sibling-donor transplants.\textsuperscript{26,30} Presence of pretransplant autoimmune
Autoimmunity and Risk of Malignancy

Presence of autoimmunity also increases the risk for development of malignancy in patients with WAS. Sullivan et al observed that 25% of patients with a history of autoimmune disease developed malignancy compared to 5% of patients without autoimmunity.25 Sallah et al demonstrated that 18% of patients with AIHA developed lymphoreticular malignancy.121

Treatment of Autoimmunity

Currently, HSCT is the best curative therapy available for WAS. Early studies on HSCT in WAS reported effective...
reconstitution of lymphoid cells, but impaired platelet engraftment. 122–124 Long-term overall survival in recipients of unrelated bone-marrow grafts is 70%–78%. 26,125 However, recent studies have reported event-free survival with HLA-identical sibling bone-marrow grafts to be 88%, with overall survival of 90%–95%. 27,30,126 Results of unrelated- and alternative-donor HSCT have also greatly improved to >90%. 30,37 HSCT with TCRαβ/CD19 depletion or posttransplant cyclophosphamide therapy for haploidentical donors has shown promising results and new opportunities for successful curative therapy in WAS/XLT. 127

Gene therapy is an evolving and promising alternative approach when a transplant is not feasible due to unavailability of matched donors. Gene therapy was attempted with a gibbon ape leukemia virus γ-retroviral vector in 2006. 77,127 Though successful engraftment was reported, it was limited by development of leukemia due to insertional leukemogenesis. Subsequently, therapy with a lentiviral vector was attempted in 31 patients with WAS. This resulted in successful engraftment, discontinuation of intravenous immunoglobulin (IVIg), improvement in platelet counts, and reduction in infections. Resolution of autoimmune manifestations was also demonstrated with gene therapy; however, the rate of de novo autoimmunity posttransplant was comparable with HSCT. 127

Chemoprophylaxis with antimicrobials and monthly IVIg are often used for prevention of infections. Management is usually individualized based on disease severity. Treatment of autoimmune manifestations is challenging, and may require require immunosuppressive therapies. These agents can further increase the risk of infections. Corticosteroids remain the first-line therapy for all autoimmune manifestations. Corticosteroids can induce variable rates of remission in patients with AIHA (Table 2). Additional agents are needed in patients who do not respond or attain partial remission. Cyclophosphamide, azathioprine, IVIg, rituximab, cyclosporine, plasma exchange, and tacrolimus have been used with variable results.

High-dose IVIg and oral or parenteral corticosteroids are used as first-line agents in patients with AIT who have significant bleeds. Rituximab is used for refractory cases. Splenectomy significantly increases and often normalizes platelet counts in refractory thrombocytopenia. 77,128,129 However, splenectomy is associated with increased risk of sepsis and necessitates lifelong antimicrobial prophylaxis. 129 Moreover, thrombocytopenia may recur after splenectomy in patients with WAS. 33 Splenectomy is reserved for very severe cases with no prospects from other curative interventions. Severe AIT after splenectomy is usually treated with IVIg, high-dose steroids, azathioprine, and cyclophosphamide. A majority of patients with skin vasculitis, arthritis, IBD, and renal disease associated with WAS respond to standard immunosuppressive regimens containing steroids and cyclosporine. 33

Conclusion

Autoimmune manifestations are well-recognized complications in WAS. Varied clinical manifestations have been associated with the syndrome. Autoimmune cytopenia is the commonest. Development of autoimmunity is a poor prognostic marker and a predictor of development of malignancy. Pathogenic mechanisms for autoimmunity are not clearly defined. Corticosteroids with or without additional immunosuppressive agents are needed for treatment of autoimmune manifestations. HSCT is curative, but there is a risk of development of posttransplant autoimmunity.

Disclosure

The authors report no conflicts of interest in this work.

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