

Autoimmunity in Wiskott-Aldrich Syndrome: Risk Factors, Clinical Features, and Outcome in a Single-Center Cohort of 55 Patients

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ABSTRACT. *Objectives.* To evaluate the occurrence of autoimmune and inflammatory complications in Wiskott-Aldrich syndrome (WAS) and to determine risk factors and the prognosis of such complications with the aim of improving the definition of treatment options.

Methods. We reviewed the records of 55 patients with WAS evaluated at Necker-Enfants Malades Hospital (Paris) from 1980 to 2000.

Results. Forty patients (72%) had at least 1 autoimmune or inflammatory complication. Autoimmune hemolytic anemia was detected in 20 cases (36%); in all cases, onset occurred before the age of 5 years. Other complications included neutropenia (25%), arthritis (29%), skin vasculitis (22%), cerebral vasculitis (7%), inflammatory bowel disease (9%), and renal disease (3%). The median survival of the entire population was 14.5 years. Two autoimmune complications and 1 biological factor were predictive of a poor prognosis in this population: autoimmune hemolytic anemia, severe thrombocytopenia recurring after splenectomy, and high serum immunoglobulin M (IgM) levels before splenectomy. Autoimmune hemolytic anemia was significantly more observed in patients with high serum IgM level.

Conclusions. High serum IgM concentration before splenectomy was identified as a risk factor for autoimmune hemolytic anemia; however, it must be confirmed. Autoimmune hemolytic anemia and severe thrombocytopenia recurring after splenectomy were 2 indicators of a poor prognosis. Those results suggest that patients with WAS and IgM levels more than mean + 2 standard deviations before splenectomy should be placed under strict surveillance. Furthermore, severe autoimmune complications should lead, as early as possible, to hematopoietic stem cell transplantation using the best available donor. *Pediatrics* 2003;111:e622-e627. URL: <http://www.pediatrics.org/cgi/content/full/111/5/e622>;

arthritis, autoimmunity, autoimmune hemolytic anemia, children, hematopoietic stem cell transplantation, immunodeficiency, thrombocytopenia, vasculitis, Wiskott-Aldrich syndrome.

ABBREVIATIONS. WAS, Wiskott-Aldrich syndrome; IVIG, intravenous immunoglobulin; IG, immunoglobulin; SD, standard deviation; HSCT, hematopoietic stem cell transplantation; AIHA, autoimmune hemolytic anemia; GVHD, graft-versus-host disease.

Wiskott-Aldrich syndrome (WAS) is an X-linked primary immunodeficiency originally described as a clinical triad of immunodeficiency, thrombocytopenia, and eczema.¹⁻³ Many patients express the full triad of clinical manifestations, but others have a milder phenotype and survive to adulthood. Phenotypic expression varies over time in a given patient.^{3,4}

Patients with autoimmune and inflammatory manifestations usually constitute a high-risk group⁴ with poor outcome, but only 2 large retrospective surveys^{4,5} have analyzed WAS and complications. We conducted this study in a cohort of patients with WAS to evaluate the occurrence of autoimmune and inflammatory complications at a single center, to define specific subgroups with a poor prognosis, and to identify prognostic factors, with the goal of improving the definition of treatment options and means of treatment.

METHODS

We analyzed retrospectively the case reports of 55 boys with WAS. All patients were referred to Necker-Enfants Malades Hospital between 1980 and 2000. Diagnosis was based on 1) persistent thrombocytopenia and a family history of WAS (15 patients [27%]), 2) persistent thrombocytopenia with low platelet volume and eczema (44 patients [80%]), and 3) persistent thrombocytopenia with documented defects in B-cell and T-cell counts or function (29 patients [52%]). Genetic analysis confirmed the diagnosis in 39 cases. No mutation was found in 1 patient, and DNA samples were not available for the other 15 cases. X-linked thrombocytopenia was excluded by the presence of eczema, infections, or evidence of immunodeficiency. Dermatitis was observed in 39 patients at the time of diagnosis of thrombocytopenia (70%). Fifty patients were very susceptible to infection. All patients received prophylactic treatment for infections with intravenous immunoglobulin (IVIG; 500 mg/kg/3 weeks) and sulfamethoxazole (25 mg/kg/2 days) after diagnosis. Autoimmune hemolytic anemia was defined as acquired hemolytic anemia caused by the presence of autoantibodies that agglutinated or lysed the patient's own red blood cells (Coombs' test positive). Autoimmune neutropenia was defined as neutropenia (<1000 polynuclear neutrophils/mm³)

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with autoantibodies against polymorphonuclear cells present. Severe autoimmune thrombopenia was defined as low platelet counts ($<50\,000$ platelets/ mm^3) associated with the presence of autoantibodies against platelets. Central nervous system vasculitis was defined as an inflammation of blood vessels within the central nervous system, suspected on the basis of clinical manifestations including headaches, seizures, and changes in behavior and confirmed by magnetic resonance imaging after 1989. Arthritis was defined as nonbacterial disease of the joint with edema. Cutaneous vasculitis was defined on clinical grounds as cutaneous lesions such as erythema, urticarial wheals, and purpuric lesions similar to Henoch-Schoenlein purpura. Skin biopsy was not performed in most cases. Gastrointestinal inflammation was suspected on the basis of clinical symptoms (chronic nonbacterial diarrhea) and confirmed in all cases by biopsy. Glomerulonephritis was confirmed in all cases by biopsy.

We quantitatively evaluated humoral immune response in all cases. Serum immunoglobulin (Ig) G, IgM, and IgA levels were determined by rate nephelometry and compared with normal values for each age group as previously described by Jolliff et al.⁶ Serum Ig values were classed as low when they were >2 standard deviations (SDs) below the mean and high when they were >2 SD above the mean for age. Thirty-three patients underwent immunologic tests before the age of 3 years, and 23 patients underwent such tests after the age of 3 years. CD3 cell count was considered low when it was $<1500/\mu\text{L}$ up to the age of 3 years, $<1000/\mu\text{L}$ between 3 and 13 years, and $<900/\mu\text{L}$ after the age of 13 years.⁷ CD4 and CD8 cell counts were considered low when they were $<800/\mu\text{L}$ and $<500/\mu\text{L}$, respectively, up to the age of 3 years, $<600/\mu\text{L}$ and $<300/\mu\text{L}$, respectively, between 3 and 13 years, and $<500/\mu\text{L}$ and $<300/\mu\text{L}$, respectively, after the age of 13 years. Lymphocyte proliferation levels were classed as normal or low, according to the standards of the laboratory, as was the antibody response to immunization antigens.

The χ^2 test was used to compare proportions, and log rank test was used for survival analysis. For both univariate and multivariate analyses, differences were considered significant if the calculated *P* value was below .05. *P* = .20 was set as the cutoff point for the selection of variables for multivariate analysis. Cox model was used for multivariate survival analysis.

RESULTS

Autoimmune or inflammatory complications were frequently observed (Table 1). We found that 72% ($n = 40$) of patients developed at least 1 autoimmune or inflammatory sign, the most common of which was hemolytic anemia (20 patients [36%]). The mean age at onset was 13.7 months (range: 1–58). Fourteen patients had neutropenia (25%). Median age at diagnosis of thrombocytopenia was 8.5 months (range: 0–84 months). Severe autoimmune thrombocytopenia ($<20\,000/\mu\text{L}$) occurred after splenectomy in 18 cases. In 11 cases, the time between splenectomy and relapse was <180 days (range: 7–150), and thrombocytopenia was associated with hemolytic anemia ($n = 8$) or cerebral vasculitis ($n = 1$). In 7 cases, the time between splenectomy and relapse was >180 days (range: 210–570). Sixteen patients had arthritis

TABLE 1. Autoimmune or Inflammatory Manifestations in a Cohort of 55 Patients With WAS

Condition	Patients		Age at Onset (Months)	
	<i>n</i>	%	Mean	Range
AIHA	20	36	13.7	0–58
Neutropenia	14	25	23.8	3–67
Arthritis	16	29	45.3	13–180
Skin vasculitis	12	22	53	11–186
Cerebral vasculitis	4	7	52	13–84
Inflammatory bowel disease	5	9	39.2	2–156
Renal disease	2	3.5	7	

(29%), 12 patients had skin vasculitis (22%), and 4 patients had cerebral vasculitis (7%). Inflammatory bowel disease occurred in 5 patients (9%). Two patients had renal disease: a 16-month-old boy, who had isolated and transient proteinuria, and a 5-year-old boy, who developed membranoproliferative glomerulonephritis. Many patients had >1 autoimmune or inflammatory complication: 20 patients had a single autoimmune complication, whereas 12 had 2 complications, 4 had 3 complications, 3 had 4 complications, and 1 had 5 complications.

The onset of autoimmune or inflammatory complications occurred between the ages of 0 and 5 years in most cases but before the age of 5 years in all cases of hemolytic anemia. The incidence of autoimmune or inflammatory complications is shown as a function of age in Fig 1.

Serum IgA levels were normal for age in 27 patients and high in 28 patients. Serum IgM level was evaluated in 49 patients and recorded before splenectomy for patients who underwent splenectomy. Serum IgM level was normal in 18 patients, high in 15 patients, and low in 16 patients (Fig 2). Before the age of 3 years, CD4+ cell counts were low in 11 patients and CD8+ cell counts were low in 21 of 32 patients examined. After the age of 3 years, CD4+ cell counts were low in 9 patients and CD8+ cell counts were low in 6 of 15 patients examined. T cell function evaluation showed that 32 patients had normal phytohemagglutinin responses and 13 had weak responses. T cell responses to tetanus toxoid were studied in 32 patients; responses were positive in 20 patients and negative in 12 patients.

Treatment of Autoimmune or Inflammatory Disorders

All patients with hemolytic anemia received steroids (2–5 mg/kg) as the first-line treatment. Steroids efficiently induced remission in 2 cases, were partially effective in 12 cases, and were ineffective in 6 cases. Cyclophosphamide (750 mg/ m^2 intravenously) was used in 3 cases and was effective in 1 case. Azathioprine (3 mg/kg/d orally) was used in 9 cases and was effective in 4 cases. All patients with autoimmune hemolytic anemia underwent hematopoietic stem cell transplantation (HSCT), except 1, who died. Twelve haploidentical, 6 sibling-matched, and 1 matched unrelated donor transplants were performed. One patient underwent HSCT twice. The mean time between the initiation of autoimmune hemolytic anemia (AIHA) treatment and HSCT was 8.8 months (range: 2–20 months).

The 18 patients with severe autoimmune thrombocytopenia after splenectomy were treated with IVIG ($n = 18$), high-dose steroids (2–5 mg/kg; $n = 12$), azathioprine ($n = 7$), and cyclophosphamide ($n = 1$). Fourteen of these patients then underwent phenotypical ($n = 1$) or haploidentical ($n = 13$) HSCT; the other 4 died before HSCT could be performed.

Other autoimmune or inflammatory complications were generally treated with steroids. This treatment, in association with cyclosporin, was effective against skin vasculitis in 8 of 12 cases, against arthritis in 10 of 16 cases, and against bowel inflammatory disease and renal disease in 1 case each. Three patients with

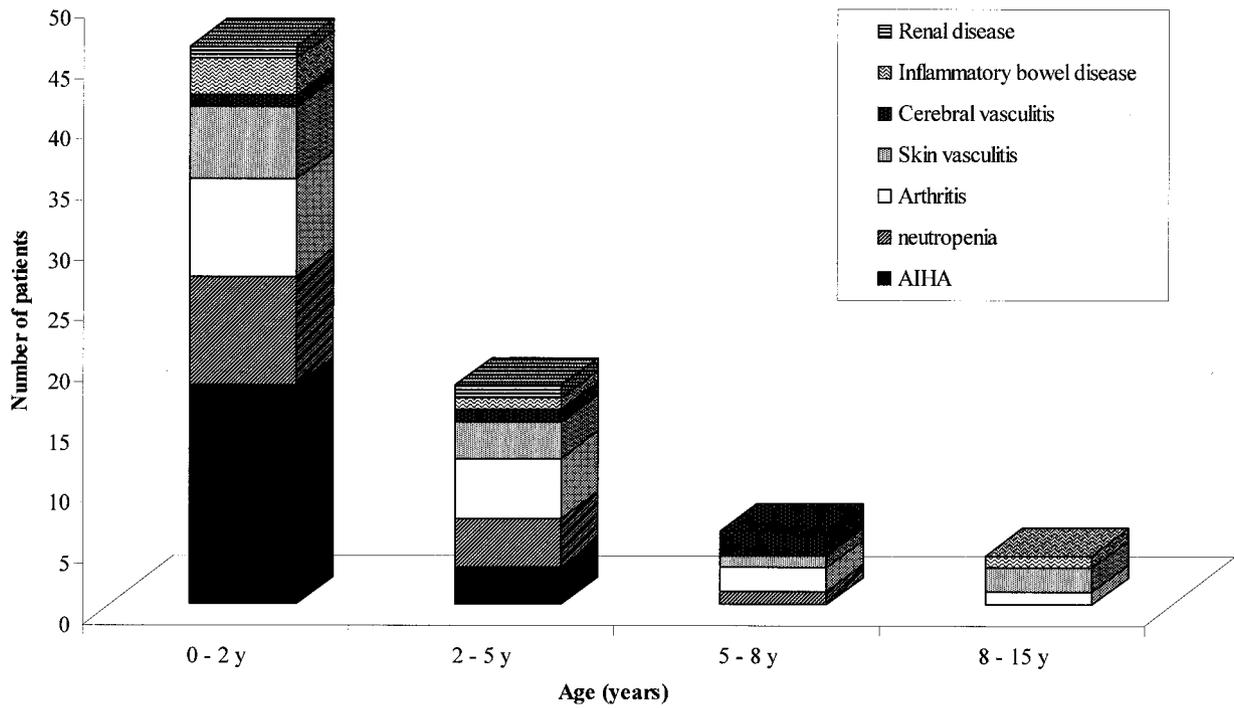


Fig 1. Age distribution of onset of autoimmune complications in 40 patients with autoimmune complications.

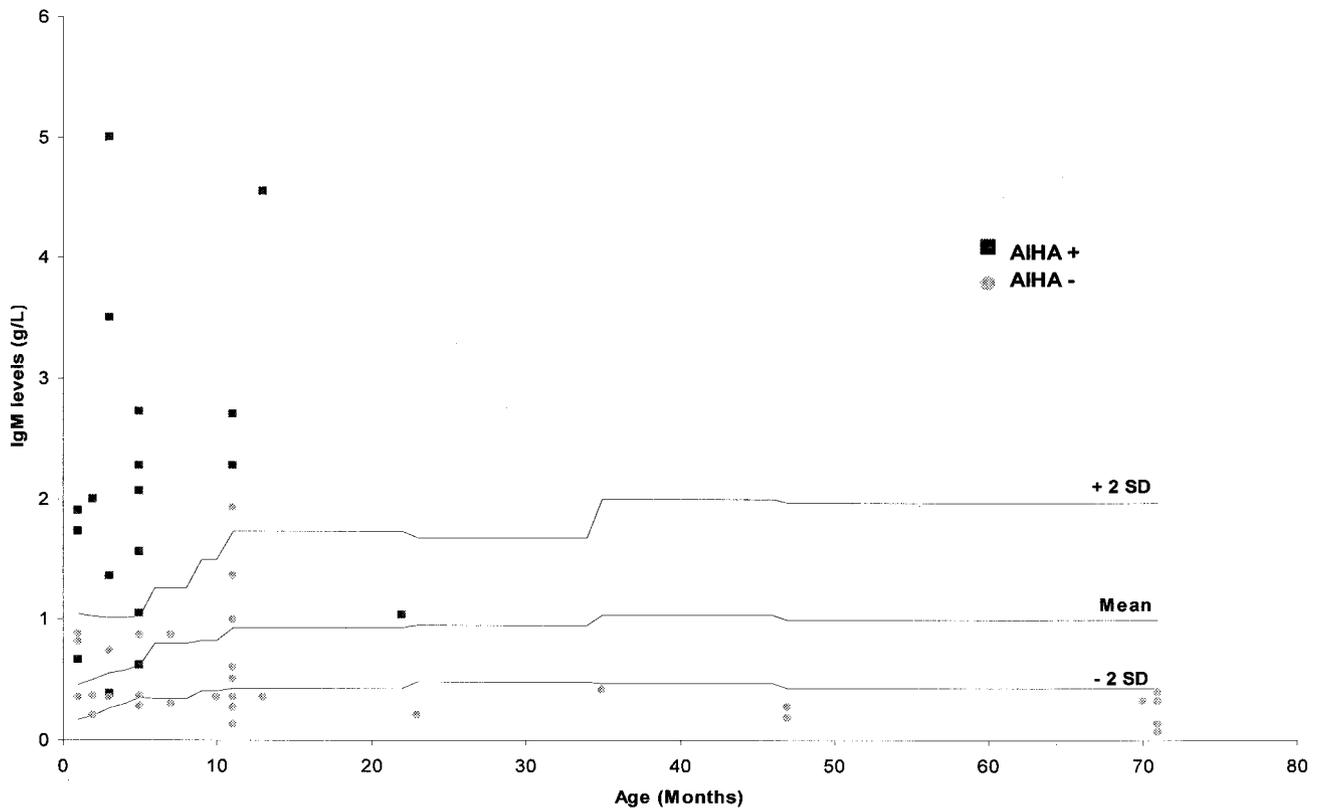


Fig 3. Overall survival of patients with WAS.

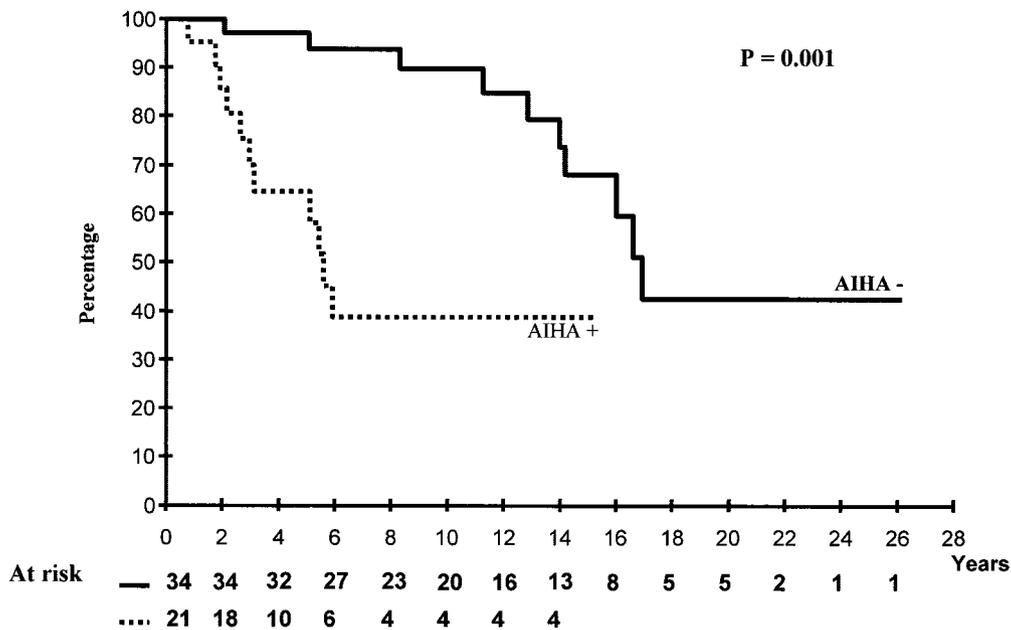
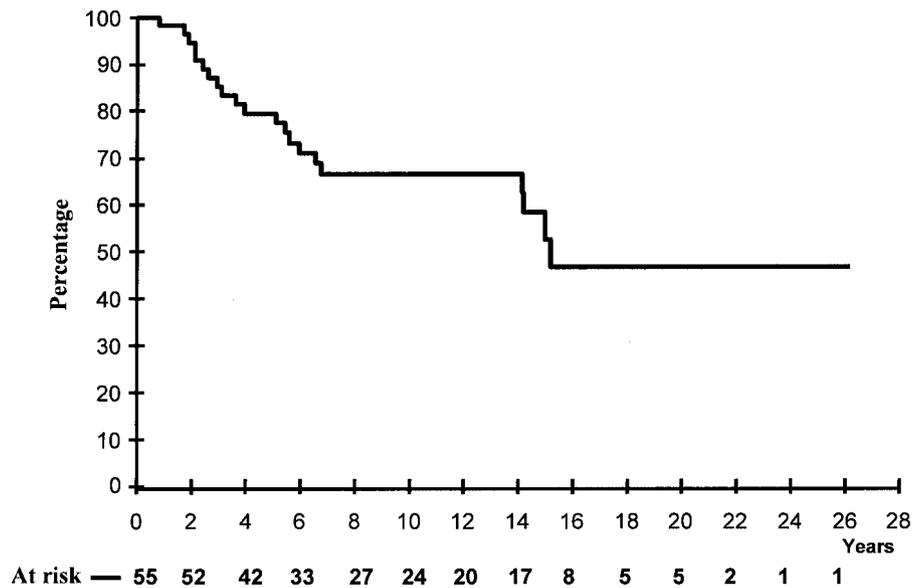


Fig 4. Survival of patients with WAS as a function of AIHA occurrence.

mean + 2 SD). Fourteen of these 15 patients developed autoimmune hemolytic anemia ($P < .001$). In contrast, low serum IgM concentration before splenectomy was a marker of a favorable prognosis. Sixteen patients had low serum IgM level (less than mean - 2 SD). In this group, no AIHA was observed ($P < .001$). In multivariate analysis, AIHA was significantly associated with poor prognosis ($P < .04$, relative risk = 2.38).

DISCUSSION

We analyzed retrospectively the frequency, severity, and treatment of autoimmune and inflammatory manifestations in a cohort of 55 patients with WAS. In previous surveys,³⁻⁵ approximately 30% of patients were reported to develop autoimmune or inflammatory complications and 15% were reported to develop AIHA. In this study, a higher incidence of

AIHA was observed. The specialization of the referral center may account for the large number of patients with very severe complications in this cohort. AIHA was frequently associated with other autoimmune manifestations. As previously described by Sullivan et al,⁴ ~20% of patients had skin vasculitis and 20% had arthritis. Cerebral vasculitis was a rare but severe complication.^{4,8} As previously reported, glomerulonephritis was a rare complication.⁹⁻¹¹ Chronic diarrhea is a classical manifestation of WAS, but histologic analysis is rarely performed. In this study, nonbacterial inflammatory bowel disease was a frequent complication and biopsy should be performed when chronic diarrhea is observed. Most autoimmune or inflammatory complications were observed before the age of 5 years, but the age of onset differed according to the type of complication. In all cases, AIHA was diagnosed before the age of 5

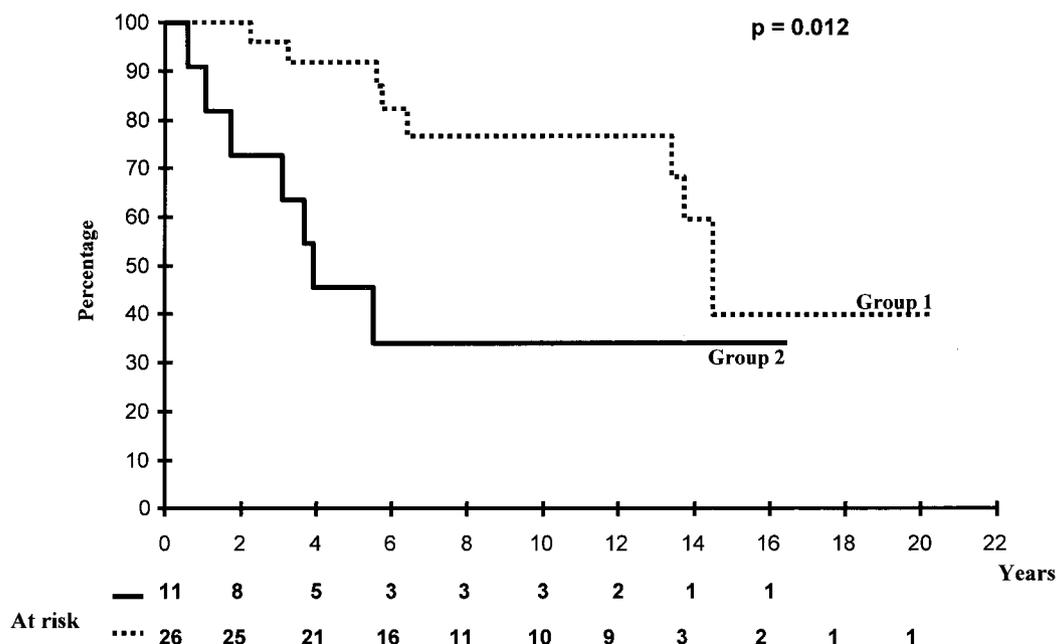


Fig 5. Survival of patients after splenectomy to maintain a platelet count $>20\,000/\mu\text{L}$ as a function of time to relapse in 2 groups. In group 1, time between splenectomy and relapse of thrombocytopenia was >6 months, and in group 2, time between splenectomy and relapse of thrombocytopenia was <6 months.

years. In contrast, arthritis, skin vasculitis, cerebral vasculitis, and glomerulonephritis were observed later in some cases. Furthermore, patients with AIHA were rapidly identified as a result of the severity of this complication and all underwent HSCT or died.

The treatment of autoimmune or inflammatory complications depends on the severity of complications. AIHA has never been cured by immunosuppressive treatments, which are only partially and transiently effective and tend to worsen the immunodeficiency. HSCT is currently the only appropriate treatment and is essential in patients with AIHA. A good response to steroids was observed for skin vasculitis and arthritis. Glomerulonephritis can be cured by medical treatment,⁹ and kidney transplantation is not necessary¹⁰ in all cases. Splenectomy is the first-line treatment of choice for thrombocytopenia,¹² but it is unclear how autoimmune thrombocytopenia after splenectomy should be treated. IVIG and steroids, although more efficient after splenectomy,⁴ are effective for only short periods of time.

Another goal of this survey was to identify specific factors that predict severe autoimmune complications, with a view to optimizing treatment. We found that AIHA was a frequent, early-onset complication that clearly predicted a poor prognosis, as previously reported.^{3,4,13,14} Early relapse of thrombocytopenia after splenectomy is also predictive of a poor prognosis.^{3,4,12} Surprisingly, we found that the results of a biological test acted as a prognostic factor. Indeed, high serum IgM concentration before splenectomy is a marker for poor outcome and an indicator of a high risk of developing AIHA. Patients with low serum IgM levels did not develop AIHA. Humoral immunity is usually affected in WAS and IgM levels are low,^{3,15} but Sullivan et al⁴ reported Ig levels to be

extremely variable. Some very young patients, younger than 2 years, had IgM values more than the mean + 2 SD, but such high levels were not detected in children older than 5 years. The reasons for the link between high serum IgM level and AIHA are unclear. A prospective study should be conducted to confirm these results. However, if confirmed, then these results suggest that patients with IgM levels more than the mean + 2 SD according to age should be placed under strict surveillance. In this survey, we did not analyze WASP gene mutations and protein levels. In previous studies, mutation analysis in typical cases of WAS has suggested that there is a link between clinical phenotype and genotype,^{3,16,17} but exceptions have been found.^{18,19} All mutations resulting in a mild phenotype (XLT) result in the production of normal-sized or truncated protein in various quantities. For typical or severe WAS, the relation is not absolute and cannot be considered to be a prognostic factor.

CONCLUSIONS

Autoimmune and inflammatory complications of WAS are frequent. AIHA and cerebral vasculitis are particularly severe, with a poor response to steroids and other immunosuppressive treatments. This leads us to suggest that patients with such conditions should be treated as early as possible, by HSCT, using the most closely matched available donor. Currently, the optimal treatment for patients with WAS is sibling-matched HSCT.^{20,21} Matched unrelated donor HSCT is successful in young children, but the success rate decreases dramatically above the age of 5 to 6 years.²² Prolonged immunosuppressive treatment and the severe autoimmunity of patients who receive haploidentical bone marrow transplants contribute to the poorer outcome.²² The relative values

of prognostic factors are currently unclear, but it would be of considerable value if a simple biological test, such as determination of IgM concentration, could be used to determine the best treatment available.

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REFERENCES

1. Wiskott A. Familiärer, angeborener Morbus Werlhofii? *Monatsschr Kinderheilkd.* 1937;68:212-216
2. Aldrich RA, Steinberg AG, Campbell C. Pedigree demonstrating a sex-linked recessive condition characterized by draining ears, eczematoid dermatitis and bloody diarrhea. *Pediatrics.* 1954;13:133-139
3. Ochs HD, Rosen FS. The Wiskott-Aldrich syndrome. In: Ochs HD, Edvard Smith CI, Puck JM, eds. *Primary Immunodeficiency Diseases.* New York, NY: Oxford University Press; 1999:292-305
4. Sullivan KE, Mullen CA, Blaese RM, Winkelstein JA. A multiinstitutional survey of the Wiskott-Aldrich syndrome. *J Pediatr.* 1994;125:876-885
5. Perry GS, Spector BD, Schuman LM. The Wiskott-Aldrich syndrome in the United States and Canada (1892-1979). *J Pediatr.* 1980;97:72-78
6. Joliff CR, Cost KM, Stivri PC. Reference intervals for serum IgG, IgM, C3 and C4 as determined by rate nephelometry. *Clin Chem.* 1982;28:126-128
7. Berthet F, Le Deist F, Duliege AM, Griscelli C, Fischer A. Clinical consequences and treatment of primary immunodeficiency syndromes characterized by functional T and B lymphocyte anomalies (combined immune deficiency). *Pediatrics.* 1994;93:265-270
8. Filipovitch AH, Krivit W, Kersey JH. Fatal arteritis as a complication of Wiskott-Aldrich syndrome. *J Pediatr.* 1979;95:742-744
9. Spittle LE, Wray BB, Mogerman S, Miller JJ, O'Reilly RJ, Lagios M. Nephropathy in the Wiskott-Aldrich syndrome. *Pediatrics.* 1980;66:391-398
10. Webb MC, Andrews PA, Koffman CG, Cameron JS. Renal transplantation in Wiskott-Aldrich syndrome. *Transplantation.* 1993;56:1585
11. DeSanto NG, Sessa A, Capodicasa G, et al. IgA glomerulonephritis in Wiskott-Aldrich syndrome. *Child Nephrol Urol.* 1988;9:118-120
12. Mullen CA, Anderson KD, Blaese RM. Splenectomy and/or bone marrow transplantation in the management of the Wiskott-Aldrich syndrome: long-term follow-up of 62 cases. *Blood.* 1993;82:2961-2966
13. Ochs HD. The Wiskott-Aldrich syndrome. *Semin Hematol.* 1998;35:332-345
14. Ochs HD. The Wiskott-Aldrich syndrome. *Clin Rev Allergy Immunol.* 2001;20:61-86
15. Inoue R, Kondo N, Kuwabara N, Orii T. Aberrant patterns of immunoglobulin levels in Wiskott-Aldrich syndrome. *Scand J Immunol.* 1995;41:188-193
16. Lemahieu V, Gastier JM, Francke U. Novel mutations in the Wiskott-Aldrich syndrome protein gene and their effects on transcriptional, translational, and clinical phenotypes. *Hum Mutat.* 1999;14:54-66
17. Zhu Q, Watanabe C, Liu T, et al. Wiskott-Aldrich syndrome/X-linked thrombocytopenia: WASP gene mutations, protein expression, and phenotype. *Blood.* 1997;90:2680-2689
18. Sullivan KE. Genetic and clinical advances in Wiskott-Aldrich syndrome. *Curr Opin Pediatr.* 1995;7:683-687
19. Schindelbauer D, Weiss M, Hellebrand H, et al. Wiskott-Aldrich syndrome: no strict genotype-phenotype correlations but clustering of missense mutations in the amino-terminal part of the WASP gene product. *Hum Genet.* 1996;98:68-76
20. Rimm IJ, Rapoport JM. Bone marrow transplantation for the Wiskott-Aldrich syndrome. Long-term follow-up. *Transplantation.* 1990;50:617-620
21. Ozsahin H, Le Deist F, Benkerrou M, et al. Bone marrow transplantation in 26 patients with Wiskott-Aldrich syndrome from a single center. *J Pediatr.* 1996;129:238-244
22. Filipovich AH, Stone JV, Tomany SC, et al. Impact of donor type on outcome of bone marrow transplantation for Wiskott-Aldrich syndrome: collaborative study of the International Bone Marrow Transplant Registry and the National Marrow Donor Program. *Blood.* 2001;97:1598-1603

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