A multiinstitutional survey of the Wiskott-Aldrich syndrome

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The Wiskott-Aldrich syndrome is an X-linked primary immunodeficiency originally characterized by the clinical triad of thrombocytopenia, eczema, and immunodeficiency. We collected clinical and laboratory information on 154 unselected patients with Wiskott-Aldrich syndrome to define better the clinical expression of this disorder. The classic triad of thrombocytopenia with small platelets, recurrent otitis media, and eczema was seen in only 27% of the study population; 5% of the study population had only infectious manifestations, and 20% of the study group had only hematologic manifestations before diagnosis. The results of immunologic evaluations varied from one patient to another and the course of the disorder varied tremendously, even within a single kindred. We conclude that many patients with Wiskott-Aldrich syndrome have an atypical presentation and that a panel of diagnostic tests is often required to establish the diagnosis. Two high-risk subgroups were identified in the study population: patients with platelet counts < 10 × 10^9/L (< 10,000/mm^3) at the time of diagnosis were at high risk of bleeding, and patients with autoimmune disorders were at increased risk of having a malignancy. (J PEDIATR 1994;125:876-85)

The Wiskott-Aldrick syndrome is an X-linked primary immunodeficiency originally described as a clinical triad of immunodeficiency, thrombocytopenia, and eczema.[1-8] Although many patients with WAS express all three of these clinical manifestations, others may have a partial or variant phenotypic expression. The abnormalities of immune response are inconsistent from one patient to another, within a single family,[9] or even within a single patient with time.[10] Differentiation of WAS from X-linked thrombocytopenia, in which patients are immunologically normal, may be difficult.[11-14] In fact, WAS and X-linked thrombocytopenia may represent different ends of a spectrum of disease.[15, 16]

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The molecular and genetic defects causing WAS are not yet known, and currently there is no single method of establishing the diagnosis. The difficulty in establishing a diagnosis has contributed to the confusion regarding phenotypic expression and natural history.

Early studies of the natural history of WAS described a uniformly fatal disorder.[1-6] Subsequent case reports have emphasized the breadth of clinical manifestations and the uncertain natural history.[14, 17-30] This multiinstitutional retrospective survey was designed to collect basic clinical and laboratory information on a large number of unselected WAS patients to define the disorder better and to identify features that could be used to describe WAS subsets with distinct natural histories.

BMT	Bone marrow transplantation
GVHD	Graft-versus-host disease
ITP	Idiopathic thrombocytopenic purpura
IVIG	Intravenously administered immune globulin
WAS	Wiskott-Aldrich syndrome

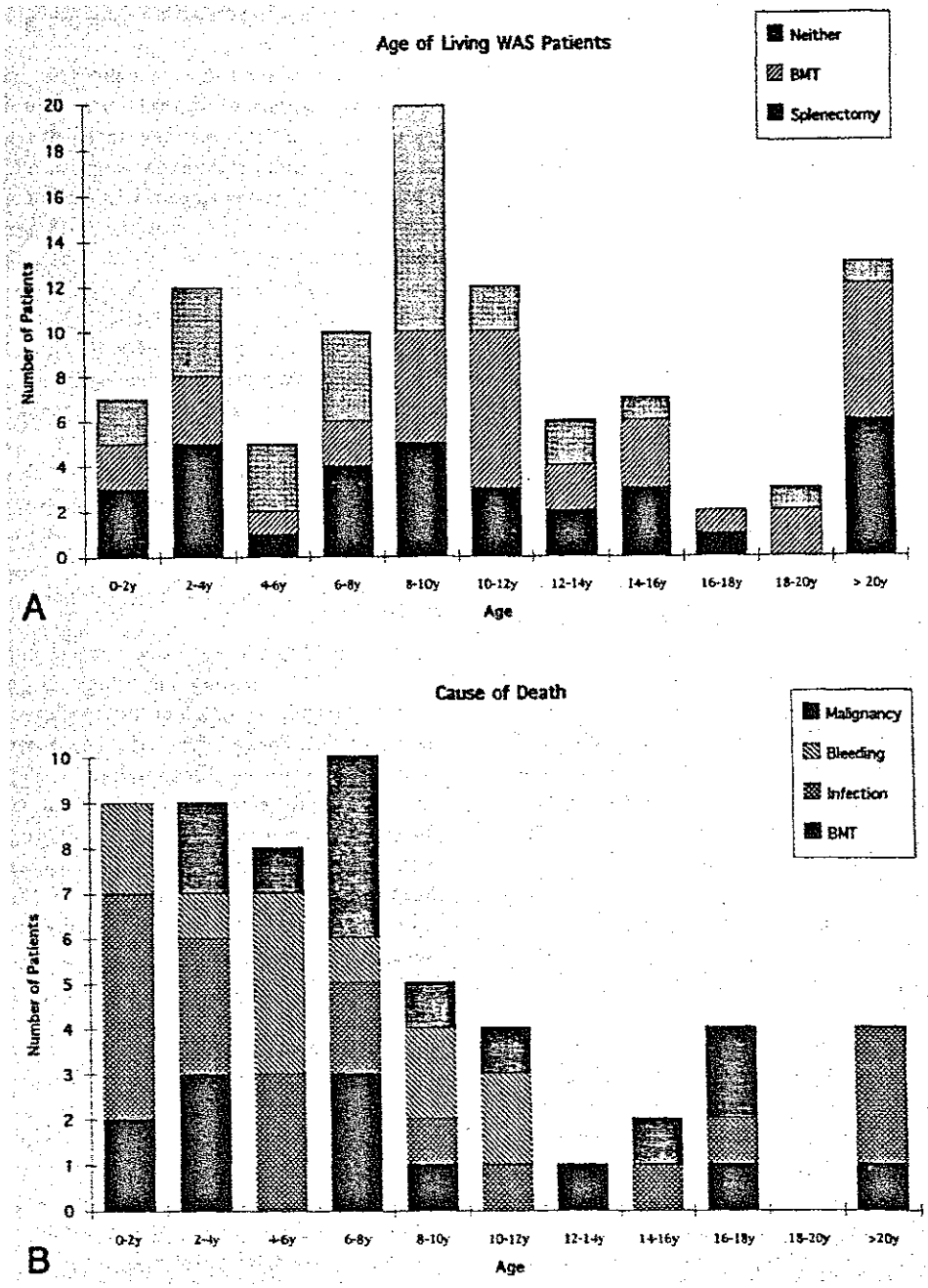

Fig. 1. Age distribution of living and deceased WAS patients. A, Number of living patients in each age group. Each *bar* designates whether each living patient has had a splenectomy, BMT, or neither intervention. B, Number of deceased patients in each age group. Each *bar* designates whether the death was principally caused by infection, bleeding, malignancy, or BMT.

METHODS

All patients were male and had been identified as having WAS. One or more of the following criteria were used by the informant to establish the diagnosis: (1) persistent thrombocytopenia with small platelets (82 patients, 53%); (2) persistent thrombocytopenia with a family history of WAS (74 patients, 48%), and (3) persistent thrombocytopenia in the presence of a documented defect in B-cell or

Table IA. Diagnostic evaluations: Hematologic studies

	Patients	
	No.	%
Platelet count at diagnosis		
$<10 \times 10^9$/L (<10,000/mm^3)	21	14
$10\text{-}20 \times 10^9$/L (10-20,000/mm^3)	46	30
$20\text{-}50 \times 10^9$/L (20-50,000/mm^3)	56	36
$50\text{-}100 \times 10^9$/L (50-100,000/mm^3)	23	15
$100\text{-}500 \times 10^9$/L (100-150,000/mm^3)	1	1
No record	7	5
Lymphopenia		
ALC $<1 \times 10^9$/L (<1000/mm^3)	34	22
ALC $>1 \times 10^9$/L (>1000/mm^3)	113	73
No record	7	5

ALC, Absolute lymphocyte count.

T-cell number or function (122 patients, 79%). Of 15 patients whose original diagnosis was based on thrombocytopenia and small platelets only, all had laboratory evidence of immunodeficiency such as poor antibody formation or impaired mitogenic responses. Of the 10 patients whose original diagnosis was based on persistent thrombocytopenia and a family history of WAS alone, eight had laboratory evidence of immunodeficiency, one died in infancy of sepsis, and one received a bone marrow transplant without additional laboratory investigations. Therefore all but one of the reported patients had persistent thrombocytopenia and evidence of immunodeficiency, although the laboratory manifestations of the immunodeficiency varied from one patient to another. Patients who had an atypical laboratory finding, such as formation of anti-polysaccharide antibodies, had additional laboratory findings characteristic of WAS.

Initial contact with prospective informants was through a request sent to hematologists, infectious disease specialists, and immunologists listed in Society for Pediatric Research, American Pediatric Society, Infectious Disease Society of America, and American Society of Hematology membership listings. Additionally, all chairmen of accredited pediatric residency training programs in the United States and Canada were asked to forward a letter to the individuals in their department who would be most likely to care for patients with WAS. The survey instruments were mailed to prospective informants in March 1992, and data collection was completed 1 year later; 159 of 227 survey instruments were returned. In one case the patient did not have persistent thrombocytopenia, and in four cases the survey instruments represented duplications of patient information, leaving 154 documented patients with WAS. Patient confidentiality was ensured by utilizing only birth date and initials as identifiers. A list of participating physicians is included in the acknowledgments (above the reference list).

The results of the lymphocyte proliferation studies that were used diagnostically by the informants were reported as normal or low according to the standards set by the laboratory. The T-cell percentage was recorded as low when it was <50%.[31] The percentage of $CD4^+$ cells was recorded as low when it was <30%, and the CD8 percentage was recorded as low when it was <18%.[31] The absolute T-cell count was recorded as low when it was $< 1.1 \times 10^9$/L (< 1100/mm^3), and the absolute $CD4^+$ cell count was recorded as low when it was $<0.7 \times 10^9$/L (< 700/mm^3).[31] The antibody responses to immunogens were recorded as normal or abnormal according to the standards set by the laboratory.

Correlation of initial platelet count with outcome was determined by the Spearman method. Measures of statistical significance were performed by the chi-square method.

RESULTS

Demographics. Survey forms were completed on 154 patients by 34 reporting physicians. A total of 1457 patient-years were reported, and 910 patient-years were directly observed by the informants. The majority of the informants were subspecialist consultants (135 patients), and 102 of the charts were reviewed by one of us. Most of the patients being reported are alive (94 patients; 61%), with an average age of 11 years; 55 deaths (36%) were recorded, and the average age at death was 8 years (Fig. 1). Five patients were lost to follow-up. Affected family members were known in 74 cases. There were 20 kindreds with affected brothers and 7 kindreds with non-first-degree affected relatives.

Diagnosis. Sustained thrombocytopenia was a prerequisite for entry into this survey. Small platelets specifically were identified in 82 patients (53%). Both small platelets and documented immunodeficiency were seen in 61 patients (40%). The triad of small platelets, laboratory-defined immunodeficiency, and eczema was noted in 46 patients (30%). Only 42 patients (27%) had manifestations similar to Aldrich's original description of thrombocytopenia with small platelets, recurrent otitis, and eczema at the time of diagnosis. The average age at diagnosis was 21 months, with a range from birth to 24.8 years. Only 9% were recognized after 3 years of age. In two patients the diagnosis was made after the age of 18 years. In 30 patients (19%), the original diagnostic evaluation was performed because a family member was known to be affected. In these cases the diagnosis was made somewhat earlier (average age 10 months) than in those patients for whom a previously affected family member was not known (average age 24 months). In nine

Table IB. Diagnostic evaluations: T-cell studies

	Normal		Low			Results			
						Positive		Negative	
	No.	%	No.	%	DTH skin test	No.	%	No.	%
Functional assay									
PHA	62	66	32	34	*Candida*	7	11	55	89
ConA	32	52	30	48	*Trichophyton*	1	3	35	97
Pokeweed mitogen	36	55	29	45	*Proteus*	1	14	6	86
Mixed lymphocyte culture	15	47	17	53	Mumps	4	14	24	86
NK cell function	1	50	1	50	Tetanus	4	11	33	89
T-cell subsets									
%T cells	38	72	15	28	Diphtheria	3	9	30	91
% $CD4^+$ cells	43	80	11	20	PPD	0	0	31	100
% $CD8^+$ cells	21	39	33	61	SKSD	3	7	38	93
Absolute No. T cells	31	76	10	24	DNCB	4	40	6	60
Absolute No. $CD4^+$ cells	28	78	8	22					

PHA, Phytohemagglutinin; *ConA*, concanavalin A; *NK*, natural killer [cell]; *DTH*, delayed-type hypersensitivity; *PPD*, purified protein derivative; *SKSD*, streptokinase-streptodornase; *DNCB*, dinitrochlorobenzene.

patients (6%), thrombocytopenia was originally detected on a routine screening study.

The results of diagnostic laboratory evaluations are presented in Table I and Fig. 2. Of note is the lack of consistent findings. The initial platelet count varied from $<10 \times 10^9$/L ($<10{,}000/mm^3$) to $>100 \times 10^9$/L ($>100{,}000/mm^3$). Individual patients had large variations in their platelet counts, often precipitated by viral syndromes. All patients in whom quantitative platelet size information was available (52 patients) had small platelets compared with the standards for platelet size determined by that institution. Platelet size was determined by diverse methods and recorded differently in different institutions, precluding comparison among reporting institutions. Lymphopenia (absolute lymphocyte count $<1.0 \times 10^9$/L, or $<1000/mm^3$) was present in 22% and eosinophilia (eosinophils $>0.5 \times 10^9$/L, or $>500/mm^3$) in 31%. Evaluation of T-cell function revealed that many patients had normal responses to phytohemagglutinin, concanavalin A, and pokeweed mitogen. Fourteen patients (26% of those tested) had low values on all three mitogen assays; 25 (46% of those tested) had normal responses. Results of delayed-type hypersensitivity skin tests were negative in the majority of patients, although this finding is not specific. Quantitative T-cell studies revealed that low $CD8^+$ cell counts were the most distinctive finding, although it was seen in only 61%.

The humoral immune response was evaluated quantitatively and by testing for response to immunizations. Figure 2 demonstrates that the quantitative immunoglobulin levels in patients with WAS were extremely variable. In general, the older patients had the quantitative immunoglobulin abnormalities typically associated with WAS. The response to protein antigens was mixed. Although the response to polysaccharide antigens has been described as deficient, appropriate titers to pneumococcal capsular polysaccharide antigens developed (in 31% of this population, and 13% had normal isohemagglutinins. The response to ΦX-174 was consistently abnormal in the nine patients examined.[10]

Table IC. Diagnostic evaluations: Humoral studies

	Normal response		Abnormal response	
	No.	%	No.	%
Immunogen				
Diphtheria	18	42	25	58
Tetanus	20	38	33	62
Polio	5	50	5	50
Measles	2	100	0	0
Mumps	2	50	2	50
Rubella	2	67	1	33
Pneumococcal vaccine (Pneumovax)	8	31	18	69
Hib conjugated	4	44	5	66
Hib unconjugated	2	29	5	71
ΦX-174	0	0	9	100
Isohemagglutinins	20	16	109	84

Hib, *Haemophilus influenzae* type b.

Clinical manifestations. Most patients who had symptoms before diagnosis had clinical signs of thrombocytopenia and increased susceptibility to infection. Only 5% of the survey patients had infectious diseases as their only symptom before diagnosis. Otitis media, pneumonia, and diarrhea were the most common infections, but some patients had life-threatening systemic infections before the diagnosis (Table II). A high number of infections typically asso-

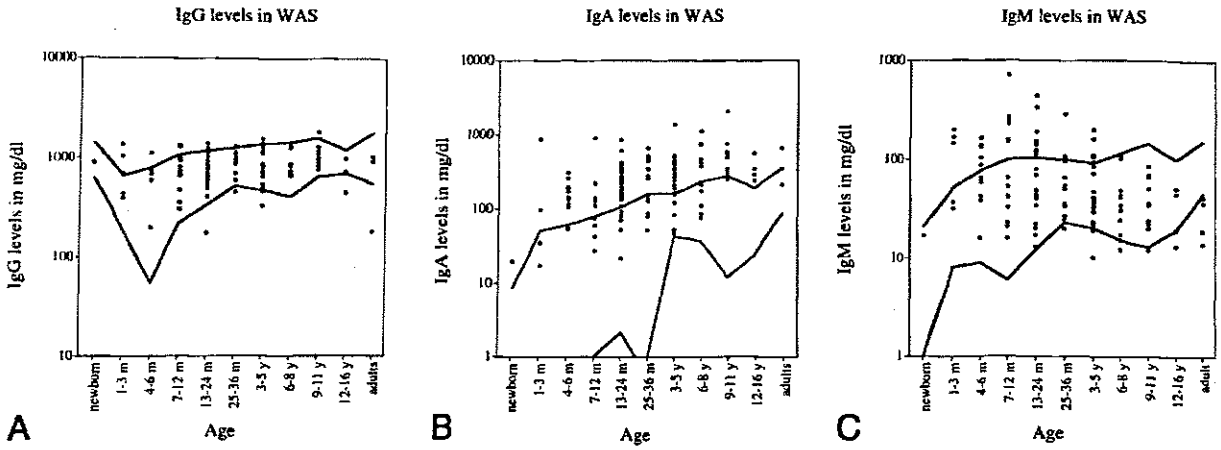

Fig. 2. Immunoglobulin levels in WAS patients: IgG (A), IgA (B), and IgM (C) values according to age. The *solid lines* correspond to the age-appropriate values in a healthy population.[51]

Table II. Infections in patients with WAS

Infection	Before diagnosis		After diagnosis		Recurrent disease†	
	No.*	%	No.	%	No.	%
Otitis media	98	64	118	78	72	47
Pneumonia	38	25	68	45	50	32
Infectious diarrhea	16	10	20	13	13	8
Sinusitis	13	8	36	24	32	21
Sepsis	11	7	36	24	13	8
Meningitis	7	4	11	7	3	2
Varicella	5	3	25	16	4	3
Epstein-barr virus	1	0.6	4	3	0	0
Cytomegalovirus	1	0.6	4	3	0	0
HSV I or HSV II	10	6	24	16	19	12
Parvovirus B-19	0	0	0	0	0	0
Polyomavirus	1	0.6	2	1	0	0
Molluscum contagiosum	0	0	13	9	11	7
Warts	2	1	10	7	6	4
Yeast/fungi	15	10	18	12	—	—
Pneumocystis carinii	1	0.6	13	9	3	2
Complication of immunization	2	1	—	—	—	—
Other infections	36	23	58	38	—	—
Other opportunistic infections	0	0	10	7	—	—

HSV, Herpes simplex virus.
*Number of patients.
†Recurrent disease was defined as more than five episodes of otitis media and more than two episodes of pneumonia, diarrhea, sinusitis, sepsis, meningitis, varicella, viral infection (Epstein-Barr virus, herpes simplex virus, polyomavirus), molluscum, warts, or *Pneumocystis*. BMT-related disease was excluded.

ciated with neutrophil disorders were noted: impetigo, cellulitis, and skin abscesses were seen in 19 patients (12%). Other deep tissue abscesses were seen in four patients, as well as staphylococcal mastoiditis, gingivitis, and an episode of necrotizing enterocolitis.

Most patients had clinical manifestations of thrombocytopenia before diagnosis (84%); the most common were petechiae or purpura (78%), although hematemesis and melena were seen in 28%. Epistaxis, oral bleeding, and intracranial hemorrhage were reported in 16%, 6%, and 2%, respectively, of patients before diagnosis. Other significant bleeding episodes were recorded in 5% of patients, including unusual bleeding from an umbilical stump, postsurgical bleeding, posttraumatic bleeding, testicular hemorrhage, and several subconjunctival hemorrhages. Life-threatening bleeding (either severe oral bleeding, gastrointestinal bleeding, or intracranial hemorrhage) was seen in 30% of the patients before diagnosis. Only 20% of the patients had

hematologic manifestations in the absence of notable infections before diagnosis.

None of the patients had eczema exclusively, although it developed in 81% at some point.

Therapy for thrombocytopenia. Information was collected on four management strategies: administration of corticosteroids, intravenous administration of immune globulin, splenectomy, and bone marrow transplantation. Thirty-one patients received one or more courses of corticosteroids specifically to treat thrombocytopenia; 10 had a rise in platelet count of at least 20×10^9/L (20,000/mm^3). Five of these ten responding patients had previously had a good response to splenectomy and were having an acute idiopathic thrombocytopenic purpura–like episode. Their response to steroid administration was greater than in the responders who had not had a splenectomy, with an average rise in platelet count of 254×10^9/L (254,000/mm^3) and an average posttreatment platelet count of 260×10^9/L (260,000/mm^3). The five responders who had not had a splenectomy had an average rise in platelet count of 44×10^9/L (44,000/mm^3) and an average posttreatment count of 62×10^9/L (62,000/mm^3). Twenty-one patients failed to respond to steroids, and there was no correlation between initial platelet count and steroid responsiveness. In the steroid-treated group, four deaths caused by infection could have been related to steroid therapy.

Twenty-six patients received IVIG specifically for thrombocytopenia. No patient had a good response to IVIG alone. Seven patients had a rise in platelet count of at least 20×10^9/L (20,000/mm^3). Two of these seven patients had previously had a good response to splenectomy and were having an acute ITP-like episode; after IVIG administration their platelet counts returned to normal. Another two of the seven responders had a response lasting less than 4 days. The remaining three responders had an average rise in platelet count of 28×10^9/L (28,000/mm^3), for an average posttreatment count of 52×10^9/L (52,000/mm^3). Nineteen patients failed to respond to IVIG, and there was no correlation between initial platelet count and IVIG responsiveness. Therapy with IVIG resulted in anaphylaxis in eight patients; none of these episodes resulted in death.

Splenectomy was used to treat thrombocytopenia in 61 patients. Two patients had insufficient information available to assess the efficacy of this treatment strategy. Of the remaining 59 patients, 54 (92%) had a sustained increase of at least 20×10^9/L (20,000/mm^3). Forty (68%) of them attained sustained platelet counts of at least 100×10^9/L (100,000/mm^3). Eight of the patients who initially responded to splenectomy had subsequent acute ITP-like episodes. There was no relation of the postsplenectomy platelet count to the subsequent development of the ITP-like syndrome. Sixteen patients (26%) had postsplenectomy sepsis; eight were receiving prophylactic antibiotics and eight were not. Nine deaths were caused by sepsis (15% of the splenectomized group). Five of these patients were reported to be taking prophylactic antibiotics and four were not.

Table III. Types of autoimmune and inflammatory conditions in WAS

Condition	Patients	
	No.	%
Autoimmune hemolytic anemia	22	14
Vasculitis	20	13
Renal disease	18	12
Transient arthritis	17	11
Chronic arthritis	15	10
Schönlein-Henoch purpura	8	5
Inflammatory bowel disease	5	3
Dermatomyositis	1	0.6
Other*	14	9

*Includes recurrent angioedema (2 patients), neutropenia (4), uveitis (3), cerebral vasculitis (2), myositis, autoimmune hepatitis, pyoderma gangrenosum, erythema nodosum, cardiac vasculitis.

Therapy for the immunodeficiency. Management of the immunodeficiency associated with WAS included IVIG replacement therapy for 38 patients and BMT for 47 patients. Although it was not possible to assess the efficacy of IVIG replacement therapy, the informants judged that IVIG had not changed the frequency of infections in 22 patients. In three patients the frequency of infections was thought to be increased, and in nine patients the frequency was believed to be decreased.

Forty-seven patients underwent BMT. Eleven haploidentical transplants, 28 sibling-matched, and five registry-matched transplantations were performed. Two BMTs used parental matched donors, and one transplant was a 5/6 parental match. Thirteen deaths were thought to be directly attributable to BMT; 8 occurred in the haploidentical BMT group (73% of the haploidentical group), and the causes of death were B-cell lymphoproliferative disease, encephalitis, viral sepsis (2 patients), graft-versus-host disease (2 patients), and preexisting lymphoma (2 patients). Of the 5 deaths occurring in the other BMT groups (14% of the nonhaploidentical groups), the causes of death were cytomegalovirus pneumonia, GVHD complicated by adenovirus infection, veno-occlusive disease, and GVHD (2 patients). Of the survivors, 1 patient has mild limitations caused by pulmonary disease but the remainder report no limitation of activities.

Course. Because bleeding is a major cause of morbidity and death in WAS, we compared the frequency of bleeding episodes in untreated versus treated patients. In 819 years of observation of untreated WAS patients, there was 0.414

Table IV. Types of malignancies and relation to autoimmune disease

Malignancy	Age at onset (yr)	Autoimmune disease
Lymphoma	2	0
Reticuloendothelial	2	AHA
Glioma	3	Vasculitis, arthritis
Lymphoma	4	Renal, IBD
Pre-B-cell lymphoma	4	Arthritis, vasculitis, angioedema
Lymphoreticular	4	0
Lymphoma	6	0
Reticulum cell sarcoma	6	Arthritis
Lymphoma	6	0
B-cell lymphoma	6	Vasculitis, AHA
Lymphoblastic leukemia	6	Renal, AHA
Malignant histiocytosis	7	Arthritis, renal, AHA, SHP
EBV + lymphoma	8	SHP, AHA, neutropenia
Lymphoma	10	0
Burkitt lymphoma	12	Arthritis, vasculitis
B cell lymphoma	15	SHP, arthritis, uveitis
Lymphoma	15	Vasculitis, arthritis
B-cell lymphoma	16	Neutropenia
Testicular carcinoma	19	Arthritis
B-cell histiocytic lymphoma	19	Arthritis, DM, AHA
Acoustic neuroma	26	Renal, vasculitis, IBD

AHA, Autoimmune hemolytic anemia; *IBD*, inflammatory bowel disease; *SHP*, Schönlein-Henoch purpura; *EBV*, Epstein-Barr virus; *DM*, dermatomyositis.

Table V. Concordance of phenotype among affected family members

Phenotype	Concordant		Discordant (no/yes)
	No/no	Yes/yes	
Platelets $<50 \times 10^9$/L ($<50{,}000/mm^3$)	1	12	10
Eczema	3	14	10
IgM <1 SD for age	13	2	6
IgA >2 SD for age	3	10	8
Lymphopenia	18	1	4
Eosinophilia	2	6	4
$CD8^+$ <15%	4	4	0
Low PHA	7	3	2
Autoimmune manifestations	16	3	8
Malignancy	20	0	7
Recurrent infection	3	10	11
Recurrent bleeding	15	0	5

significant bleeding episode per patient-year. In 354 years of observation of patients after splenectomy, there was 0.079 significant bleeding episode per patient-year, and in 283 years of observation after bone marrow transplantation (in which peritransplantation bleeding was excluded) there was a single event related to intestinal polyps. We also attempted to establish whether the initial platelet count was predictive of either frequency or severity of bleeding episodes. Using death caused by bleeding as an end point for severity, we found that the initial platelet count was *not* predictive of severe bleeding episodes. Approximately 4% to 10% of the patients died of bleeding regardless of whether their platelet count at the time of diagnosis was <10, 10 to 20, 20 to 50, or 50 to 100 $\times 10^9$/L. However, when total bleeding episodes were enumerated in patient groups according to initial platelet count, there was a clear correlation between initial platelet count and risk of bleeding. All patients with a platelet count of $< 10 \times 10^9$/L at the time of diagnosis had a significant bleeding episode and had an average of 3.85 bleeding episodes per patient-year. Only 39% of patients with a platelet count of 50 to 100 $\times 10^9$/L at the time of diagnosis had a significant bleeding episode, and that subgroup had an average of 1.08 bleeding episodes per patient-year ($p = 0.03$).

Patients with WAS had infections typical of both humoral and cellular immunodeficiences; certain infections suggested compromised neutrophil function, such as staphylococcal abscesses, *Pseudomonas* adenitis, and parotitis. Infections constitute significant morbidity for WAS patients, with a high incidence of recurrent disease (Table II). Recurrent otitis media, pneumonia, sinusitis, and herpes were the most common recurrent infections.

Approximately 40% (61 patients) of the patients in this survey had autoimmune or inflammatory manifestations of WAS (Table III). The most common was autoimmune hemolytic anemia. Many patients had more than one autoimmune process: 23 patients had a single autoimmune disorder, 22 had 2 disorders, 11 had 3 disorders, 4 had 4 disorders, and 1 had 5 disorders. In most cases the autoimmune disorders were not coincident. Inflammatory bowel disease, uveitis, and autoimmune neutropenia were seen in several patients. Autoimmune and inflammatory disorders seen in other immunodeficient patient populations, such as systemic lupus erythematosus, Sjögren syndrome, autoimmune endocrinopathies, and sarcoidosis were not seen in this population.

Malignancy developed in 21 patients (13%). The average age at onset was 9.5 years. The majority of the malignancies were lymphoreticular. One case of lymphoma occurred 6 months after haploidentical transplantation and could have been a result of that intervention. A glioma, acoustic neuroma, and testicular carcinoma were the only three nonlymphoreticular malignancies. Bone marrow transplan-

tation was attempted five times for malignancy; none of the five patients survived more than 6 months. Only one patient with a malignancy is alive more than 2 years after the diagnosis.

Patients who had an autoimmune disease were significantly ($p = 0.0009$) more likely to have a malignancy than those patients who did not (Table IV); 15 (75%) of 20 of the nonperitransplantation malignancies occurred in patients with a history of autoimmune disease. Conversely, 25% of the patients with a history of autoimmune disease ultimately had a malignancy, in comparison with just 5% of the patients who did not have a history of autoimmune disease. There was no association with reported steroid use.

Family analysis. We examined whether the phenotype was expressed similarly among affected members within a given kindred. For this purpose, 12 variables were compared in affected members. Variables were chosen to minimize institutional variation or questions of interpretation. Results are reported in terms of numbers of pairs concordant for a given finding versus those discordant (Table V). None of the variables was statistically more frequently concordant in family members than expected on the basis of the frequencies in the nonfamilial WAS group. Only the concordance of low $CD8^+$ cell counts in family members was significant ($p = 0.05$).

Correlations. To identify laboratory measures that might aid in the recognition of subgroups with a distinct natural history, we examined four laboratory measurements and five outcome measures. Low phytohemagglutinin responsiveness, $CD8^+$ cells <15%, T-cell numbers $< 0.8 \times 10^9$/L ($<800/mm^3$), and serum IgA >4 gm/L (>400 mg/dl) were examined as markers for poor outcome. The five measures of outcome were death, recurrent herpes, recurrent bleeding, malignancy, and autoimmune disease. None of the laboratory measures identified a subgroup with an increase in any of the measures of poor outcome.

DISCUSSION

Wiskott-Aldrich syndrome is typically considered a fatal disorder, although many patients not only survive into adulthood but are spared the most feared complications.[11, 12, 22, 32] The exact biochemical defect responsible for WAS is not yet known, and it has not been clear whether "mild variants" are the result of different mutations, different genetic background, or favorable environmental effects. A specific O-glycosylation defect has been described in WAS,[33, 34] but this has not yet been utilized as a tool for identifying subsets of patients. Identification of severe and mild subgroups of WAS would be of benefit in counseling families; one of the goals of this survey was to identify specific subgroups or to predict distinctive natural histories. As a first step to defining subgroups, this study examined the breadth of phenotypic expression in the WAS population as a whole.

Many patients were examined for relatively mild symptoms such as otitis media or petechiae; however, a minority had life-threatening events such as intracranial hemorrhage or cryptococcal pneumonia. In some cases the diagnosis was delayed for many years when the classic triad was not present. Our findings indicate that the classic triad is most often absent at onset.

The laboratory diagnosis of WAS has been problematic. Because of the inconsistent laboratory abnormalities, often only the most severely affected patients were ascertained. Small platelet size appears to be relatively specific for WAS or X-linked thrombocytopenia.[35, 36] The assay is widely available and standards have been established. The only disadvantage of this technique is that splenectomy may normalize or nearly normalize the platelet size.[37, 38] Quantitative abnormalities of immunoglobulin levels have been described in many patients with WAS,[7, 8] although in this series the characteristic elevated IgA and low IgM levels were seen most frequently in older patients. The absence of isohemagglutinins[6, 9, 10] or other antibodies to T-cell–independent polysaccharide antigens is a common finding, but our series demonstrates that its sensitivity as a diagnostic assay is less than 100%. Anti-CD43 antibody and periodate have been used in diagnostic assays for WAS,[8, 34, 39] but published series demonstrating specificity and sensitivity are not available. This study demonstrated that no one standard assay of immunologic function is consistently abnormal in WAS. At this point, the diagnosis must rest on a compatible constellation of findings. Supportive evidence includes small platelets, abnormal T- or B-cell function, and/or a compatible pattern of maternal X chromosome inactivation.[40, 41]

We analyzed four treatment strategies for thrombocytopenia. Although effective in some cases,[42] IVIG was not beneficial in this series except in patients who had acute ITP-like episodes after splenectomy. Corticosteroids were of modest efficacy and were most beneficial in the postsplenectomy group. Others have reported that splenectomy and BMT are both effective in reducing the incidence of bleeding episodes.[38, 43-49] In this series of patients (which includes some patients previously reported), splenectomy and BMT reduced the incidence of bleeding per patient-year by 81% and 99%, respectively. These two treatment strategies are not directly comparable because BMT provides additional benefit by effectively treating the immunodeficiency of WAS.

We were able to identify two high-risk groups. Patients with platelet counts $< 10 \times 10^9$/L ($<10{,}000/mm^3$) at the time of diagnosis universally had a significant bleeding episode. Bleeding was common in all platelet count subgroups,

and a high initial platelet count was not protective. A very low platelet count did not appear to be a marker for more generalized severe disease; non-bleeding-related deaths did not appear to be significantly increased in this group. The number of bleeding-related deaths was similar in all platelet count subgroups, suggesting that life-threatening bleeding events may occur in patients with relatively high initial platelet counts. Patients with autoimmune disease constitute the other high-risk group. These patients are at high risk of having a malignancy; nearly all the malignancies developed in this minority of patients.

Affected family members were examined in 26 pairs in an effort to determine whether any WAS manifestations could be predicted on the basis of experience with an affected relative, but there was little concordance among affected family members. We conclude that it is not always possible to predict natural history in one child on the basis of experiences with another affected family member.

The last large study of WAS was published in 1980.[50] That study noted that life expectancy had increased from 8 months in patients born before 1935 to 6.5 years in patients born after 1964. Further progress has been made in the last 13 years. The average age of living patients in our study was 11 years, with a range of 1 to 35 years; 16 patients are older than 18 years of age. The average age of those deceased was 8 years. Our findings of the causes of death are similar to those previously published; deaths caused by bleeding (23% of the non-BMT deaths), infection (44% of the non-BMT deaths), and malignancy (26% of the non-BMT deaths) account for the majority of the deaths.

ADDENDUM

The molecular defect in three WAS kindreds was recently identified: cell 78:635-44.

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