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ORIGINAL ARTICLE

The clinical features of autoimmunity in 53 patients with Wiskott–Aldrich syndrome in China: a single-center study

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Abstract Autoimmune disease (AD) is common in patients with Wiskott-Aldrich syndrome (WAS) and patients with WAS who has an AD usually constitute a high-risk group with poor outcome. However, knowledge of AD in WAS is limited in China. In this study, medical records of 53 patients with WAS at Children´s Hospital of Chongqing Medical University from April 2004 to January 2014 were evaluated retrospectively and 14 patients (26%) had at least one AD. Autoimmune hemolytic anemia (AIHA) was the most common and detected in 12 patients (23%), other complications included immune thrombocytopenia (n = 1), immune neutropenia (n = 1), autoimmune arthritis (n = 1), and renal injury (n = 1). No significant differences were found in the level of serum immunoglobulins and lymphocyte subsets between the AD group and non-AD group. Although eight patients with AD received hematopoietic stem cell transplantation (HSCT), three patients died of pulmonary infection after HSCT.

Conclusions: AD is frequent in Chinese patients with WAS and AIHA was the most common. AD is a poor prognosis factor for WAS and should be treated as early as possible by HSCT.

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What is Known:

- *Autoimmune disease is common in patients with WAS.*
- *Manifestations, follow-up finding, and treatment approaches of autoimmune disease in Chinese patients with WAS have received less attention in the literature.*

What is New:

- *This study is firstly intended for evaluation of the clinical and immune characteristics of autoimmune disease in a large series Chinese patients with WAS.*
- *AD is frequent in Chinese patients with WAS and AIHA is the most common.*

Keywords Wiskott–Aldrich syndrome · Autoimmune disease · Autoimmune hemolytic anemia · Hematopoietic stem cell transplantation

Abbreviations

AD	Autoimmune disease
HSCT	Hematopoietic stem cell transplantation
ITP	Immune thrombocytopenia
IVIG	Intravenous immunoglobulin
WAS	Wiskott–Aldrich syndrome

Introduction

Wiskott–Aldrich syndrome (WAS) is a complex and severe X-linked disorder characterized by microthrombocytopenia, eczema, immunodeficiency, and an increased risk of autoimmunity and lymphomas [1, 16]. Patients with WAS who have an autoimmune disease (AD) usually constitute a high-risk group with poor outcome and an increased risk of developing a malignancy. In recent study, autoimmune diseases are closely related with heredity and race [8]. However, to date, knowledge of autoimmune complications in WAS is limited in China. We studied 53 patients with WAS to evaluate the clinical manifestations, organ involvement, progression, treatment and prognosis of autoimmune complications, with the goal of improving early diagnosis and treatment options.

Methods

Selection of patients, data collection and definitions

We retrospectively analyzed the clinical data of 53 patients with WAS. All the patients were referred to Children's Hospital of Chongqing Medical University between April 2004 and January 2014. They were diagnosed definitively by WAS gene analysis. The clinical features of the patients with AD were subsequently analyzed. Signed consent of all children or their parents was obtained, and the study was approved by the ethics committee of Children's Hospital of Chongqing Medical University.

Data collected included age, sex, family history, past history, the signs and symptoms, auxiliary examination, diagnosis, treatment, and prognosis. Patients were divided into an AD group and a non-AD group according to whether they had an AD. Immunological indicators in the two groups were compared by statistical analysis.

Autoimmune hemolytic anemia (AIHA) was defined as: (1) hemolysis with anemia, jaundice, and a change in urine color; (2) the presence of autoantibodies that agglutinated or lysed the patient's own red blood cells (a positive Coombs' test); and (3) clinical manifestations that were improved by steroid therapy. Immune thrombocytopenia (ITP) was defined as: (1) low platelet counts (<100,000 platelets/mm^3); (2) an increased level of platelet-associated immunoglobulin; and (3) hematological malignancy excluded by bone marrow examination. Autoimmune neutropenia was defined as neutropenia (<1,000 polynuclear neutrophils/mm^3) except for that caused by infections, drugs or malignant disease, or the presence of autoantibodies against polymorphonuclear cells. Immune arthritis was defined as pain and swelling in joints except for that caused by suppurative infection, hematological malignancy, or connective tissue disease. Renal injury was defined as hematuria and proteinuria with renal function damage.

Cure of AIHA was divided into three levels according to established criteria. Complete remission was defined as normal hemoglobin levels and reticulocyte levels <0.05. Partial remission was defined as hemoglobin levels >80 g/L. No remission was defined as not meeting the criteria for complete or partial remission. Recurrence was defined as hemoglobin levels <100 g/L after complete remission.

Flow cytometry of regulatory T cells

Ten patients in AD group and 11 patients in non-AD group received analysis of regulatory T cells by flow cytometry. Peripheral blood mononuclear cells (PBMCs) were isolated by density gradient centrifugation with lymphocyte separation medium (TBD, CHN) within 4 h and then incubated with CD4 (IgG1, FITC, clone RPA-T4) and CD25 (IgG1, PE, clone BC96) monoclonal antibodies (mAbs) separately for 30 min at 4 C. Following fixation, permeabilization was performed according to the manufacturer's instructions. Then, anti-human FOXP3 (IgG2a κ, PE-CY5, clone PCH101) was added followed by incubation at 4 C for at least 30 min in the dark. After washing, the expressions of CD4, CD25, and FOXP3 were determined using a flow cytometer (FACSCalibur; Becton Dickinson, Mountain View, CA, USA) after live cell gating determined by scatter characteristics, and the data were analyzed using FLOWJO software (Tree Star, Ashland, OR, USA). To avoid non-specific staining, isotype control mouse anti-human mAbs were used: IgG1 (PE, clone P3) for CD25 and IgG2a κ (PE-CY5, clone G155-178) for FOXP3. All mAbs were purchased from ebioscience Immunocytometry System (eBioscience, San Diego, CA, USA).

Follow-up

All patients with AD were followed-up until February 28, 2014. Patients with AIHA were followed-up for the hemolytic symptoms of anemia, jaundice, dark urine, and hemoglobin, and reticulocyte count, bilirubin levels and Coombs' test results were assessed. Bleeding, platelet levels, and the presence of platelet-associated antibodies were examined during the follow-up of WAS patients with ITP. Symptoms of pain and swelling of joints and imaging test findings were followed-up in patients with arthritis. In patients with renal injury, hematuria, proteinuria, and renal function results were followed-up.

Statistical analysis

SPSS17.0 software was used for statistical analysis and data processing. Enumeration data were compared with the χ^2 test and differences in measurement data were compared with the t test. Differences were considered significant if the calculated P value was below 0.05.

Results

The incidence of AD

Fifty-three patients with WAS were enrolled in the study and the mean age of diagnosed WAS was 12 months (range, 1–147 months). AD were frequently observed and 14 (26 %) of the patients developed at least one AD. In the AD group, the mean diagnostic age of WAS was 30.9 months and the mean age of diagnosed AD was 17.5 months (range, 4–98 months). Arthritis and renal injury occurred after 8 years of age. Thirty-nine WAS patients without AD were enrolled and most of their clinical scores were between 3 and 4. The mean diagnostic age of WAS in the non-AD group was 20.7 months and 19 patients had positive family history. (Table 1) The most common AD was AIHA (n=12) and the mean age of diagnosed AIHA was 16.5 months (range 4–40 months). Other autoimmune complications included ITP in one patient, neutropenia in one patient, arthritis in one patient, and renal injury in one patient. Twelve patients had a single autoimmune complication, whereas two patients had two complications: one patient had AIHA and ITP, the other had AIHA and autoimmune neutropenia (Fig. 1).

The clinical manifestations of AIHA

Of the 12 patients with AIHA, anemia was the most common manifestation (n=12), followed by hepatomegaly (n=5), splenomegaly (n=4), jaundice (n=3), and dark urine (n=2). Severe anemia was detected in four patients, and the level of hemoglobin ranged from 29 to 56 g/L. The direct antiglobulin test of all 12 patients with AIHA was positive. The direct antiglobulin test and indirect antiglobulin test were positive in seven patients. In ten patients with AIHA, the diagnosis had occurred after the diagnosis of WAS, and in two patients the diagnosis had occurred when WAS was diagnosed. Cytomegalovirus infection was detected in five patients and Epstein–Barr virus co-infection in one patient. In addition, aspergillus infection was identified in two patients with severe anemia (Table 2).

Table 1 Clinical data of the WAS patients with autoimmune disease and without autoimmune disease

	AD	non-AD
Clinical phenotype		
WAS	13	33
XLT	1	6
Clinical score		
2	0	6
3	0	15
4	0	17
5	14	1
Onset age of WAS (month)		
Mean	1.5	1.7
Range	0–6	0–17
Diagnostic age of WAS (month)		
Mean	30.9	20.7
Range	2–147	1–127
Family history		
Positive	8	19
Negative	6	20

AD autoimmune disease

The treatment and outcome of AIHA

Three patients with AIHA did not receive immunosuppressive therapy because the hemolysis was not severe. They only received blood transfusion and one patient achieved complete remission, while two patients reached partial remission. Most of the 12 patients with AIHA (n=9) received steroids as the first-line treatment. Only one of these patients reached complete remission with a single treatment of steroids and the other eight patients received other treatments, including intravenous immunoglobulin (IVIG; n=8), rituximab (n=3), cyclosporine A (n=2), plasma exchange (n=2), tacrolimus (n=1), and splenectomy (n=1). The median duration of treatment was 1 month (range, 1 week to 6 months). After treatment, five patients (42 %) achieved complete remission, four patients (33 %) achieved partial remission, two patients (17 %) did not achieve remission and one patient relapsed (8 %). A total of eight patients with AIHA had undergone hematopoietic stem cell transplantation (HSCT). WASP and short tandem repeats (STR) were detected as the evidence of engraftment. All the eight patients exhibited normal expression of WASP and full chimerisms were also detected 50 days after transplantation. Full chimerism was defined by the presence of 95 % or more donor blood cells. Hematopoietic stem cell source was HLA-matched bone marrow from the sibling of one case and unrelated HLA-mismatched cord blood in seven cases.

AIHA occurred before transplantation in three patients and after transplantation in five patients. In these five patients, AIHA appeared at a median of 2 months after HSCT (range, 1–7 months). Three patients who received HSCT died of severe pulmonary infection and two patients without HSCT died, one of intracranial hemorrhage, and one of pulmonary hemorrhage.

In patient 11, AIHA occurred 3 months after HSCT. He received steroids, IVIG, and repeated blood transfusion as first-line treatment, but it proved ineffective. Even after receiving cyclosporine A (CsA), rituximab, and plasma exchange, the condition of the patient did not improve and he required a daily transfusion. After the patient underwent

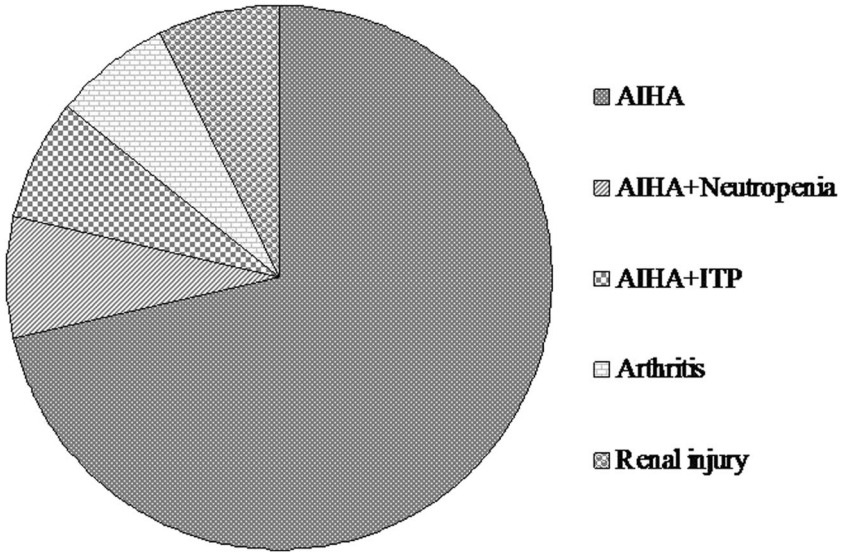

Fig. 1 A pie chart depicting autoimmune disease in patients

splenectomy due to hepatomegaly and hypersplenism, the frequency of transfusion decreased and hemolysis improved gradually until the patient finally achieved partial remission. Hemolysis in patient 12 was partially controlled with steroids and IVIG, but he relapsed when steroid dosage was decreased. The patient then received CsA, rituximab, plasma exchange, and transfusion in combination, which led to partial remission; however, four additional relapses occurred during treatment. The patient died of acute respiratory distress syndrome and cardiorespiratory failure.

Four patients did not undergo HSCT and two of these patients (patients 2 and 10) died. Patient 2 received steroids, IVIG and repeated transfusions of red blood cells and platelets, but remission was not achieved. The patient died of pulmonary hemorrhage after treatment for 1 week because of rapid worsening of AIHA. Patient 10 with AIHA and ITP received treatment with steroids and IVIG but failed to achieve remission. Rituximab and transfusion also proved ineffective. The patient died of intracranial hemorrhage and cerebral hernia at 5 months old.

Table 2 The clinical manifestations and laboratory examination of 12 patients with AIHA

Patient	AD	Age at diagnosed (months)	Clinical manifestations	Laboratory examination					
				Coombs		Hb	Ret	SB	Autoantibody/other
				DAT	IAT	(g/L)			
1	AIHA	7	Anemia	+	+	77	↑	N	–
2	AIHA	7	Anemia hepatosplenomegaly	+	+	56	↑	↑	ND
3	AIHA	16	Anemia jaundice	+	–	77	↑	↑	Anti-ssDNA(+)
4	AIHA	17	Anemia	+	+	67	ND	↑	ND
5	AIHA+ neutropenia	25	Anemia hepatosplenomegaly	+	–	76	ND	N	–
6	AIHA	7	Anemia	+	–	74	ND	N	ND
7	AIHA	37	Anemia	+	–	75	↑	N	–
8	AIHA	25	Anemia; hepatomegaly	+	–	75	↑	N	Anti-ANuA(+)
9	AIHA	18	Anemia	+	–	85	↑	N	ND
10	AIHA+ITP	4	Anemia; intracranial hemorrhage	+	+	48	↑	↑	ND/PAIgG(+)
11	AIHA	14	Anemia; jaundice; dark urine; hepatosplenomegaly	+	+	29	↑	↑	ND
12	AIHA	40	Anemia; jaundice; dark urine; hepatosplenomegaly	+	+	54	↑	↑	Anti-ssDNA(+)

AIHA autoimmune hemolytic anemia, *ITP* immune thrombocytopenia, *DAT* direct antiglobulin test, *IAT* indirect antiglobulin test, *Hb* hemoglobin, *Ret* reticulocyte, *SB* serum bilirubin, *PAIgG* platelet-associated IgG, *N* normal, *ND* not determined, + weakly positive, −: negative, ↑ increase

Clinical characteristics of other ADs

Other ADs were identified in four patients, including arthritis, renal injury, ITP, and neutropenia in one patient each. One patient with AIHA also had ITP and another patient with AIHA had neutropenia. A patient with a reverse mutation (second-site mutation) of the WAS gene was ill with persistent arthritis for several years, which was partially controlled by treatment with IVIG and the biological agent etanercept. Unfortunately, the patient died of extensive pulmonary fibrosis in October of 2013.

The patient with renal injury presented with recurrent hematuria, mainly microscopic hematuria, with a small amount of protein in the urine. IgA nephropathy was under clinical consideration, but renal biopsy was contraindicated because of thrombocytopenia. Remission of hematuria and proteinuria was not obvious after therapy with oral steroids for 1 month. The condition deteriorated and albuminuria achieved significant levels even after combined treatment with oral steroids and *Tripterygium wilfordii* for 1 year. Thereafter, the condition of the patient progressed to chronic renal function failure.

Immunological examination

The data about the immunological examination in the AD group have been obtained at the onset of the disease. Serum immunoglobulin tests were conducted in 11 patients with AD (Table 3). Serum IgG level was normal in three patients and elevated in eight patients. IgA level was elevated in six patients and normal in five patients. IgM level was reduced in six patients, normal in four patients, and elevated in one patient. Lymphocyte subset analysis was conducted in 11 patients (Table 4). Percentage of $CD3^+$ T cell counts were normal in seven patients and reduced in four patients. Percentage of $CD19^+$ B cell counts were normal in four patients and $CD56^+16^+$ natural killer cell counts were normal in eight patients, elevated in two patients, and reduced in one patient. The absolute counts of the lymphocyte subsets were also evaluated and CD3+ T cell counts reduced in eight patients and were normal in two patients. $CD19^+$ B cell absolute counts reduced in eight patients and $CD56^+16^+$ natural killer cell absolute counts elevated in five patients.

Twenty-six of the 39 patients in the non-AD group had immunoglobulin test results. In this non-AD group, mean levels of IgG and IgA were elevated and IgM levels were reduced; however, levels of IgG, IgA and IgM were not significantly different from those in the AD group. Twenty-two patients in the non-AD group had lymphocyte subset examinations. No significant difference was found between the AD group and non-AD group.

Frequency of CD4+CD25+FOXP3+ Tregs in PBMCs in AD group and non-AD group

Ten patients in AD group and 11 patients in non-AD group were selected randomly to detect the frequency of CD4+ CD25+FOXP3+ Tregs in PBMCs. No significant differences were found between the patients from AD group and non-AD group (3.8±0.63 % versus 3.4±0.45 %) (Fig. 2).

Table 3 The immunoglobin level of 11 patients of WAS with AD

P	Age (month)	Immunoglobin (g/L)					
		IgG	Normal range	IgA	Normal range	IgM	Normal range
1	7	19.1	4.090~7.030	0.35	0.210~0.470	0.63	0.330~0.730
2	7	ND		ND		ND	
3	16	16.8	5.090~10.090	2.29	0.310~0.670	1.23	0.980~1.780
4	17	15.8	5.090~10.090	2.95	0.310~0.670	1.15	0.980~1.780
5	25	7.37	5.090~10.090	0.404	0.310~0.670	0.22	0.980~1.780
6	7	21.3	4.090~7.030	0.92	0.210~0.470	2.17	0.330~0.730
7	37	12.5	6.600~10.390	1.97	0.580~1.000	0.32	1.100~1.800
8	35	23.5	5.090~10.090	0.51	0.310~0.670	0.28	0.980~1.780
9	18	13.4	5.090~10.090	0.43	0.310~0.670	0.34	0.980~1.780
10	4	ND		ND		ND	
11	14	ND		ND		ND	
12	40	10.8	6.600~10.390	1.82	0.580~1.000	1.15	1.100~1.800
13	147	12.6	8.270~14.170	1.75	0.860~1.920	0.98	1.220~2.560
14	125	12.5	7.910~13.070	8.54	0.850~1.710	0.28	1.200~2.260

ND not detected

Table 4 Analysis of lymphocyte subsets in WAS patients with autoimmune disease

P	Age (month)	Lymphocyte subsets									
		CD3+	Normal	CD4+	Normal	CD8+	Normal	B	Normal	NK	Normal
1	7	55	45~79	15	36~61	33	16~34	21	19~31	20	7~40
		990	2280~6450	270	1690~4600	594	720~2490	378	500~1500	360	200~800
2	7	ND		ND		ND		ND		ND	
3	16	67	53~81	21	31~54	45	16~38	20	19~31	13	7~40
		914	1460~5440	286	1020~3600	614	570~2230	273	500~1500	177	100~1100
4	17	53	53~81	36	31~54	16	16~38	21	19~31	24	7~40
		979	1460~5440	665	1020~3600	296	570~2230	388	500~1500	443	100~1100
5	25	26	62~80	22	35~51	3	22~38	10	21~28	63	7~40
		1499	1610~4230	1269	900~2860	173	630~1910	577	700~1300	3806	100~700
6	7	60	45~79	17	36~61	42	16~34	6	19~31	33	7~40
		2364	2280~6450	670	1690~4600	1655	720~2490	236	500~1500	1300	200~800
7	37	ND		ND		ND		ND		ND	
8	35	ND		ND		ND		ND		ND	
9	18	81	53~81	23	31~54	54	16~38	7	19~31	11	7~40
		10975	1460~5440	3116	1020~3600	7316	570~2230	948	500~1500	1490	100~1100
10	4	75	45~79	63	36~61	10	16~34	16	19~31	4	7~40
		1448	2280~6450	1216	1690~4600	193	720~2490	309	500~1500	77	200~900
11	14	70	53~81	35	31~54	33	16~38	21	19 ~31	8	7~40
		1005	1460~5440	503	1020~3600	474	570~2230	302	1 500~1500	115	200~900
12	40	19	62~80	13	35~51	6	22~38	50	21~28	28	7~40
		484	1610~4230	331	900~2860	153	630~1910	1274	700~1300	714	100~700
13	147	49	66~76	35	33~41	17	27~35	39	12~22	9	7~40
		1532	1400~2000	1094	700~1100	532	600~900	1219	300~500	181	100~700
14	125	36	66~76	16	33~41	20	27~35	5	12~22	57	7~40
		1019	1400~2000	453	700~1100	566	600~900	142	300~500	1614	100~700

The percentage of lymphocyte subsets was located in the first line and absolute number of lymphocyte subsets was located in the second line

Discussion

WAS is an X-linked primary immunodeficiency originally described as a clinical triad of immunodeficiency, thrombocytopenia, and eczema. Autoimmune complications are a cause of considerable morbidity and not infrequent mortality in patients with WAS, and the true prevalence of these complications is not clearly established and data on AD in Chinese patients with WAS is limited. In the study, clinical data about the frequency, severity, and treatment of AD were analyzed in a cohort of 53 Chinese patients with WAS from April 2004 to January 2014. Fourteen patients (26 %) developed at least one AD. By contrast, the prevalence of autoimmunity in WAS is high in the USA and Europe, affecting 40–72 % of patients [25, 6]. The prevalence of AD in our study was markedly lower than that observed in the study from the USA [26], but could be underestimated because AD may not have occurred by the time of follow-up termination. This possibility stresses the need for continuous follow-up clinical information. In addition, some of the patients with WAS may have died before the onset of AD.

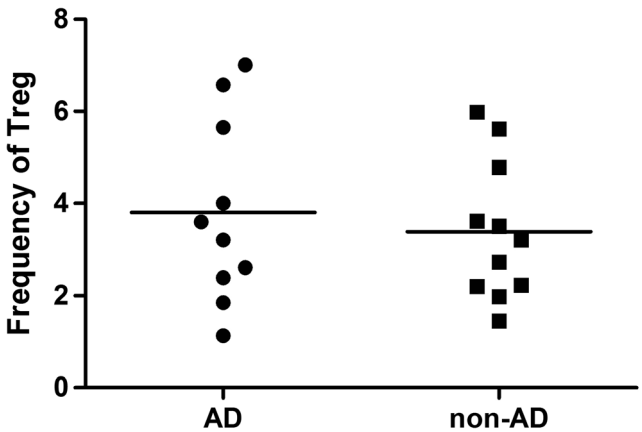

Fig. 2 Frequency of CD4+CD25+FOXP3+ Tregs in PBMCs in AD group and non-AD group

The common ADs in WAS are AIHA, vasculitis, arthritis, and nephropathy, followed by inflammatory bowel disease, ITP, and neutropenia [22, 18]. Similar to previous studies

[25, 6, 17], AIHA was the most common AD in Chinese patients with WAS. In our study, 12 of 53 patients with WAS developed AIHA, including one patient who also had ITP and another patient who also had immune neutropenia. The mean age of diagnosed AIHA was 17.5 months, consistent with previous studies [25, 6, 11]. Renal injury was originally thought to be rare in patients with WAS and affected 3.5–12 % of patients [6, 9, 23, 25]. Knowledge of the mechanisms of nephropathy in WAS patients is limited and renal biopsies are often contraindicated in patients with WAS because of thrombocytopenia. The few biopsies performed have shown various pathologies including membranoproliferative glomerulonephritis, mesangial proliferation, interstitial nephritis, and IgA nephropathy [27, 6, 12]. In our study, IgA nephropathy was under clinical consideration in an X-linked thrombocytopenia (XLT) patient, but renal biopsy was contraindicated. In this patient, chronic renal function failure occurred after treatment with steroids combined with mycophenolate mofetil for 1 year. In consequence, great attention should be paid to the evaluation of the renal function in patients with WAS, especially in older children. In WAS, chronic arthritis has been described in approximately 10 % of patients, and patients with rheumatoid arthritis have been found to have a higher relative risk of developing lymphomas than the general population [3]. In our study, a patient with a reversion mutation of the *WAS* gene had arthritis and although the clinical symptoms of infection improved, the symptoms of arthritis persisted for several years and could be controlled only partially by treatment with the biological agent etanercept. Unfortunately, the patient developed right paralysis in August 2013 and died of extensive pulmonary fibrosis 2 months later. Chronic arthritis may be a risk factor of poor prognosis and should be carefully monitored.

In previous studies, the level of IgG was normal or reduced, the level of IgA was elevated and the level of IgM was reduced in most patients with WAS [10, 13]. In our study, no significant difference was found in the level of immunoglobulins or percentage and absolute number of lymphocyte subsets between the AD group and non-AD group. The mechanisms of autoimmunity in WAS are not clear, but may be related to an inability to clear pathogens completely and to defects in autoantigen tolerance [4, 5, 7, 14]. In addition, defects in Treg ($CD4^+CD25^+FoxP3^+$) function [15], impaired phagocytosis, decreased production of interleukin 2, and increased production of autoantibodies owing to B cell intrinsic dysfunction may also contribute to autoimmunity [2, 20]. However, in our study, there was no significant difference between AD and non-AD group about frequency of CD4+CD25+FOXP3+ Tregs in PBMCs. A high serum IgM level is a risk factor for poor prognosis in WAS patients with AIHA [6]. Only one patient with AIHA had a high level of IgM in our study. Prognostic indicators of AIHA do not only depend on the level of IgM because immunoglobulin levels vary greatly in patients with WAS, and AIHA should be considered if hemorrhage is mild but anemia is severe. The relationship between IgM levels and prognosis of AIHA needs to be confirmed.

AIHA was a frequent, early-onset complication that clearly predicted a poor prognosis, and is one of the most common indications for HSCT in patients with WAS [6, 4, 24, 28]. In our study, eight patients with AIHA received HSCT and three of these patients died of severe pulmonary infection. In a previous study, Ozsahin et al. [19] observed that 20 % of patients with WAS developed autoimmunity after HSCT, which was independent of chronic graft-versus-host disease but significantly associated with mixed/split chimerism. Autoimmunity developed at a median of 1.5 years after HSCT (range, 4 months to 10 years) and ADs were more frequent in recipients of matched unrelated donors and mismatched related donors than related HLA-identical donors. In our study, of the five patients who developed AIHA after HSCT, the median time to development of AIHA was 2 months and all the five patients exhibited normal expression of WASP, and full chimerisms were also detected 50 days after transplantation. Optimization of conditioning, stem cell number and choice of suitable donor for transplantation perhaps alleviates autoimmune complications after transplantation. In a study of 107 patients with AIHA, 18 % developed a malignant lymphoproliferative disorder [21]. A relationship appears to exist between AIHA and the subsequent appearance of lymphoid malignancies. No malignancies were identified in patients with AIHA in our study, but continuous follow-up should be conducted in this patient group.

Autoimmune complications are frequent in Chinese patients with WAS. AIHA is the most common AD and is associated with a poor prognosis, especially in patients with a poor response to steroids and other immunosuppressive treatments. Recognizing and appropriately managing autoimmune complications in patients with WAS is particularly challenging. Nevertheless, our improved understanding of the basic mechanisms of autoimmunity will hopefully inform both the search for the underlying causes of common ADs and potential pathways that may be targeted therapeutically to modulate immunity.

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Author's contributions Xiao-Dong Zhao conceived and designed the study.

Nan Chen Zhi-Yong Zhang collected clinical data, performed the data analyses and wrote the manuscript (contributed equally).

Da-Wei LiuWei Liu, Xue-Mei Tang helped perform the analysis with constructive discussions.

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