Clinical profile and genetic basis of Wiskott-Aldrich syndrome at Chandigarh, north India

Deepti Suri,[1] Surjit Singh,[1] Amit Rawat,[1] Anju Gupta,[1] Chikako Kamae,[2] Kenichi Honma,[2] Noriko Nakagawa,[2] Kohsuke Imai,[2] Shigeaki Nonoyama,[2] Koichi Oshima,[3] Noriko Mitsuiki,[3] Osamu Ohara,[3] Chrystèle Bilhou-Nabera,[4] Alexis Proust,[4] Jasmina Ahluwalia,[5] Sunil Dogra,[6] Biman Saikia,[7] Ranjana Walker Minz[7] and Shobha Sehgal[7]

Summary

Background: **The Wiskott-Aldrich syndrome (WAS) is a rare X-linked immunodeficiency disorder characterized by thrombocytopenia with small sized platelets, eczema, and recurrent infections. There is paucity of information on WAS from the Indian subcontinent. We describe the clinical and molecular profile of 8 patients with WAS as seen in the Pediatric Immunodeficiency Clinic at the Advanced Pediatrics Centre, Postgraduate Institute of Medical Education and Research, Chandigarh, India.**

Methods: **A detailed analysis of the clinical profiles, investigations and outcome of the 8 children diagnosed with WAS during the period 2006- 2010 was performed. Confirmation of the genetic diagnosis was done at the Service d'Hématologie, d'Immunologie et de Cytogénétique, Hôpital de Bicêtre, Le Kremlin-Bicêtre, France and the National Defense Medical College, Saitama, Japan.**

Results: **8 patients were diagnosed as WAS in 5 years. The ages at diagnosis ranged from 13 weeks to 9 years while the mean age of onset of the symptoms was 117 days ± 136 days. The diagnosis was established within a mean period of 31 months (ranging1-108 months) from the onset of symptoms. Recurrent infections and diarrhea were seen in 6 and 7 out of the 8 patients, respectively, while eczema was variable. Autoimmunity manifestations were observed in 2 children. Thrombocytopenia and small platelet size was the hallmark of the disease and the main clinical clue to diagnosis in our patients. Mutations in the *WASP* gene were seen in 8 children, out of which 2 were novel mutations. While one child successfully underwent bone marrow transplantation, two children are doing well on immunoglobulin replacement and cotrimoxazole prophylaxis. Out of 8 children 4 children in our cohort died - all had high WAS scores and could not be offered hematopoietic stem cell transplantation.**

Conclusion: **WAS should be suspected clinically in any male infant with persistent unexplained thrombocytopenia and especially if the platelet size is small. Clinical presentation can be very variable and it is therefore important to recognize the entire spectrum of the disease. Understanding the molecular basis has important implications for the diagnosis, treatment, and genetic counseling of patients with WAS. *(Asian Pac J Allergy Immunol 2012;30:71-8)***

Key words: *Wiskott-Aldrich Syndrome, Thrombocytopenia, North India*

From the 1. Departments of Pediatrics, Postgraduate Institute of Medical Education and Research, Chandigarh, India.
2. National Defense Medical College, Tokorozawa, Saitama, Japan.
3. Kazusa DNA Research Institute, Kisarazu, Chiba, Japan.
4. Service Hématologie, Immunologie et de Cytogénétique, Hôpital de Bicêtre, Le Kremlin Bicêtre, France.
5. Department of Hematology, Postgraduate Institute of Medical Education and Research, Chandigarh, India.
6. Department of Dermatology, Postgraduate Institute of Medical Education and Research, Chandigarh, India.
7. Department of Immunopathology, Postgraduate Institute of Medical Education and Research, Chandigarh, India
Corresponding author: Surjit Singh
E-mail: surjitsinghpgi@rediffmail.com
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Key Messages/ Clinical Implications:

One should suspect Wiskott-Aldrich syndrome in boys who have persistent unexplained thrombo-cytopenia.

Introduction

The Wiskott-Aldrich syndrome (WAS) is a rare X-linked immunodeficiency disorder characterized by a clinical phenotype that includes thrombo-cytopenia with small platelets, eczema, and recurrent infections. The condition was first described by Wiskott in 1937[1] while the X-linked nature of the syndrome was identified by Aldrich in 1954.[2] The identification of the molecular defect in 1994 by Derry et al.[3] has broadened the clinical spectrum of the syndrome to include chronic or intermittent X-linked thrombocytopenia (XLT), a relatively mild form of WAS[4,5,6] and X-linked neutropenia caused by arrest of myelopoiesis.[7] The *Wiskott-Aldrich Syndrome Protein (WASP)* gene codes for a protein selectively expressed in the hematopoietic system and is involved in the cytoskeletal-organizing complex, its maturation, activation and transport of blood elements.[8]

The incidence of WAS is estimated to be between 1-10/million of the population.[9,10] Recent reports however, suggest that this may be an underestimate, as the phenotype of the disorder is much broader than hitherto recognized[11,12]. However, there is paucity of information on WAS from the Indian subcontinent.

The present paper describes clinical experience in managing 8 patients suffering from WAS as seen at the Pediatric Allergy Immunology Unit, Postgraduate Institute of Medical Education and Research, Chandigarh, India.

Methods

Patients and methods:

The case records of all children attending the Pediatric Immunodeficiency Clinic at the Advanced Pediatrics Centre, Post Graduate Institute of Medical Education and Research, Chandigarh from January 2006 to December 2010 were reviewed. The institute serves as a tertiary care referral center for North West India. A detailed analysis of clinical profiles, investigations and outcome of the children with this syndrome was carried out. The severity of WAS-associated symptoms was expressed as a clinical score of 1-5, based on a previously published scoring system.[13,14] Skin biopsy was performed in patient with cutaneous vasculitis and subjected to histopathology and immunoflorescence studies . Serum IgG, IgM and IgA were estimated by end-point nephelometry on a semi-automated nephelometer while IgE was estimated by enzyme immunoassay.

The confirmation of the genetic diagnosis was carried out with the consent of the parents at Service d'Hématologie, d'Immunologie et de Cytogénétique, Hôpital de Bicêtre, Le Kremlin-Bicêtre, France and at the National Defense Medical College, Saitama, Japan.

Results

During this period of 5 years, WAS was clinically suspected in 13 patients, all of Caucasian ethnicity. The diagnosis was genetically confirmed in 8 patients. No mutations could be demonstrated in the *WASP* gene in 3 children, while 2 were lost to follow-up.

The ages at diagnosis ranged from 13 weeks - 9 years, while the mean age of onset of the symptoms was 117 days $\pm$ 136 days. The diagnosis was established within a mean of 31.9 months, from the onset of symptoms ranging from1-108 months.

Clinical features

Out of the total of 8 children, 7 (87.5%) presented with loose stools with 6 (75%) having blood in them. Recurrent infections were very prominent in all except patient numbers 2 and 6 (75%). Major infections included pneumonia (75%), otitis media (37.5%), septic arthritis and osteomyelitis (37.5%), meningitis (25%), and Herpes zoster (12.5%). The details are shown in Table 1. Patients 1 and 7 suffered from many pyogenic infections before the diagnosis was established. The degree of eczema was variable and was extremely difficult to control in patient 4. Autoimmunity was observed in two children [patient 3 and patient 8]. Patient 3 had a prominent vasculitic rash on the dorsum of the hands and feet, while patient 7 had developed vasculitic skin lesions and scrotal gangrene. A detailed family history revealed the death of a maternal uncle in early infancy in 3 families.

Investigations

Thrombocytopenia was the hallmark and the main clue to diagnosis. Even though the mean platelet volume was not very low, the small platelet morphology was observed on smear by an experienced hematologist. Ig M was low in 4, normal in 3 and high in 1 child. Ig G was increased in 4 children, while Ig A and Ig E fractions were

Table 1. Clinical Features of patients with Wiskott Aldrich Syndrome Patient

Patient	State of residence	Age at onset of symptoms (days)	Age at diagnosis (months)	Infections/manifestations	Bleeding	Eczema	Auto immunity	WAS score	Family history	Treatment	Age at last follow up (years)	Approximate follow up duration (years)	Present status/comments
Patient 1	Karnataka	60	54	Diarrhoea; Staphylococcal epidermidis meningitis; pneumonia; septic arthritis; gluteal abscess; otitis media	Blood in stools	+	none	4	2nd degree consanguinity	IV Ig	8.5	4	Presently well, no major hospitalizations
Patient 2	Himachal Pradesh	45	2.5	Loose stools with blood	Epistaxis	+	none	3	Death of maternal uncles	IV Ig HSCT	4	4	Well
Patient 3	Chandigarh	15	2.5	Staphylococcal osteomyelitis of tibia; Varicella zoster over scalp; Candidaemia disseminated candidiasis with meningitis and pneumonia; loose stools with blood	Blood in stools	+	Leucocytoclastic vaculitis on dorsum of hands and feet	5	Not significant	IV Ig; Steroids for vasculitis, splenectomy done before diagnosis of WAS established	3.5	3.5	Died; pre-terminally developed intractable diarrhea and pneumonia
Patient 4	Haryana	180	12	Staphlococcal aureus otitis media;pneumonia; anemia; micronutrient deficiency	Hemetemesis	+ +	none	4	Death of maternal uncles	IVIg	3	2	Died; at home
Patient 5*	Uttar Pradesh	5	5	Pneumonia; Diarrhoea	Blood in stools	+ +	none	4	Cousin of patient 4	No treatment	-	No follow up	Died; at home
Patient 6	West Bengal	8	4.5	Loose stools with blood;	Hematuria, skin bleeds	+	none	4	Death of maternal uncles	IV Ig	4.9	4	Well
Patient 7*	Punjab	360	108	Pneumonia; septic arthritis; diarrhea	Hemoptysis, skin bleeds	+	none	4	Not significant	No treatment	9	No follow up	Died; at home
Patient 8	Haryana	270	60	Pneumonia; otitis media;anemia	Skin bleeds	-/+	Leucocytoclastic vasculitis with scrotal gangrene	5	Not significant	Steroids for vasculitis	8	3	Well

increased in all patients. Table 2 summarizes the laboratory findings in all the 8 patients.

The genetic mutation analysis was done at the Hôpital de Bicêtre, Le Kremlin-Bicêtre, France and at National Defense Medical College, Saitama, Japan. Out of the 8 mutations identified, 6 were point mutations and 2 frame shift mutations. Out of the point mutations, 2 novel mutations - 1 in intron 9 and another in exon 1 (patients 1 and patient 6) were noted. The 2 frame shift mutations in patients 2 and patient 7 were identical, involving the exon 10. Patient 2 was diagnosed early and managed by Hematopoietic stem cell transplant and is doing well whereas patient 7 did not take any treatment and died.

Amongst the 2 novel mutations mentioned above, patient 1 had severe life threatening infections with minimal eczema but is doing well on immunoglobulin supplementation. Patient 6 had mild infections with predominant bleeding manifestations and is also doing well on immune-globulin therapy. The details of mutations and outcome of therapy for all patients are presented in Table 1 and 3.

Discussion

Wiskott-Aldrich Syndrome is a rare primary immunodeficiency disorder with variable clinical presentations. With the advent and availability of molecular diagnosis, laboratory confirmation of the condition is now possible. However, there are hardly any data on this condition from the Indian subcontinent. A review of literature revealed occasional case reports but there is no information on molecular abnormalities in WAS from India.[15,16,17]

A perusal of the records of the Pediatric Immunodeficiency Clinic and the Pediatric Allergy Immunology Unit in the Advanced Pediatrics Centre at Post Graduate Institute of Medical Education and Research shows that till 2006, this condition had been suspected in only 2 patients. The diagnosis was presumptive and was based on the features of persistent thrombocytopenia in a boy along with other clinical features and supporting laboratory profile. Facilities for molecular diagnosis, however, were not available till very recently. Both the children were treated with prophylactic antimicrobials but did not survive for long.

In 2007, we were able to arrange for the molecular diagnosis of WAS at the Hôpital de Bicêtre, Le Kremlin-Bicêtre, France and later at National Defense Medical College, Saitama, Japan. Since then 8 children have had a confirmed diagnosis of WAS, out of 13 patients in whom the diagnosis was suspected. It was clinically suspected in 3 but no mutation was found in the *WAS* gene; 2 children were lost to follow up before the diagnosis could be genetically confirmed.

An increase in awareness could have resulted in an increasing number of children diagnosed during the period 2006-2010. It is likely that many children with WAS may have died undiagnosed and untreated prior to 2006. Considering the rarity of the condition in the general population, the number observed within a span of 3-5 years seems high. This calls for a concerted efforts to screen males with thrombocytopenia who are refractory to conventional therapy for WAS.

Table 2. Summary of the investigations

Patients	Platelet count	MPV (fL)	Ig G (G/L)	Ig A (G/L)	Ig M (G/L)	Ig E (IU/ml)
1	$38x10^9$/L	7.3	21.91 (4.9-16.1)	5.86 (0.4-2.0)	1.21 (0.5-2.0)	400 (0.3-25.0)
2	$18x10^9$/L	7	13.03 (2.1-7.7)	1.57 (0.05-0.4)	1.44 (0.15-0.7)	260 (0-6.6)
3	$72x10^9$/L	6.7	5.84 (2.1-7.7)	6.19 (0.05-0.4)	0.15 (0.15-0.7)	500 (0-6.6)
4	$50x10^9$/L	small	16.00 (3.1-13.8)	2.51 (0.3-1.2)	0.41 (0.5-2.2)	480 (0-20)
5	$142x10^9$/L	small	14.21 (2.4-8.8)	3.2 (0.1-0.5)	0.64 (0.2-1.0)	360 (0-6.6)
6	$9x10^9$/L	6.5	7.35 (2.4-8.8)	3.9 (0.1-0.5)	0.13 (0.2-1.0)	464 (0-6.6)
7	$67x10^9$/L	7.0	8.26 (5.4-16.1)	3.6 (0.7-2.5)	0.42 (0.5-1.8)	330 (3.6-81.0)
8	$33x10^9$ L	7.2	6.34 (4.9-16.1)	2.42 (0.4-2.0)	1.20 (0.5-2.0)	250 (0.2-17.6)

Figures in parenthesis indicate range of age related normal values for the respective patients.MPV: mean platelet volume; (G/L):grams/litre; (IU):International units

The clinical spectrum of WAS is very broad.[12,18-20] General pediatricians, as well as those working in pediatric sub-specialties, need to be aware of this disorder. Most of our patients had initially presented to other specialties like Pediatric Gastroenterology, Pediatric Dermatology and Pediatric Hematology. The classical triad of eczema, thrombocytopenia and immune deficiency at first presentation was seen in 6 out of 8 patients. The average incidence of bleeding manifestations before diagnosis is reported to be more than 80%,[21] consisting of petechiae and ecchymoses in most cases. We found bleeding from the GI tract in the form of bloody diarrhea and or haemetemesis as the most consistent symptoms and were seen in 75% of the children. This is also probably the earliest symptom which should raise the suspicion of this disorder among the treating physicians.

Patients with WAS are more susceptible to bacterial infections as well as viral and fungal infections. Polysaccharide-coated bacteria pose a special risk because of the impaired capacity to produce antibodies of the IgG2 subclass against polysaccharide antigens. In our cohort of children, recurrent infections were the dominant features in 6 children (Table 2). Pneumonia was the commonest infection and was seen in 6 children. Otitis media, meningitis, deep seated abscess, osteomyelitis, and septic arthritis were other infections encountered. Patient 3 developed disseminated candidiasis with meningitis and also varicella zoster infection. Eczema affects 80% of WAS patients during the disease.[21] In the present cohort eczema was seen in all, though it was mild in 3 children while severe and difficult to treat in 2 children. In a multicentric series analyzed by Sullivan et al. in 1994, 40% of patients had at least one autoimmune event and 25% had several manifestations. In a series of patients analysed in a single centre study (Hospital Necker, Paris) published,[22] 72% of patients presented at least one autoimmune event and 36% had multiple manifestations. Autoimmune or inflammatory events were reported in 24% of patients by Imai et al.[11] Autoimmune hemolytic anemia, cutaneous vasculitis, including Schoenlein-Henoch syndrome, nephropathies and arthritis, together have being reported to account for more than 80% of autoimmune manifestations. Among our patients, 1 child had an unusual presentation of acute hemorrhagic edema on hands and feet which on biopsy revealed leucocytoclastic vasculitis.[23]

It may be noted that persistent unexplained thrombocytopenia in boys is the most important clinical clue to the diagnosis of WAS. MPV in patients with WAS varies and there is no absolute diagnostic range. Interpretation depends on expertise and should be made considering the clinical context. MPV was found to be between 6-7.3 fL in our subset of children.

Immunologic abnormalities observed in WAS are complex and involve both B and T cell function. Affected male infants have a normal number of circulating lymphocytes but develop lymphopenia by 6 to 8 years of age due to a loss of T lymphocytes.[24] Classical features include normal levels of IgG, moderately reduced serum IgM levels, whereas IgA and IgE are elevated. However, these

Table 3. Details of mutation analysis

Patient	WAS score	Mutation	Type of mutation	Screening/Carrier/Status
Patient 1	4	intron 9,c.931+1>A	Point mutation Intronic /Splice defect	Not done
Patient 2	3	exon 10, c.1031delC, p.Pro344Leufs*101	Deletion, frameshift mutation	Not done
Patient 3	5	exon 1, c.91G>A, p.Glu31Lys	Point mutation, missense mutation	Mother and sister carrier
Patient 4*	4	exon 1, c.37C>T, p.Arg13*	Point mutation, nonsense mutation	Mother, maternal aunt carrier
Patient 5*	4	exon 1, c.37C>T, p.Arg13*	Point mutation, nonsense mutation	Mother, maternal aunt carrier
Patient 6	4	exon 1, c.100C>T, p.Arg34*	Point mutation, nonsense mutation	Mother carrier
Patient 7	4	exon 10, c.1031delC, p.Pro344Leufs*101	Deletion, frameshift mutation	Not done
Patient 8	5	exon 2, c.257G>A, p.Arg86His	Point mutation, missense mutation	Not done

*Patient 4 and 5 are related.

changes are not constant features and mainly affect older patients. A significant number of WAS subjects present with normal or even raised IgM values, the latter being a risk factor for the development of autoimmunity. Eczema is also often associated with raised IgE. The immunoglobulin profiles in our children showed decreased IgM in 50% children while IgA and E were elevated in all.

The severity of the clinical presentation can vary depending largely on the mutation and its effect on protein expression.[18,25] Understanding the molecular basis also has important implications for the diagnosis, treatment, genetic counseling and gene therapy of patients with WAS. The *WASP* gene, which encodes for the WAS protein (WASP), has 12 exons and 5 major functional domains. *WASP* gene mutations can impair all or part of the protein's expression and function. The severity of impaired protein expression is directly correlated with the severity of the clinical phenotype.[18] In particular, missense mutations in exons 1 and 2 (which usually diminish but do not suppress protein expression) are associated with a milder phenotype, with thrombocytopenia (XLT) being the major manifestation. Conversely, nonsense mutations or mutations impairing the reading frame of the RNA messenger, disrupts the protein's aminoacid sequence, abolishes or radically reduces protein expression and tends to be associated with a severe clinical phenotype (WAS).

In our series, there were 2 patients with novel mutations. Patient 6, had a mutation in the exon 1, with a WAS score of 4 and is presently doing well with immunoglobulin replacement therapy. The other patient (patient 1) had a new mutation in intron 9, with same WAS score and is also doing well with replacement immunoglobulins. Unfortunately, we were not able to quantify the WASP protein in our patients for better phenotypic-genotypic correlation. Genotype–phenotype correlation in WAS/XLT is not absolute and progression to a severe phenotype is possible. The arginine residue at position 86 is a mutation hotspot, as it is located in the CpG island. Missense mutations in the R86 residue are more commonly associated with XLT phenotype, but in a recent paper, Albert et al. described patients with R86H mutations progressing from a WAS score 1 or 2 to 5 due to development of autoimmunity.[26] Patient 8 in our series with a mutation in exon 2, c.257G> A, p.Arg86His has also shown a similar progressive trend from WAS score of 2 to 5 on development of autoimmunity in the form of cutaneous vasculitis.

Management of patients with WAS continues to present major challenges in resource poor settings, as is evident from the fact that two of our patients died at home as the parents could not afford any form of therapy. Early diagnosis is most important for effective prophylaxis and treatment. The natural history of disease progression is less predictable, especially in the attenuated phenotypes. At present, the only curative therapy is hematopoietic stem cell transplantation (HSCT). The results are promising for patients with HLA-matched family or unrelated donors or partially matched cord blood donors but less satisfactory for other donor types.[27,28] One of our patient successfully underwent a related HLA matched bone marrow transplantation at a sister institute.[29]

Immunoglobulin therapy was given to 5 out of the 8 patients based on clinical assessment. This significantly improved the quality of life in these patients. The number of infections decreased and so did the hospitalization for serious infections. However, we do not have any double blind data to prove this contention. At present, two children are doing well on immunoglobulin replacement and cotrimoxazole prophylaxis.

Mortality continues to be high in India and 50% children died in our cohort. The patient who was given HSCT therapy is still doing well after 4 years of follow up. However, there is an urgent need to create awareness regarding proper implementation of therapy, particularly with regards to the beneficial effects of HSCT. At present there are no regional or national level registries for patients with primary immune deficiencies in India. A centre for diagnosis and research is under consideration at our institute. Transplant facilities are available in 10-12 centres in India, though predominantly for hematological malignancies. Transplants for immune deficiencies are being actively considered at several centres.

As such, efforts to promote general and educational awareness of not only WAS but all primary immune deficiency diseases has been initiated by the Indian Patients' Society for Primary Immune Deficiency (www.ipspiindia.org). In order to further the cause of these patients, this year the Indian Society for Primary Immunodeficiency Diseases has been established with an objective to create awareness amongst the medical fraternity associated with the diagnosis, management and treatment of these multidisciplinary disorders.

Conclusions

WAS, though a rare primary immunodeficiency disorder, should be suspected clinically in any male infant who presents with bloody loose stools and persistent thrombocytopenia. Mutations in the *WASP* gene result in phenotypically unique disease entities, depending on the effect of the mutation on WASP expression. Understanding the molecular basics has important implications for the diagnosis, treatment and genetic counseling of patients with WAS.

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