

Wiskott Aldrich syndrome: an immunodeficiency syndrome not rare in Western Australia

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Wiskott Aldrich syndrome, a combined cellular and humoral X-linked immunodeficiency, is generally considered to be rare. The aim of this study was to ascertain the true prevalence in the paediatric population in Western Australia, describe the clinical features, and summarise the current literature on this unusual condition. All cases of Wiskott Aldrich syndrome presenting to Princess Margaret Hospital in Perth during the period from January 1960 to January 1990 were identified by a retrospective review of case records and by interviewing hospital immunology, haematology and general clinical staff. Nine cases of Wiskott Aldrich syndrome are described, demonstrating that the prevalence of Wiskott Aldrich syndrome in Western Australia is nine times that expected from previous reports. Death occurred in a number of patients before the correct diagnosis was recognised. The clinical features in this group are quite variable. Low isohaemagglutinins, elevated IgE, blunted DTH skin multitest, and very low CD8 numbers are however consistent features. Wiskott Aldrich syndrome may be more prevalent than previously recognised, and should be considered in males with thrombocytopenia and infection.

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Wiskott Aldrich syndrome (WAS) is a rare immunodeficiency syndrome with an incidence of about 4 per million live male births (1). The immunological defects in WAS are variable, including an often elevated IgA and IgE, low IgM, poor antibody response to polysaccharide antigens and low isohaemagglutinins. T cell numbers and function are often poor (2).

Partially expressed forms of WAS with less severe bleeding and immune deficits are being increasingly recognised (3–7). The existence of partially expressed forms of WAS means that many cases are probably not detected and so the true prevalence of the disease may be underestimated. Indeed, it has been suggested that the diagnosis of WAS should be sought in all male children with 'idiopathic' thrombocytopenia (3, 5, 7–12). Support for this proposition is found in genetic studies that place the locus for WAS on the short arm of the X-chromosome (13) and the demonstration that this site is closely linked to the one for X-linked recessive thrombocytopenia (9).

The observation by one of us (KDF) that there appeared to be a high prevalence of WAS patients in Western Australia led us to review the records of such patients identified at Princess Margaret Hospital over the past 20 years. There were nine cases ascertained, giving the incidence in Western Australia at least eight times greater than expected. These cases are described, and the abnormalities of WAS reviewed.

Methods

All cases of WAS presenting to PMH during the period from January 1960 to January 1990 were identified by a retrospective review of case records and by interviewing hospital immunology, haematology and general clinical staff. In all patients the diagnosis of WAS was based on the presence of the clinical triad of thrombocytopenia, eczema and recurrent infection in a male child. Supportive laboratory evidence was also sought as detailed

Table 1. Clinical features of the WAS patients, consistent with the diagnostic hallmarks of WAS with the triad of thrombocytopenia, eczema and recurrent infection. Additional features of renal disease, bone disease, arthritis and non-eczema rash are noted less frequently.

Patient No.	1 [□]	2 [□]	3 [□]	4 [*]	5 [*]	6	7	8	9
Thrombocytopenic purpura	+	+	+	+	+	+	+	+	+
Eczema	—	+	+	+	+	+	+	+	+
Recurrent infection	†	+	+	+	+	+	—	+	+
Bloody diarrhoea	—	+	+	+	—	—	—	—	—
Hepatosplenomegaly	—	+	—	—	—	—	—	—	+
Lymphadenopathy	—	—	+	—	—	+	—	—	+
Malignancy									
Nephropathy/Haematuria	+	+							
Corticoid hyperostosis						+			
Arthritis	+	+							
Rash	+	+							
Age at death	13 yr		8 yr			3 mt			
Current age		12 yr		*4 yr	2 yr		13 yr	2 yr	15 yr

□ Members same family; * Members same family; † Post splenectomy; * Post BM transplant

below. Platelet sizing was not routinely used. All records of likely patients were fully reviewed and clinical and laboratory information obtained. All families had been checked by our genetics department to ensure that none were related. Some of the patients described here were identified as WAS after death. In these there is minimal immunological data. In addition some were recognised prior to immune function testing being readily available.

Immunoglobulins IgG, IgA and IgM were measured by rate nephelometry (Beckman array). IgE was estimated using the RIACT assay (Pharmacia), and isohaemagglutinins by direct haemagglutination using Group A or B cells. Skin multitest was performed using Multitest CMI™ (Institut Mérieux Lyon, France), containing tetanus, diphtheria, streptococcus, tuberculin, candida, trichophyton, and proteus antigens in a 70% glycerin solution, applied firmly to normal skin on the forearm, and read at 48 h. Lymphocyte surface markers were enumerated by using either directly conjugated antibodies in whole blood (more recently) or Ficoll-Hypaque separated lymphocytes and unconjugated antibodies. Analysis was performed on a Becton Dickinson FACScan™ using Simulset software (BD). Lymphocyte proliferative responses were estimated using ³H-thymidine (Amersham) after 5 days incubation with phytohaemagglutinin (PHA) (Bacto) used at 0.1, 0.2, 0.5 mg/mL, pokeweed mitogen (PWM) (Gibco) at 1:100, 1:20, 1:2 dilutions, and concanavalin A (ConA) (Calbiochem) at 0.025, 0.05, 0.1 mg/mL. Highest proliferative responses obtained were the values reported. All results were compared with laboratory reference ranges adjusted for subject age.

Results

Nine patients fulfilling the clinical criteria of WAS were identified (Table 1). Patients 1 through 3 were all siblings in the same family, there being one other sister. There was no consanguinity. All three initially presented with thrombocytopenia, the eldest at age 14 months and the youngest at day one. The diagnosis in this family was only suggested when the middle child developed fulminant varicella, pneumonitis and haemorrhage at age four. This was only several months before the eldest died from pneumococcal meningitis. Both a maternal uncle and a male cousin died in infancy of unknown cause. Currently, patient 2, the middle sibling, is the only surviving member, at age 12. He continues to have intermittent joint pain, fleeting erythematous rashes and eczema, extensive molluscum contagiosum and persistent haematuria. He remains on prophylactic antibiotics, but is rarely troubled by his thrombocytopenia.

Patients 4 and 5, also siblings, are of aboriginal descent. In both, thrombocytopenia in the first few days of life was the presenting feature. At age two the eldest underwent a bone marrow transplant from his sister with remarkable resolution of his thrombocytopenia and almost complete attenuation of his eczema and asthma. Unfortunately, to date a suitable marrow donor has not been found for his younger brother who continues to have severe, recurrent infection, despite prophylactic antibiotics and regular gammaglobulin infusions. Compliance and follow-up are a significant management problem.

Patient 6 fits the classic description for WAS with failure to thrive from two months, severe eczema and recurrent minor infections, usually of the ears. Admission at three months of age with bloody diarrhoea and a petechial rash revealed

Table 2. Immunological indices in WAS subjects

Patient No.	1 [□]	2 [□]	3 [□]	4 [×]	5 [×]	6	7	8	9
IgG	N	↑	N	↑	N	↓	↑	N	↓
IgA	↑	N	N	↑	↑	↓	↓	N	↓
IgM	N	↓	N	N	N	↓	N	N	N
IgE	↑	↑	↑	↑	↑	↓	↑	↑	↓
Isohaemagglutinins	↓	↓	↓	↓	↓	↓	↓	↓	↓
Pneumococcal Abs									
CMI Multitest		↓	Anergy	↓			Anergy	↓	Anergy
Proliferation: PHA		N	N		↓		↓	N	N
PWM		↓	N				↓	N	↓
Con A		N	N				↓	N	N
CD3			N	↓	↓	N	N	↓	↓
CD4				N	↓		↓	N	↓
CD8				↓	↓		N	↓	N
CD16									
CD19			N	N	N			N	N
CD43					87%+		95%+	86%+	88%+
Total Nos.			N	N	N	N	N	N	N
ANA	N	N					N		N
Platelet size						↓		↓	

Blanks (no test result available), N (result within reference range). Although IgE levels are consistently raised, the other immunoglobulins show variable levels. Isohaemagglutinins and skin multitest are blunted, with marked CD8 depression in the majority tested. [□] Members same family; [×] Members same family.

thrombocytopenia. He rapidly deteriorated and eventually succumbed to a generalised CMV infection associated with intracranial haemorrhage. Interestingly, X-rays revealed classical changes of infantile cortical hyperostosis which is now a well described finding with WAS (14, 15).

Patient 7 presented at 12 years with six months of bruising and epistaxis, with a platelet count of 11,000. As can be seen from Table 2 he had demonstrable abnormalities of both B and T cell function, but has had no significant infective episodes to date. He also had congenital cataracts, as did his non-identical twin sibling and his father suffered from haemochromatosis.

Patient 8 has had only minor problems with infection, but a maternal uncle aged 18 years died post-splenectomy for ITP with meningococcal sepsis (he had apparently also suffered from eczema and multiple infection including severe chicken pox). This patient was also diagnosed as having ITP at eight months of age, rapidly followed by the development of severe eczema. Platelet size was noted to be uniformly small. Tests of immune function showed elevated IgE, decreased isohaemagglutinins, and low CD3 and CD8 numbers.

The final case is a boy of 15 years first referred at 22 months of age for assessment of lymphadenopathy and splenomegaly and found histologically on lymph node biopsy to have only lymphoid hyperplasia. He developed thrombocytopenia with no other evidence of hypersplenism. Over the ensuing 12–18 months he progressed to have recurrent infection, and defects in both T and B cell function with low platelet counts. He was com-

menced on regular IV gammaglobulin. This treatment has controlled his bouts of infection and apart from eczema he remains stable.

Discussion

Wiskott & Aldrich's original reports from 1937 and 1954 respectively (16, 17) were of male children with failure to thrive associated with sepsis, eczema and thrombocytopenia. Initially most children were thought to die in infancy. To date, there are at least 8 case reports of patients with WAS surviving to over 18 years of age (18–25). In this paper we describe 9 children identified at Princess Margaret Hospital over the last 20 years with features consistent with WAS.

Approximately 12,500 live male children are born in Western Australia each year (26). If the incidence of WAS here were four per million live male births, as it is elsewhere in the world (1, 27) we could expect to see only one new case every 20 years. However the number of cases we report is nine times the expected. Indeed, even if we only consider the number of families rather than individuals we still have an incidence six times more than expected.

Western Australia's population is mainly descended from European background and this same observation was true for our cohort of patients. Perry (1) also found that there did not appear to be any other ethnic bias amongst other groups of WAS patients. It is interesting however, that two of our patients were of aboriginal descent, a race not previously recognised as being affected.

The humoral immune defects seen in WAS are very variable. Stiehm (2) describes low serum IgM, elevated IgE and levels of IgA and IgG which are either normal or elevated. Not all will fit this description and indeed some variants may have elevated IgA only (11). In this series of patients the immunoglobulin levels are quite variable from patient to patient. In all subjects tested however the total IgE was elevated and isohaemagglutinins were low, as has been reported previously (28, 29). Specific responses to polysaccharide antigens are poor as a rule (30). Many feel that these tests of immune function may show attrition with age (2).

Deficiencies of T-cell number and function can be frequently demonstrated. Within T cell subsets both increased and decreased numbers of CD4 and CD8 positive cells have been reported (31–33). In this group of patients total white cell numbers were generally normal, with variable decreases in CD4 or more particularly CD8 numbers. Three of the five patients who had CD8 numbers recorded showed marked reduction in CD8 counts. Skin test anergy or a blunted CMI multitest was found in all our patients. Mitogenic responses to the three mitogens tested were variable. Decreased lymphocyte function are fairly uniform findings in WAS (29–31, 34); it may be that more specific mitogens such as antiCD3 would give more reliable mitogen results.

Utilising flow cytometry for lymphocyte surface markers, two populations of WAS patients have been identified. One has an elevation of CD16+ NK cells and the other elevation of γ/δ T-cell receptor (TCR1) bearing T-cells (32). The significance of this finding is unclear but it is interesting that some other primary immunodeficiencies have been found to have elevated γ/δ TCR1 bearing lymphocytes (35).

The exact nature of the primary abnormality in WAS is unknown, but the available evidence supports primarily a T cell defect rather than a B cell one (36, 37). Inability to produce anticarbohydrate antibodies has been recognised as due to a T cell defect. In WAS a T lymphocyte graft alone has been reported to correct both the immune defect and eczema (38). Additionally, it has been suggested that poor cytotoxic function of CD8 lymphocytes could result in persistent antigenaemia which coupled with abnormal T helper lymphocytes might lead to greater B cell activation and elevated immunoglobulins (31).

At the molecular level, abnormal surface glycoproteins have been recognised both on platelets and lymphocytes in WAS. Parkman et al. (39, 40) were the first to describe this defect in the 1980's. They found that a protein, a component of the T cell and platelet cell membrane was either absent,

decreased in amount or structurally abnormal in the cells of patients with WAS. The glycoprotein was later characterised and given a number of different names by different authors, including sialophorin (39), gp L115 (39), LSGP (41), leukosialin (42) and CD43 (43). CD43 is a large acidic glycoprotein found in two forms with MW of 115,000 and 135,000 (44). There is a large intracellular domain and a single transmembrane and extracellular domain (45). The large negative charge it possesses probably acts to maintain lymphocytes in the circulation as well as contributing to their surface morphology (42, 46). Monoclonal antibodies against the protein, will in the presence of monocytes, induce rapid proliferation of human T lymphocytes, independently of the T-cell receptor (47, 48), suggesting CD43 is involved in T cell activation. CD43 is encoded on chromosome 16 rather than the X-chromosome (44, 45). Thus a mutation of the CD43 structural gene cannot be the primary defect. It has been suggested however that the X-chromosome carries a gene which is necessary for the post translational glycosylation or transport of CD43 (44, 49, 50). This is supported by the finding that CD43 from WAS lymphocytes has a structurally different principal oligosaccharide when compared with normal cells (50). If fibroblasts from patients with WAS are transfected with cDNA for CD43 from normal cells then they will produce structurally normal protein, in normal amounts (51). This would suggest that any defective enzymes involved in CD43 glycosylation must be restricted to the haemopoietic lineage above. A study by Higgins et al. (49) using immortalised (EBV) B cell lines is consistent with this in finding that at least two of the developmentally regulated glycosyltransferase enzymes in B cells, T cells and platelets of WAS patients are markedly abnormal in their activity. More evidence is provided by lymphocyte stimulation with lectins that react with surface galactosyl residues rather than sialic acid residues (for example galactose oxidase) and which stimulate WAS lymphocytes markedly (52).

To date only four of our patients have had CD43 measured by immunofluorescence and all have had detectable antigen. The monoclonal antibody used will recognise only a part of the molecule however, and does not provide information on overall CD43 structure or function. Some authors have found differing amounts of CD43 between T cell lines in culture and fresh cells and have postulated that in WAS there may be accelerated degradation of the glycoproteins (52, 53). The value of CD43 estimation in WAS is therefore undetermined.

Thrombocytopenia is the other predominant problem in WAS. It was often the presenting symptom in our patients. The bleeding tendency

can vary from life threatening to very mild. In some variants the characteristic thrombocytopenia and small platelet size are found together with eczema, elevated IgA and nephropathy but otherwise normal immunity and life expectancy (4, 11). One child in our series died from a massive cerebral haemorrhage. Two were largely asymptomatic despite low platelets and the rest had episodic thrombocytopenia which required treatment. Management may include platelet transfusion if counts are less than 10,000 or if there are hemorrhagic complications.

Conservative management of thrombocytopenia is recommended but in cases where it is severe and persistent splenectomy may be the only way to produce a sustained elevation in platelet count. It has been recognised that there is an increased risk of death from infection following splenectomy in patients with WAS (6, 7) but others have argued that this can be prevented by adequate use of prophylactic antibiotics (54). In our patients, of the two who died from sepsis, one was only three months old whilst the other older child was several years post splenectomy. He died as a teenager when compliance with treatment was poor. Unfortunately the diagnosis of WAS was only made retrospectively at the time that his brothers were diagnosed as having the condition. Standen (55) reported a similar case in twin boys who had an identical fatal outcome. He points out that in boys with thrombocytopenia it is essential to check that they do not have WAS. This is even more important if splenectomy is contemplated as it should influence the decision making process. Partial splenic embolization has been used in this condition and may be less likely to be associated with septic complications, though it carries with it its own unique set of problems (56).

The cause of the thrombocytopenia remains undetermined although it is clearly multifactorial. Survival of autologous platelets is generally reduced but not sufficiently to totally account for the level of thrombocytopenia (30, 57). This suggests an intrinsically abnormal platelet. However splenectomy completely restores platelet size and number to normal and suggests more of a primary destructive process (54). The finding of small platelets in WAS is of interest as most disorders with diminished platelet survival demonstrate platelets with increased volume (58). Platelet function as well as number is abnormal in WAS. There is generally diminished aggregation to a number of thrombotic stimulants. Major deficiencies of the surface glycoproteins GP1a and GP1b that constitute the von Willebrand factor receptor have been described (59) and are probably partly responsible for the decreased aggregation. Glycoprotein defi-

ciency reduces net surface negative charges and will render the platelets less deformable and more likely to be sequestered by the spleen. Some authors have proposed a role for immune mediated thrombocytopenia in WAS (51). There is no conclusive evidence to support this hypothesis despite the elevated platelet associated immunoglobulin which is found in some patients (30, 60, 61). The latter finding may be a consequence of the abnormal platelets. Similarly, whilst WAS platelets can be shown to be metabolically abnormal with reduced glucose consumption and lactate production and low oxidative ATP resynthesis (62, 63), these defects could not alone explain the abnormal platelet morphology and function and may well therefore be a consequence of some other basic deficiency.

Within our series of patients, many demonstrated some of the lesser known associations of WAS. Spitler et al. (64) were amongst the first to describe nephropathy in five of a group of 32 patients with WAS. We found a similar incidence amongst our cohort. Generally a nephritic picture is seen but a nephrotic form has been reported. As previously stated, there is a well-recognised variant with eczema, hyper-IgA and mild nephropathy which is a distinct entity from Bergers disease (11).

Non-septic, transient arthritis also occurs with WAS (10, 29). Two siblings in one family we described suffered from mild arthritis of large joints. Indeed Patient 2 was initially considered as having Henoch Schönlein Purpura because of his presentation with arthritis, haematuria and a rash.

McEnery & Nash (15) and Abinum et al. (14) both independently found the coexistence of infantile cortical hyperostosis and WAS. This was a useful correlation to us in that the diagnosis in patient 6 became apparent because of radiological changes consistent with infantile cortical hyperostosis, and then led to specific investigations for WAS.

It is to be noted that eczema and purpura are not the only cutaneous manifestations of WAS. Cellulitis, conjunctivitis and molluscum contagiosum are common consequences of the immune deficits. Mucosal ulceration of the oral cavity, urethra, rectum and foreskin has been found in association with high levels of circulating immune complexes (31). At least two patients in our group also experienced recurrent urticarial rashes, often associated with exacerbations of their arthritis or nephritis. These may also represent immune complex mediated phenomena. An awareness of these lesser known associations is useful as they may provide a clue to diagnosis, particularly in milder or more subtle forms of the disease.

To date, none of our group have developed a malignancy although statistically we could expect more than one in ten to do so. The risk seems to increase with each year of life (1). The malignancy is usually either leukaemic (20%) or lymphoreticular (70%), the latter frequently being extra nodal and often only found at autopsy (1, 65). The juxtaposition of the oncogene LA-raf-1 and the WAS mutation on the proximal short arm of the X chromosome led some to speculate that altered expression of oncogenes might be the cause of tumour development (66). As yet most evidence however supports the notion that they arise as a consequence of the T cell dysfunction.

The prevalence of atypical forms of WAS and the serious consequences of a missed diagnosis make the need for better diagnostic tools even greater. Most tests to confirm the diagnosis have relied on finding abnormalities in the mothers of these children. Carrier detection of course is valuable for counselling and so serves two roles. One of the first methods was described by Shapiro in 1978 (67). This test relied upon demonstrating differential inhibition of adrenalin induced aggregations of platelets by 2-deoxy D glucose. Subsequently however this has been proven to be unreliable and should no longer be used (62).

Currently linkage studies are yielding more useful data for carrier detection. Kwan et al. (68) has mapped the gene for WAS to the proximal short arm of the X chromosome between two markers DXS-7 and DXS-14. Subsequently further studies have found another marker DXS-255, which is even more closely linked to the defective gene site but is still known to lie between the other sites (69, 70). This gene is thought now to lie within a small area bounded by the RLFP markers TIMP (Xp11.3) and DXS-255 (Xp11.22). One study at least has found conflicting results to these but it was later realised that germ line mosaicism had given rise to the conflicting linkage results (71). This genetic possibility had not previously been recognised. The one major shortcoming in using RLFP's is that even in an informative family they can only give a probability that the mother is a carrier, they are not conclusive. It has now been clearly shown that the combination of linked probes with analysis of X chromosome inactivation patterns in peripheral lymphocytes permits definitive diagnosis, even when there is no family history (72, 73).

Carriers in three other X-linked immunodeficiencies also show non-random X inactivation; X-linked agammaglobulinaemia, severe combined immunodeficiency and X-linked chronic granulomatous disease. The specific immunocyte affected however varies with the disease (74). In WAS gra-

nulocytes, lymphocytes, monocytes and platelets are all affected. In our hospital we are currently unable to assess non-random X inactivation.

Bone marrow transplantation provides the only cure for this disease and in fact, WAS was the first genetic disease of the haemopoietic stem cells to be completely corrected by allogeneic marrow transplantation. The initial reports of success were from Bach et al. (75) and Gatti et al. (76). Numerous follow-up studies are now available and show complete recovery of lymphocyte and platelet function together with resolution of their eczema (77, 78, 79). The one case in this series who was transplanted received additional benefit with almost complete resolution of his asthma. The effect of marrow transplant on later risk of development of malignancy is unknown. Unfortunately, the majority of patients do not have suitable donors and it can only be hoped that with improved immunosuppression and marrow purging techniques, survival from unmatched grafts will improve.

Clinical diagnosis of WAS based purely on the presence of the textbook triad of thrombocytopenia, infections and eczema is insufficient. Today, all male patients with thrombocytopenia should be further investigated immunologically at initial presentation and probably again 12 to 24 months post-diagnosis. Given the immunological data in the patients described here, we would recommend emphasis on type-specific antibody levels, DTH skin testing, and lymphocyte surface markers.

In summary we have described a much higher incidence of WAS in Western Australia than would be expected. There appears to be no obvious explanation for this although we suspect that other studies have underestimated the true incidence because they failed to include the more subtle forms of presentation, many of whom will die before the diagnosis is made. In other ways the cohort we describe is similar to those found elsewhere. The need to immunologically screen all patients with apparent X-linked thrombocytopenia is emphasised. Delay in diagnosis may prove fatal but at the least has profound social ramifications for the patients families.

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