Archives of Disease in Childhood 1996;75:436–439

Intravenous immunoglobulin, splenectomy, and antibiotic prophylaxis in Wiskott-Aldrich syndrome

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Abstract

***Aim*—To assess the results of supportive treatment with intravenous immunoglobulin (IVIG) and antibiotic prophylaxis in combination with splenectomy in patients with Wiskott-Aldrich syndrome.**

***Study design*—Retrospective review of case records of 21 patients from March 1984 to February 1996.**

***Results*—Thrombocytopenia was cured in 14 of 15 patients who had splenectomy, but it recurred intermittently in three. Mean platelet volume (MPV) was normal transiently in some patients, but all MPV values were subnormal 8–23 months after splenectomy. Antibiotic and IVIG prophylaxis may have contributed to the lack of a detectable increase in the number of severe acute bacterial infections in the 451 months after splenectomy. Four patients died in 2205 months of observation before and after splenectomy (median 82, range 16–248): two of cerebral B cell lymphoma, one of progressive multifocal leucoencephalopathy, and one with severe chronic chest disease of pneumonia.**

***Conclusion*—Adequate supportive treatment with IVIG and antibiotic prophylaxis together with splenectomy enables good survival and quality of life in the short and medium term in patients with Wiskott-Aldrich syndrome. Persistence of infection, bleeding, and vasculitic and allergic symptoms in a significant minority and the risk of development of lymphoma, however, suggest that bone marrow transplantation may be indicated if an HLA identical donor is available.**

(*Arch Dis Child* 1996;75:436–439)

Keywords: Wiskott-Aldrich syndrome, splenectomy, intravenous immunoglobulin, thrombocytopenia.

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Accepted 19 July 1996

The Wiskott-Aldrich syndrome is a rare X linked disease characterised by thrombocytopenia, eczema, and increased susceptibility to infections.[1] The gene responsible for the disease has recently been cloned.[2] HLA identical, but not mismatched, bone marrow transplantation (BMT) has a success rate of 73–100%.[3–7] Patients without an HLA identical donor require alternative treatment as survival in patients aged 10 years between 1965 and 1978 did not exceed 40%.[8] Splenectomy,[6 9 10] prophylactic antibiotics, and intravenous immunoglobulin (IVIG)[10] have been recommended individually in Wiskott-Aldrich syndrome. The effect of the combination of these three treatments on infection and bleeding was assessed retrospectively. Some benefit of the systematic use of IVIG, prophylactic antibiotics, and splenectomy in patients with this syndrome is suggested.

Patients and methods

Twenty one patients with an unequivocal diagnosis of Wiskott-Aldrich syndrome were followed up from March 1984 to February 1996 at Great Ormond Street Hospital for Children, London (total 1348, median 55 (range 18–131) months). Wiskott-Aldrich syndrome was diagnosed on the basis of the triad of immunodeficiency (table 1), thrombocytopenia (table 2), and eczema. The time of death or BMT was considered as an end point.

From 1990, further to favourable reports,[9] splenectomy by experienced paediatric surgeons was offered to 19 non-transplanted patients. Four refused despite bleeding and platelet counts between 10 and 40 $\times$ 10^9/l. Splenectomy was not offered to two patients who underwent HLA identical BMT. BMT was recommended if an HLA identical bone marrow donor was identified.

Patients were given IVIG (0.18–0.58 g/kg every 2–4 weeks) and prophylactic antimicrobial drugs, most frequently co-trimoxazole (trimethoprim 5 mg/kg/day); some also received acyclovir 200 mg twice daily or fluconazole 3 mg/kg/day, or both. Thirteen patients were given pneumococcal and seven meningococcal and haemophilus vaccines before operation and 13 received penicillin in addition to co-trimoxazole if undergoing splenectomy.

Platelet number and size were recorded before and within four days of splenectomy and also after 8–23 months. Septicaemia, pneumonia requiring intravenous antibiotic treatment, severe gastroenteritis, or deep abscesses were considered as severe acute infections; intracranial haemorrhage or gastrointestinal bleeding requiring blood transfusion was considered as a severe bleeding episode.

Statistical analysis was performed by the paired Student's *t* test.

Results

The median age at diagnosis and the end of the study was 13 (range 1–84) and 82 (range 16–248) months, respectively. Three splenectomised and one non-splenectomised patients died during the total observation period of

Table 1 Serum immunoglobulin concentrations and isohaemagglutinin titres before splenectomy. IgG concentrations are supported by IVIG

Patient No	*Age (months)*	*IgG (g/l)*	*IgA (g/l)*	*IgM (g/l)*	*Anti-A (titre)*	*Anti-B (titre)*	*IgE (IU/ml)*
1	6	19.50	1.60*	0.89	ND	ND	967
2	18	8.85	0.74	0.11		<2	94
3	23	15.36	2.47*	0.49	2	<2	>400
4	23	8.42	1.60*	0.32	ND	ND	440
5	28	6.60	1.36	0.30	512	2	3
6	30	15.11	2.11	0.25	<2		5
7	32	8.19	1.59	0.27		<2	88
8	34	6.81	1.55	0.61	ND	ND	187
9	35	6.52	1.85	<0.06	<2		6
10	44	15.35	0.92	0.25		4	5
11	47	12.94	3.65	1.11		<2	239
12	55	23.00	0.61	0.42	16	4	46
13	93	8.33	1.68	0.87	256		<4
14	105	10.27	4.42	0.46	4	<2	21
15	108	10.21	1.44	0.65		64	<4
16	110	11.63	5.16	0.09	8		354
17	124	10.55	6.87	0.09		16	91
18	158	9.85	2.15	<0.06	8		22
19	164	6.91	2.77	0.38	ND	ND	149
20	167	10.6	3.75	0.16	2	2	25
21	212	6.88	1.12	0.07		<2	142
Reference range		3.7–16. 1	0.3–2.8	0.5–2.2	16–256	4–512	3–150

ND= not done.
* Greater than upper limit of normal for given age (0.4;1.3 g/l).

2205 (median 82, range 16–248) months: two aged 4.5 and 7 years of cerebral B cell lymphoma, one aged 20 years of chronic multifocal leucoencephalopathy, and one aged 5.5 years with severe chronic chest disease of respiratory failure due to pneumonia.

BMT from HLA matched sibling donors was performed in four patients aged between 2 and 6 years. One patient died of graft-versus-host disease five months after BMT, the other three are well five months to nine years later. Three patients required immunosuppression for autoimmune (vasculitis, autoimmune haemolytic anaemia) and allergic (severe eczema) disorders.

A total of 11 episodes of severe bleeding (two intracranial and nine gastrointestinal) occurred before splenectomy, which was performed at a median age of 48 (range 6 – 171) months. The only postoperative complication was a single episode of intussusception.

The platelet count rose to normal values (150–350 × 10^9/l) in all patients except one within four days (table 2). This patient required azathioprine, corticosteroids, and two courses of plasmapheresis to control thrombocytopenia, which was associated with haemolysis. The platelet count declined intermittently to between 5 and 50 × 10^9/l 12–34 months after splenectomy in three patients.

There was an increase in mean platelet volume (MPV) ($p<0.001$, 95% confidence interval (CI) 1.4 to 2.8 fl) (table 2) by day four after splenectomy, which reached normal values (7.8 to 11.0 fl) in five patients. MPV values declined ($p = 0.008$, CI 0.6 to 2.0 fl) to below normal in all patients between 8 and 23 months later, but remained increased (p =

Table 2 Platelet count (range 150–350 × 10^9/l) and MPV (range 7.8–11.0 fl) before, 2-4 days, and 8–23 months after splenectomy

	Before splenectomy		*After splenectomy*		*8–23 Months after splenectomy*	
Patient No	*Platelet count (×10^9/l)*	*MPV (fl)*	*Platelet count (×10^9/l)*	*MPV (fl)*	*Platelet count (×10^9/l)*	*MPV (fl)*
1	5	4.2	4	5.1	36	5.4
2	63	4.5	198	7.8	203	6.3
3	86	ND				
4	28	5.7				
5	69	4.3	214	7.2	157	6.7
6	14	4.4	220	7.0	85	5.9
7	39	4.4				
8	ND	ND	ND	ND	295	6.5
9	32	5.0	184	ND	234	7.1
10	19	5.1	175	ND	165	6.4
11	29	6.7	243	6.8	293	6.8
12	31	6.3	311	ND	404	7.6
13	22	6.5	378	8.1	151	5.1
14	25	5.9	212	8.0	550	6.1
15	18	6.1	157	8.5	162	6.1
16	25	4.6	265	ND	244	7.4
17	11	5.4	212	8.0	269	6.8
18	7	3.6	176	5.7		
19	24	5.1				
20	10	5.8				
21	12	5.0				
Mean	28	5.1	210	7.2	232	6.4
SD	21	0.9	84	1.1	130	0.7

ND = not done.

0.004, CI 0.5 to 1.7 fl) compared with values before splenectomy.

Limited but clinically useful increases in platelet numbers occurred after IVIG (0.4–2.0 g/kg/day for one to five days) in two of seven patients before splenectomy. Each had evidence of autoimmune disease (positivity of platelet associated immunoglobulin in one, vasculitis in the other); one of them also received corticosteroid treatment for vasculitis. Sustained resolution of thrombocytopenia was also achieved with high dose IVIG in one patient after splenectomy.

Fourteen of a total of 18 episodes of severe acute bacterial infection involved the lung. The other severe infection was an episode of *Pneumocystis carinii* pneumonia in a patient receiving immunosuppressive treatment. The rate of severe acute bacterial infection before splenectomy was 0.10 per annum (14 in 1754 patient months) and after splenectomy 0.11 (four in 451 patient months).

Symptoms of significant chronic lung disease started before splenectomy in two patients. Lobectomy for aspergillus (two) and actinomycosis (one) was performed 4–15 months after splenectomy. Frequent herpes simplex exacerbations (three), extensive *Molluscum contagiosum* (three), and chronic multifocal leucoencephalopathy affected the five patients with significant chronic viral infection.

Discussion

Splenectomy was associated with a reduction in the number of bleeding episodes in 15 patients with Wiskott-Aldrich syndrome, as reported in other studies.[6 9 11] Thrombocytopenia recurred or persisted in four of these 15 patients,[6 11] but only minor bleeding problems were encountered.

An increase in MPV was observed in all patients after splenectomy, supporting a critical role for the spleen in determining low MPV in Wiskott-Aldrich syndrome.[9 12 13] In contrast with most studies[9 12] and as described in two previously reported patients,[13 14] normal range values for MPV after splenectomy were not achieved in all patients in the present study. Further, there was a subsequent decrease in MPV during the 8–23 months' follow up after splenectomy. The mechanism of the characteristic reduction of MPV[12 15] and its relation to abnormalities of platelet function in Wiskott-Aldrich syndrome are unclear. The findings suggest that, as well as the splenic process,[1 6 12] other mechanisms, such as non-splenic reticuloendothelial system activity or antiplatelet antibody production,[12] may also contribute to low MPV in Wiskott-Aldrich syndrome. Moreover, several platelet abnormalities have been described in these patients,[16–19] which may contribute directly or indirectly to their destruction.[19]

The beneficial effects of high doses of IVIG on platelet numbers in patients with Wiskott-Aldrich syndrome have been reported.[14 20] IVIG was not as consistently beneficial as in idiopathic thrombocytopenic purpura [11 21] despite the presence of platelet associated immunoglobulin in a substantial proportion of patients.[12] We observed similar limited efficacy before splenectomy, and one patient responded to high dose IVIG after splenectomy.

Death from infection still occurred after splenectomy in patients with Wiskott-Aldrich syndrome despite antibiotic prophylaxis.[6 11] Splenectomy was previously considered to be contraindicated in patients with Wiskott-Aldrich syndrome,[22] because of the danger of exacerbating the established and progressive immunodeficiency.[13 23] It is encouraging that there were only four episodes of severe acute bacterial infection in our group in 451 patient months after splenectomy; this may be associated with the use of IVIG together with antibiotic prophylaxis. Immunoglobulin replacement is a rational form of treatment in Wiskott-Aldrich syndrome in view of the disturbed antibody production,[24 25] but no controlled clinical trials evaluating the efficacy of IVIG or antibiotic prophylaxis in Wiskott-Aldrich syndrome have been performed or are likely because of the rarity of the disorder.

Eighty one per cent of patients were alive at a median age of 82 months. Most had a good quality of life, however longer follow up is required to establish whether this comparatively good survival rate will be sustained. Fewer deaths from haemorrhage can be anticipated and the combination of IVIG, penicillin, and co-trimoxazole may be adequate in preventing postsplenectomy sepsis. Three patients died after splenectomy and three others developed allergic or autoimmune symptoms requiring high levels of immunosuppression. These problems were probably not related to splenectomy but indicate that BMT should be carried out at an early stage if a related, or possibly an unrelated, HLA identical donor is available.

We thank the paediatricians and physicians who referred these patients and who perform a large part of their continuing care.
The work was partly supported by grant No 1088 of the Cost program of the Commission of the European Communities.

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