Immune Deficiency State in a Girl with Eczema and Low Serum IgM

Possible Female Variant of Wiskott-Aldrich Syndrome

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Evans, D. I. K., and Holzel, A. (1970). *Archives of Disease in Childhood*, 45, 527. **Immune deficiency state in a girl with eczema and low serum IgM. Possible female variant of Wiskott-Aldrich syndrome.** This report concerns an immune deficiency disorder in a girl with eczema. She has had recurrent infections including three severe attacks of herpes simplex and five attacks of pneumococcal meningitis. There is a moderate lymphopenia, dysgammaglobulinaemia with high IgG, high IgA, and low IgM; lymphocyte transformation with phytohaemagglutinin is impaired. Production of circulating antibody is abnormal, as are delayed hypersensitivity reactions. Although there is no thrombocytopenia, the resemblance to the Wiskott-Aldrich syndrome is discussed.

The Wiskott-Aldrich syndrome (Wiskott, 1937; Aldrich, Steinberg, and Campbell, 1954) is a sex-linked disorder affecting boys who have eczema, thrombocytopenia, low serum IgM, with absent iso-haemagglutinins and a susceptibility to recurrent infections. It has been suggested that this is a defect of antigen processing (Blæse *et al.*, 1968; Cooper *et al.*, 1968). We have observed, from the age of 3 months to her present age of 11, a girl who has eczema, low serum IgM, and failure of lymphocytes to respond to polysaccharide antigens—features that are described in the Wiskott-Aldrich syndrome. However, her platelet count is normal.

Case Report

The patient, a girl, is now 11 years old. She has been under observation since the age of 3 months when she first developed a generalized atopic eczema. Several months later this was complicated by a severe impetigo which, however, cleared with the appropriate antibiotic treatment.

At the age of 16 months a generalized herpetic infection of the Kaposi varicelliform eruption type supervened. The child was desperately ill and the impression obtained at the time was that repeated intravenous infusions of plasma saved her life. A second attack involving both corneae occurred eight months later. In the interval she contracted pertussis. Yet a third recrudescence of the herpetic infection, but of the

secondary type, accompanied an episode of pneumococcal meningitis 7 years later (see Fig. 1 to 3).

Besides the illnesses already mentioned, she had repeated attacks of otitis media, and was admitted to hospital with an enteritis due to *Salmonella meleagridis*, a suppurative mastitis, and three incidents of pneumonia. Over a period of two years she had five attacks of pneumococcal meningitis.

In the course of the third attack of pneumococcal meningitis she developed a right-sided hemiplegia and right-sided convulsions. The EEG suggested a focal lesion in the left cerebral hemisphere, but carotid angiograms did not confirm it. She gradually recovered consciousness, normal speech, and the full range of movement in the paralysed limbs.

The infections which she has suffered are listed in Table I.

TABLE I

List of Infections

Impetigo; herpes simplex (Kaposi's varicelliform eruption); pertussis; meningitis; otitis media; mastitis; enteritis; pneumonia

The eczema was troublesome throughout but could be controlled periodically by the administration of small doses of steroids orally in addition to steroid ointments. For one year minor attacks of asthma added to the child's discomfort but never reached any menacing degree of severity. They were readily controlled with bronchodilators.

Her mother died at the age of 40 from a meningioma.

Fig. 1

Fig. 2

FIG. 1.—The primary lesion of herpes simplex (aged 16 months).

FIG. 2.—The second attack of herpes simplex (aged 24 months).

No details are available of blood counts or immunoglobulin levels, but there was no history of recurrent infection or eczema. Her parents were separated, and the father, who is Polish, is not available for study. Two brothers and the maternal grandfather have normal blood counts and immunoglobulin levels (Table II). None has eczema.

TABLE II

Lymphocyte Counts and Serum Immunoglobulin Levels of Available Relatives

	Lymphocytes per cu.mm.	Serum Immunoglobulins (mg./100 ml.)		
		IgG	IgA	IgM
Grandfather	3300	1050	295	62
Brother	3200	1150	210	76
Brother	1530	1050	140	195

Clinical examination. Both corneae were clouded from past keratitis. The skin showed generalized changes of atopic eczema. There were warts on the hands and scars of old infections. Her weight was normal, but she was slightly under the normal height for her age. Some small lymph nodes (0.5 cm. diameter) were palpable in the posterior triangle of the neck. The tonsils were small. The liver and spleen were not palpable. No attempt was made to visualize the thymus by x-ray examination.

Laboratory tests. The lymphocyte count was slightly reduced: usually about 1000 per cu.mm., with 780 and 3200 as the lowest and highest counts recorded (see Fig. 4.). The platelet count was normal (e.g. 192,000 per cu.mm.), and there was no abnormal bleeding.

A bone-marrow aspirate from the posterior ilium showed normal lymphocytes (17%) and plasma cells (1.6%). A neutrophil leucocytosis accompanied infections.

The immunoglobulin levels were first measured in February 1967, and showed IgG 2340 mg./100 ml., IgA 152% of a standard normal serum, and IgM 36% of a standard normal serum measured by radial immunodiffusion (Mancini, Carbonara, and Heremans, 1965). Subsequent estimations have confirmed this pattern of low IgM with high or normal IgG and IgA (Table III).

There was no clinical evidence of malabsorption, and

TABLE III
*Immunoglobulin Levels**

Date	IgG (mg./ 100 ml.)	IgA (mg./ 100 ml.)	IgM (mg./ 100 ml.)	IgD (% Std normal)
1 Feb. 1967 (1)	2340	456	25	—
3 Oct. 1967 (2)	2470	1125	26	—
24 Jan. 1968 (3)	3080	600	15	—
7 Oct. 1968 (4)	2320	600	11	34

*IgD as proportion of pooled normal serum; others as mg./100 ml. serum by courtesy of Drs. D. S. Rowe and R. Thomson.

FIG. 3a, b, and c.—Secondary herpetic lesions accompanying the third attack of pneumococcal meningitis (aged 9 years).

a 3-day faecal fat excretion test (2.3 g. per day) and xylose absorption test (26% of dose excreted) both gave normal results.

She is blood group O. The isohaemagglutinins, though not absent, were low: anti A 1/16, anti B 1/8. Antistreptolysin titre: 360 units/ml. Mantoux test negative at 1:1000. 0.1 mg. dinitrochlorobenzene (DNCB) applied to the forearm failed to elicit any response 14 days after a sensitizing dose of 1 mg. There

was no delayed reaction to two different candida antigens, though an immediate wheal and flare response were seen.

Sera have also been tested by Dr. P. J. L. Sequeira for the following viral antibodies, with negative results (titres did not exceed 1/8): herpes simplex, adenovirus, respiratory syncytial virus, influenza A and B, and parainfluenza 1.

The pathogens isolated during the course of the disease are listed in Table IV.

FIG. 4.—White cell counts and pneumococcal infections during a period of 18 months.

TABLE IV

Pathogenic Organisms Recovered During Infections

Staphylococcus aureus; β haemolytic streptococcus; *Proteus vulgaris*; *Escherichia coli* 0111; *Salmonella meleagridis*; *Haemophilus influenzae*; *Streptococcus pneumoniae*, type 6, type 23, and untyped varieties; herpes simplex

Humoral antibody titres were studied after antigenic stimulation.

(1) After two injections of TAB containing heat-killed *S. typhi* and para B, *S. typhi* 'H' antibodies were detected to a titre of 1/250 and para B 'H' to 1/125. There was no response to 'O' antigens, which are represented by the IgM response (see Fig. 5).

(2) Three doses of alum-precipitated diphtheria toxoid (PTAP) produced an antibody response which

FIG. 5.—Response to TAB (1000 million *S. typhi*, 500 million *S. paratyphi* A, and 500 million *S. paratyphi* B/ml.).

lay between 0.01 and 0.1 A.U. per ml. (Dr. P. M. Bradstreet), and converted her from Schick positive to Schick negative (see Fig. 6).

(3) Three injections of Salk vaccine were given in 1959. Eight years later neutralizing antibody titres were all less than 1 in 8. After two further injections titres to types 1 and 3 were 1/16 or more, but type 2 was less than 1/16. A third dose brought levels of antibodies to all three types of 1/16 or more. Five months later titres to types 2 and 3 remained high, but the titre to type 1 had fallen to less than 1/8 (see Fig. 7) (Dr. F. O. MacCallum).

In vitro lymphocyte transformation with phytohaemagglutinin in autologous plasma was studied several times. After three days there was 20–25% blast cell transformation. Chromosome analysis (Anders, Moores, and Emanuel, 1966) showed a normal female karyotype, with no chromosomal defects. After the onset of the third attack of pneumococcal meningitis (due to pneumococcus type 23), lymphocyte transforma-

FIG. 6.—Response to diphtheria toxoid.

FIG. 7.—Response to Salk vaccine.

tion was studied using as a mitogen the identical pneumococcus, killed by heating, which had been isolated from the CSF two weeks previously. After three days no blast cell transformation had occurred, though control lymphocytes from a normal adult showed 74% blast cell transformation. No cytotoxic antibodies to her own or to donor leucocytes were detected in the serum using a modification of the trypan blue technique (Engelfriet and Britten, 1965).

Treatment. She has been taking 2.5 mg. prednisone daily for the past three years: this has helped control the eczema. γ -globulin was kindly supplied by Dr. L. Hill of the Medical Research Council Hypogammaglobulinaemia Trial. Treatment with a weekly injection of 0.025 g./kg. per week for seven months was ineffectual: two further attacks of pneumococcal meningitis occurred during this period. For the past year she has been taking penicillin V tablets 250 mg. b.d., and has remained free from infection and in remarkably good health.

Discussion

This girl had recurrent infections, associated with eczema, low serum IgM, low circulating lymphocytes, and impaired delayed hypersensitivity reactions. She illustrates the abnormal susceptibility to meningitis shown by patients with IgM deficiency (Hobbs, Milner, and Watt, 1967). There was a failure to produce antibody to the lipopolysaccharide 'O' antigen of *Salmonella typhi* and para-B. No circulating antibody to herpes simplex was present in spite of three attacks of generalized herpes simplex infection. This immunological defect is strongly suggestive of the Wiskott-Aldrich syndrome, and the principal features of the case are compared with those of this syndrome in Table V. Recent studies (Cooper *et al.*, 1968; Blaese *et al.*, 1968) suggest that the

TABLE V
Comparison between Patient and Known Cases of Wiskott-Aldrich Syndrome*

	Wiskott-Aldrich Syndrome	This Case
Sex	Male	Female
Familial disorder	Yes	No
Thrombocytopenia	Yes	No
Recurrent infection	Yes	Yes
Eczema	Yes	Yes
Low isohaemagglutinins	Yes	Yes
Immunoglobulins:		
Raised IgG and/or IgA	Yes	Yes
Low IgM	Yes	Yes
Antibody response to polysaccharide antigens	Poor	Poor
Delayed hypersensitivity reactions (skin tests)	Poor	Poor
Lymphopenia	Yes	Yes
Lymphocyte transformation	Normal	Poor

*Data from Bach *et al.* (1968); Blaese *et al.* (1968); Cooper *et al.* (1968); Berglund *et al.* (1968); and Seligmann *et al.* (1968).

defect in the Wiskott-Aldrich syndrome is a diminished response to lipopolysaccharide antigens with impaired function of thymus-dependent lymphocytes and a low circulating lymphocyte level, leading to low IgM levels from failure of adequate stimulation, i.e. there is impairment of antigen processing or recognition. This patient has essentially the same features but no thrombocytopenia; and anti-A and anti-B titres, though low, are detectable. She has a normal chromosome complement and an XX karyotype.

However, the differences require consideration. Though skin tests for delayed hypersensitivity are impaired in boys with Wiskott-Aldrich syndrome, lymphocyte transformation rates were normal in 6 of the 6 cases where this test was performed (Blaese *et al.*, 1968; Bach *et al.*, 1968). In our case the lymphocytes responded poorly on repeated testing with phytohaemagglutinin (PHA) and did not respond at all to killed pneumococci.

Characteristically the isohaemagglutinin titre in boys with the Wiskott-Aldrich syndrome is very low; and this case has higher titres than usually accepted as part of the syndrome. However, of the 6 cases of Wiskott-Aldrich syndrome reported by Berglund *et al.* (1968), 3 had anti-A titres of at least 1/32, and one of these had an anti-B titre of 1/256; so this feature is not an invariable finding.

Other cases have been reported superficially resembling this (Kretschmer, Janeway, and Rosen, 1968). A girl was shown to have impaired pro-

duction of IgM resulting from poor lymphocyte function due to lymphocytotoxic antibody acting as an auto-antibody and having the same functional result as treatment with antilymphocyte serum. The patient's lymphocyte count fell at the onset of each infection. Our patient did not show these clinical features and we failed to demonstrate any lymphocytotoxic antibody.

Two other similar cases, both boys, have been reported (Kouvalainen, Backman, and Rehtijärvi, 1966; Stoelinga, 1967). They may represent an incomplete form of the disease, showing the immunological deficiency and eczema of Wiskott-Aldrich syndrome, without thrombocytopenia, though a bleeding disorder is usually an intrinsic part of the clinical picture in affected boys. The mother of the three boys reported by Midulla (1959) had mild thrombocytopenia; and Dalloz *et al.* (1965) reported the case of a boy with Wiskott-Aldrich syndrome whose mother had a bleeding tendency with mild thrombocytopenia (platelets about 150,000 per cu. mm.) and reduced platelet survival. They suggested that this was evidence that she was a carrier of the abnormal gene; but they also pointed out that in most reported cases of the syndrome, the mothers had no blood abnormality. But if the disorder is a primary immune defect we should test the immune response of the mothers of affected children: this has not been done.

Certainly, immune deficiency states are rarer in girls. The girl reported by Blecher *et al.* (1968) had normal immunoglobulin levels but an impaired response to some antigens and a normal response to others. No isoagglutinins were detected, but delayed hypersensitivity and lymphocyte transformation were normal. She also had a temporary thrombocytopenia together with haemolytic anaemia. The authors point out the similarity with Wiskott-Aldrich syndrome, but the case differs from the present one in many respects. Another girl reported by Buckley *et al.* (1968) had chronic mucocutaneous moniliasis with absence of delayed hypersensitivity reactions, impaired lymphocyte transformation, and impaired homograft rejection. But this is not the general pattern in this very rare disorder. Chilgren *et al.* (1969) point out that lymphocytes from 5 of 6 other patients reported have normal blast transformation. In contrast to the Wiskott-Aldrich syndrome, the defect appears to lie in the mediator of the efferent limb, not the afferent limb of immunity.

Why should an immune deficiency state be associated with thrombocytopenia? In boys with Wiskott-Aldrich syndrome it has been shown that thrombocytopenia is due to abnormal platelet

function associated with impaired platelet aggregation with ADP (Grøttum *et al.*, 1969; Kim *et al.*, 1969). But this platelet defect can exist independently of any immunological defect, as for instance in the family with thrombasthenia reported by Sheth and Pranker (1968). Canales and Mauer (1967) reported a family with congenital sex-linked thrombocytopenia but without immune defect whom they proposed to classify as incomplete Wiskott-Aldrich syndrome. This is unnecessary, as familial thrombocytopenia exists as an entity without immune defect (Ata, Fisher, and Holman, 1965), and, of greater interest, though males are predominantly affected, females may sometimes be affected too.

It is becoming clear that there may be considerable overlap and variation from case to case of immune disorder, even within the same family (Soothill, 1967; Seligmann, Fudenberg, and Good, 1968). This renders the classification of these cases difficult; and complicated classifications on the basis of minor variations in the symptomatology or pathophysiology are spurious. Furthermore, the recent demonstration that levels of IgM are related to the X chromosome (Rhodes *et al.*, 1969) may have a bearing on these disorders.

Our case has many similarities with the Wiskott-Aldrich syndrome, i.e. eczema, poor response to polysaccharides, and impaired delayed hypersensitivity reactions, recurrent infections (including herpes simplex), lymphopenia, low IgM, and low isohaemagglutinins (see Table V). The points of difference are that she is a girl, has no thrombocytopenia, and her lymphocytes transform poorly. This last feature is not an invariable finding in another similar disorder, chronic mucocutaneous candidiasis, and it is not impossible that boys with otherwise typical Wiskott-Aldrich syndrome may be found who also show impaired lymphocyte transformation. The thrombocytopenia of this syndrome is not obviously part of the immune disorder (indeed, 4 of the 6 boys reported by Berglund *et al.* (1968) had platelet counts as high as 150,000 per cu. mm. at some stage), and the absence of this finding does not exclude the real possibility that this patient has the immune deficiency state of Wiskott-Aldrich syndrome.

As more cases of these immune deficiency disorders come to light slight individual differences will undoubtedly occur in broadly similar groups. These minor differences must not be allowed to obscure the more basic points of similarity.

Many colleagues have helped our investigations: we express our gratitude to them.

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Addendum

Since this report was submitted the patient has had another attack of meningitis and pneumonia due to *Streptococcus pneumoniae* type 12, which was successfully treated with penicillin. Oral prophylactic penicillin, which has been continued successfully for over a year, had been stopped a few weeks previously.