THE TRIAD OF THROMBOCYTOPENIA, ECZEMA AND INFECTION (WISKOTT-ALDRICH'S SYNDROME)

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In 1937, Wiskott[1] was the first to describe in infants a syndrome consisting of thrombocytopenic purpura, eczema and recurrent infections. In 1954 Aldrich *et al.*[2] reported a sex-linked recessive disorder characterized by 'draining ears, eczematoid dermatitis and bloody diarrhoea' occurring in young male infants and resulting in early death. The syndrome described by Aldrich and his co-workers was identical to that described 17 years previously by Wiskott. For this reason the syndrome, although usually referred to as the Aldrich's syndrome, should more correctly be called the Wiskott-Aldrich's syndrome.

The essential triad of signs for the diagnosis is thrombocytopenia, eczema, and recurrent infection. The type of infection varies from otitis media[2-4] to pyodermia,[2, 3, 5] septicaemia,[2-4] meningitis,[5] and pneumonia[5, 6] alone or in varying combinations. The sex-linked inheritance of this disorder has been confirmed by a number of authors. The aetiology is unknown.

In addition to the clinical triad of signs, other features such as splenomegaly,[2, 3, 7] anaemia,[2, 3, 7] eosinophilia,[3, 7] increased serum globulin,[3] and an absent or low titre of iso-agglutinins in the serum have been described.[3] Isolated reports have included such features as the presence of circulating antibodies to whole cow's milk[7] and subperiosteal haemorrhage with calcification[8] and one case had a giant cell pneumonia and generalized cytomegalic inclusion disease at autopsy.[7]

Since the description of this syndrome 17 families, to the best of our knowledge, have been reported which carry this abnormal gene: (Wiskott (1),[1] Aldrich *et al.* (1),[2] Krivit and Good (2),[3] Gordon (1),[4] Huntley and Dees (1),[5] Mills and Winkelmann (2),[6] Wolff and Bertucio (1),[9] Germain (1),[10] Gualdoni (1),[11] Kobayashi and Konoshita (1),[12] Baker *et al.* (3),[13] Johnson *et al.* (1),[14] and Vestermark and Vestermark (1).[15] Although this syndrome is uncommon, the paediatrician, haematologist and dermatologist should be familiar with the clinical findings, since the patient may present with any one component of this syndrome.

Most cases have been recorded in Caucasians, although cases have also been reported in Negroes,[9, 13] and Orientals.[12] The syndrome is world-wide in distribution, having been reported from America,[2, 3, 9, 13] Great Britain,[4] Europe,[10, 11, 15] and Asia.[12] To the best of our knowledge no case has been reported in Africa and the purpose of this paper is to report a case in a Cape Coloured infant.

Case Report

The patient, E.C., a Cape Coloured male infant, was brought to the Red Cross War Memorial Children's Hospital at the age of 1 month on account of diarrhoea. After having been treated as an outpatient for 1 month for repeated bouts of diarrhoea unresponsive to dietetic, antibiotic and resuscitative measures, he was admitted to hospital. There he had repeated episodes of diarrhoea and dehydration requiring intravenous therapy. Some of the bouts of diarrhoea were associated with blood and mucus in the stool. He also had an epistaxis, conjunctival petechiae and microscopic haematuria while in hospital. In addition he developed oral and perianal thrush, abscesses on the scalp, neck and thigh from which *Staphylococcus aureus* was grown, repeated bouts of bronchopneumonia, urinary infection and a salmonella group-D septicaemia during his stay in hospital.

Family history. He was the only child of unrelated parents. His mother, who was of Cape Malay stock, had only one brother who had pyodermia and died as an infant. His father, who had Chinese ancestry on paternal and Cape Coloured stock on maternal side, had 2 brothers who were alive and well. Although the family history is incomplete, it is consistent with a sex-linked recessive disorder.

Physical examination. At 7 months of age, physical examination showed an underweight (5·5 kg.), pale infant, with eczematoid dermatitis of both cheeks and purpura on face, trunk and palate (Fig. 1). Minimal bilateral rib recession was present with coarse crepitations at the base of the left lung. Both liver and spleen were firm and palpable one

finger breadth below the costal margin. The urine analysis showed no abnormality.

Laboratory investigations. The haematological investigations are shown in Table I. The Heaf test and second strength PPD were repeatedly negative. Cultures of gastric washings and bone marrow for acid-fast bacilli were negative and repeated stool cultures did not produce any pathogens. Serum albumin was 3·3 G/100 ml., serum globulin 3·4 G/100 ml. and serum electrophoresis showed a slight rise in the gamma globulin concentration. Immuno-electrophoresis of the serum showed increased gamma$_1$ A globulin. Thymol turbidity was 10·8 units, zinc turbidity 23·4 units and SGOT 52·0 units. Wassermann, Paul-Bunnel, Widal, Weil-Felix and Brucella agglutination tests were all negative. No acid phosphatase was detected in the serum. Latex fixation test was negative. Antibodies to the somatic antigen of salmonella group D were not present.

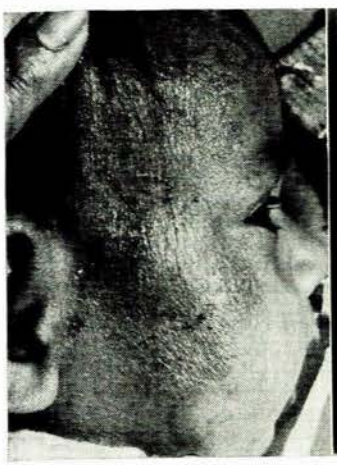

Fig. 1. Appearance of patient on first admission.

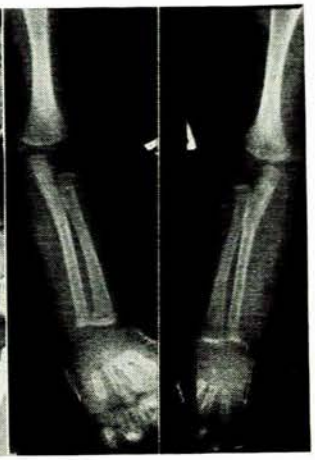

Fig. 2. Roentgenograms of upper limbs showing periosteal thickening.

TABLE I. HAEMATOLOGICAL INVESTIGATIONS

Haemoglobin: 9·6 G/100 ml.
Volume of packed red cells: 33%
Mean corpuscular haemoglobin concentration: 29%
Leucocyte count: 13,000/cu.mm.
  Neutrophils: 16%
  Lymphocytes: 64%
  Monocytes: 8%
  Eosinophils: 12%
Erythrocyte sedimentation rate: 50 mm. in first hour (Westergren).
Platelet count: 9,000/cu.mm.
Schulman platelet-stimulating factor: present
  Mean platelet count before plasma administration: 13,000/cu.mm.
  Mean platelet count after plasma administration: 7,000/cu.mm.
Quick's one-stage prothrombin time: 15 seconds
  Control: 15 seconds
Celite clotting time: 58 seconds
  Control: 43 seconds
Partial thromboplastin time: 85 seconds
  Control: 43 seconds
AHG (Factor VIII) assay: 180%
PTC (Factor IX) assay: 67%
PTA (Factor XI) assay: 59%
Serum iron: 67·7 micrograms/100 ml.
Unbound iron-binding capacity: 546 micrograms/100 ml.
Iron saturation: 12·4%
Serum folate: 4·01 millimicrograms/ml.
Serum vitamin B_{12}: 606 micromicrograms/ml.
Genotype: O.CDe/cde (R,r) MMP Fy$^{(a)}$ Le$^{(a)}$
Anti-A agglutinin titre: 1:2
Anti-B agglutinin titre: 1:4
Phagocytic activity of polymorphs for Staphylococcus (*in vitro*): Normal
Bone marrow: no abnormality. Megakaryocytes normal in number and morphology.

Using the agar gel diffusion technique, 2 precipitin bands to cow's milk were demonstrated in the serum. No precipitin bands were seen against egg, wheat, toxocara or ascara antigens.

Roentgenograms of the chest showed bilateral consolidation involving the right lower lobe and extending throughout the left lung. The cardiac shadow was normal and no enlarged mediastinal lymph nodes were present. Skeletal survey showed periosteal thickening involving the long bones of the upper and lower limbs (Fig. 2).

DISCUSSION

The findings in this male infant of marked thrombocytopenia, eczema, and repeated infections of skin, gastrointestinal tract, lungs, and salmonella septicaemia associated with a compatible family history established the diagnosis of the Wiskott-Aldrich's syndrome. The anaemia, hepatosplenomegaly, petechiae and eosinophilia found in this case are frequently present in this syndrome.

The thrombocytopenia in cases with the Wiskott-Aldrich's syndrome may result in purpura, epistaxis, 'bloody diarrhoea', haematuria and cerebral haemorrhage. Indeed, haemorrhage into a vital organ such as the adrenals or brain has been a common cause of death in these cases.[4, 13, 15]

The cause of the thrombocytopenia is obscure. Adequate numbers of megakaryocytes of normal morphology are present in the bone marrow so that either they do not produce enough platelets or the platelets they do produce have a shortened life-span. Krivit and Good[3] were unable to demonstrate platelet-agglutinating antibodies in 2 of their cases. This may suggest that some defect in the production of platelets is more likely than excessive destruction of normal platelets. We demonstrated that in this case the thrombocytopenia was not due to the lack of the Schulman platelet-stimulating factor.[16]

The infections in these infants are of the usual variety and are characterized by their frequency, severity and poor response to antibiotics. The repeated bouts of fever associated with roentgenographic evidence of pulmonary infiltration may be a result of pulmonary haemorrhage owing to the thrombocytopenia rather than to infection. In our patient, gamma globulin concentration was higher than normal, the leucocyte count was adequate with a normal endowment of lymphocytes of normal morphology and *in vitro* studies showed that the polymorphs were competent in the phagocytosis of staphylococci. Krivit and Good[3] performed intensive investigations into the immune mechanisms and leucocyte function in their cases and were unable to find any definite deviation from normal. There is, therefore, no explanation to date for the liability to infection in these infants and infection is the commonest cause of death despite antibiotic therapy.

The eczema that occurs is identical to infantile eczema but may be modified clinically in certain cases by the presence of superimposed purpura. The severity varies considerably from one patient to another and from time to time in the same patient.

From the cases described in the literature the genetic inheritance of this syndrome as a sex-linked recessive appears clear-cut. A study of the bone marrow showed a modal chromosome number of 46 in this condition.[7]

The average age of onset of symptoms is 6 weeks, although in 1 case it was at birth.[6] They may present with any one or with several components of the syndrome. These children usually die at an early age from either haemorrhage or infection[4] although isolated cases have survived until 7 years,[5] and 10½ years of age.[13] Vestermark and Vestermark[15] describe a family with this syndrome, one of whom with mild disease was alive at 40 years of age.

A superficial resemblance exists between this syndrome and histiocytosis X (Letterer-Siwe's disease). However, more critical comparison shows consistent differences between these 2 disorders. Letterer-Siwe's disease does not have the strong family history and has a characteristic seborrhoeic haemorrhagic maculo-papular rash compared with the eczematoid dermatitis which occurs in the Wiskott-Aldrich's syndrome. The pathology of the lymphoid tissue is entirely different in the 2 diseases.

The presence of circulating antibodies to whole cow's milk was demonstrated in the serum of the patient described in this paper as well as in the case described by Root and Speicher.[7] The significance of this finding is not clear at present.

Treatment, by and large, has little effect on the course of this disorder. ACTH and steroids have been used with poor effect.[3, 4] Splenectomy has been performed on many cases reported in the literature.[4, 15] King and Shumacker[17] and Smith and his co-workers,[18] on the other hand, have shown that increased susceptibility to infections occur generally in infants who have undergone splenectomy under 2 years of age. For this reason it would appear unwise to subject these children, with their inherent liability to infection, to splenectomy. Indeed, Krivit[19] has considered that splenectomy is contraindicated in this disease, since many children who had had splenectomy died within months following operation. Good constant conservative therapy, with careful and judicious use of antibiotics, may provide the most satisfactory results.

SUMMARY

A case of Wiskott-Aldrich's syndrome, the first reported on the continent of Africa, is described and the literature on the subject is reviewed.

ADDENDUM

The patient was re-admitted to hospital at 11 months of age with cyanosis and respiratory distress. A radiograph showed bilateral pulmonary infiltration. The course was one of progressive deterioration and he died suddenly after 4 days in hospital, despite treatment with Pantofenicol (chloramphenicol calcium pantothenate complex palmitate) and hydrocortisone therapy. The last platelet count recorded a day before death was 6,000/cu. mm. Autopsy was refused.

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