Wiskott-Aldrich Syndrome

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The Wiskott-Aldrich syndrome is characterized by thrombocytopenia with associated haemorrhagic phenomena, eczema, and recurrent infections. The clinical features were first described by Wiskott in 1937. Seventeen years later Aldrich, Steinberg, and Campbell (1954) described the symptom complex in a 6-month-old infant. Study of this child's family indicated transmission of the disorder as a sex-linked recessive trait. The condition is rare; about 60 cases have been reported. Only one reference to the occurrence of the syndrome in the British Isles has been traced. This was a family with two affected members reported by Gordon (1960). The present communication describes two new patients with this syndrome, each of whom had a male relative who died during childhood from an identical disorder. As far as is known, these two families are not related to each other.

Case Reports

Case 1. P.S., a male infant, was born in January 1966. Blood in the stools was first seen when he was 2 weeks old; purpuric spots appeared a few days later. Fresh intestinal bleeding occurred at the age of 16 weeks, when he was admitted to the Royal Belfast Hospital for Sick Children. On examination he appeared pale, and there were purpuric lesions scattered over the body, especially over the extremities. He had a slight seborrhoeic rash on the forehead and behind the ears. There was no lymphadenopathy or hepatosplenomegaly.

Investigations. Hb 8.2 g./100 ml., red cells 2.91 M./c.mm., reticulocytes 3.5%, white cells 3800/c.mm., polymorphs 40%, lymphocytes 59%, eosinophils 1%, platelets 20,000/c.mm. Bone-marrow smear showed normal erythroid and granulocyte elements. Megakaryocytes were reduced in number and showed lack of maturation; their cytoplasmic content appeared much reduced and very few platelets were seen being budded off. Plasma proteins 7.8 g./100 ml., albumin 3.56 g., α_1 -globulin 0.85 g., α_2 -globulin 0.85 g., β -globulin 1.11 g., γ -globulin 1.43. The IgG, IgA, and IgM immunoglobulin levels were all in excess of the expected values for age (Table). Blood group A Rhesus positive, anti-B isoagglutinin titre 1/4 (normal 1/64). Radio-

graphs of chest, skull, and extremities, and excretion pyelography showed no abnormality.

After 2 weeks on oral iron Hb had risen to 9.3 g./100 ml. and the reticulocytes to 7.5%. The stools gave a positive reaction for occult blood for a few weeks after admission, but there was no recurrence of frank bleeding. He was discharged after 3 weeks. When reviewed a month later at the age of 6 months, he was found to have septic spots over both thighs and groins; he had passed streaks of fresh blood on several occasions and petechial spots had continued to appear. Seborrhoeic eczema was noted over the scalp and forehead. The platelet count was 30,000/c.mm.

Inquiry into the *family history* revealed that his brother, the eldest child in the family, had suffered from a similar disorder. This brother, W.S., was born in November 1954. At the age of 3 weeks 'red spots' were noticed on the back of the neck and chest, eventually spreading all over the body. A few weeks later flecks of fresh blood were noticed in the stools. These symptoms recurred on several occasions and he was admitted to The Hospital for Sick Children, Great Ormond Street, in March 1955. On examination there was seborrhoeic eczema affecting the scalp, groins, and behind the ears, a generalized petechial rash, and a few scattered bruises. The liver was palpable two fingers' breadth below the costal margin; the spleen was just palpable.

Investigations (W.S.). Hb 10.3 g./100 ml., white cells 10,800/c.mm., platelets 18,200/c.mm. Chest x-ray film and a skin biopsy were normal. A splenectomy was carried out in May. The platelet count 10 days later was 299,600/c.mm., though petechiae were present at this stage. The child was discharged at the end of

TABLE
Serum Immunoglobulin Values in Cases 1 and 2.

Case No.	Age	IgG (% adult value)	IgA (% adult value)	IgM (% adult value)
1	16 wk.	140 (37)	89 (14)	110 (43)
2	10 yr.	82 (97)	270 (66)	23 (80)

Note: Immunoglobulin values were determined by a commercial modification of the immunodiffusion technique of Fahey and Lawrence (1963). The mean adult values for this method are, IgG 1100 mg./100 ml.; IgA 220 mg./100 ml.; IgM 75 mg./100 ml. Results are expressed as a percentage of mean adult values.

Percentage figures for healthy children of similar age to patients are shown in brackets (Stiehm and Fudenberg, 1966).

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May but was readmitted 10 days later because of a recurrence of melaena; the platelet count was then 190,000/c.mm. He was discharged after a week. At the age of 16 months (10 months after splenectomy) he died suddenly. Necropsy was not performed, but the cause of death was thought to be a cerebral haemorrhage.

In retrospect there is little doubt that this child also suffered from the Wiskott-Aldrich syndrome, even though pyogenic infections were not recorded as a feature of his illness. The family pedigree is shown.

FIG.—Pedigree of Family 1.

Case 2. B.M., a male child, was born in August 1956. A circumcision was performed when he was 2 weeks old without any complication. Bruising of the legs was first noticed when he was 8 months old. He had also passed small amounts of bright red blood in the stools on several occasions. He was admitted to the Royal Belfast Hospital for Sick Children in July 1959 for investigation of purpura. Examination showed the presence of numerous ecchymoses all over the body, especially on the cheeks, legs, and buttocks. There were many submucosal haemorrhages inside the mouth. He had no eczema. The platelet count was 20,000/c.mm. He was discharged after 5 weeks without any specific therapy. He subsequently developed recurrent septic spots and boils and had several epistaxes. When examined 4 months later he had multiple boils, most numerous on both legs. He also had eczematous lesions on his elbows, posterior aspects of the knees, and behind the left ear. Since then he has continued to suffer from eczema, recurrent skin infections, and epistaxes. The platelet count on several occasions has been less than 60,000/c.mm. His last admission to hospital was in May 1966 when the following studies were carried out. Hb 8.6 g./100 ml., platelets 36,000/c.mm., plasma proteins 7.1 g./100 ml., albumin 3.32 g., α_1 -globulin 0.64 g., α_2 -globulin 0.78 g., β -globulin 1.01 g., γ -globulin 1.35 g. The serum immunoglobulin values showed a reduction in IgM and a marked rise in IgA (Table). Blood group A Rhesus positive, anti-B isoagglutinin titre 1/1 (normal 1/64).

Unfortunately, it has not been possible to obtain detailed information of this child's family. It is, however, known that his first cousin suffered from a similar illness which showed all the clinical features of

the Wiskott-Aldrich syndrome. This was a male child, C.C., who was born in October 1947. Facial eczema was noticed when he was 3 months old. He had bronchopneumonia at 1 year. He was admitted to the Belfast City Hospital in December 1950 for the treatment of severe eczema. At this stage he also suffered from sinusitis and bilateral corneal ulceration. Hb 6.7 g./100 ml.; tuberculin test negative. He was discharged after 3 months. He continued to suffer from eczema and sinusitis and, in addition, developed recurrent epistaxes. He was readmitted to hospital in November 1952 (at the age of 5 years), when extensive eczema and petechiae were noted. The platelet count was 20,000/c.mm. Over the following years these symptoms continued to recur, and he also suffered from extensive bilateral corneal ulceration on two occasions. Low platelet counts and iron deficiency anaemia were recorded on these occasions. When 12 years old he developed rheumatic fever with cardiac involvement, and was treated with salicylates and prednisolone. He made a complete recovery. Bouts of epistaxis and purpura continue to punctuate the course of his illness. His final admission to hospital was at 13½ years. He had complained of nausea, abdominal pains, and nose bleeds for 3 weeks before admission. On examination he appeared pale and ill. Hb 5.4 g./100 ml. and blood urea 475 mg./100 ml. The urine contained albumin and a growth of coliforms was obtained on culture. Despite a blood transfusion and two dialyses his condition deteriorated rapidly, and he died 3 weeks after admission. Permission for a full necropsy was not obtained; a renal biopsy, however, was done immediately after death. On microscopical examination of the specimen no changes were found in the glomeruli. The tubular epithelium showed extensive infiltration with polymorphonuclear cells and the over-all picture was suggestive of abscess formation and pyelonephrosis.

Discussion

All reported patients have been male. The mode of inheritance of this syndrome as a sex-linked recessive trait appears to be well established. However, sporadic examples of the disorder have also been described with no clear-cut evidence of the condition in other members of the family (Kildeberg, 1961; Johnson, Burke, and Burgert, 1964).

Purpura and melaena are the most prominent clinical manifestations, and often the presenting features. These invariably start in early infancy. The severity of eczema is variable and, as in Case 1, may be minimal. The eczematous areas are often the sites of infection and haemorrhage, as was observed in Case 2.

Recurrent episodes of infection are an important feature of this syndrome. Superficial pyrogenic infections are the commonest and most obvious, and include furunculosis, impetigo, and conjunctivitis.

However, otitis media, sinusitis, and bronchopneumonia have also been frequently reported. The patient C.C. suffered from recurrent corneal ulcers of undetermined aetiology, a feature also noted by ten Bensel, Stadlan, and Krivit (1966) in one of their patients.

Thrombocytopenia is a constant feature. The bone-marrow examination has usually revealed the presence of an adequate number of megakaryocytes. However, Pearson, Shulman, Oski, and Eitzman (1966) reported an unusual appearance of the megakaryocytes in two patients, in whom more than half of these cells showed a pronounced degree of hypersegmentation, karyorrhexis, and degenerative appearance of the nuclei, despite little active platelet formation. In Case 1, morphologically abnormal megakaryocytes were observed. Homologous platelet survival was studied in three patients by Pearson *et al.* (1966) who found the survival time to be normal. No evidence of a platelet-agglutinating antibody was found by Krivit and Good (1959) in two patients. On the basis of these findings, inadequate production of platelets rather than their increased peripheral destruction appears to be the cause of the thrombocytopenia.

Though the electrophoretic pattern of the plasma is usually not significantly altered, an abnormal finding in the great majority of cases has been the absence or a much diminished titre of blood group isoagglutinins. In a study of the defense mechanisms of patients with this syndrome, Cooper, Chase, St. Geme, Krivit, and Good (1964) have reported low serum IgM immunoglobulin levels, an abnormal host response to certain viruses (herpes simplex and measles), and absolute lymphopenia. A low concentration of IgM was found in Case 2; on the other hand, a raised value was recorded in Case 1. The foregoing observations could be considered to signify an abnormality in immunological competence, predisposing to recurrent infections. It is notable that recurrent infections are also a feature of such varied disorders as systemic lupus and related conditions, acute granulomatous disorders, and leukaemia, in all of which a disordered immunological state is postulated. Recently, an increased incidence of sino-pulmonary infections has been described in patients with ataxia-telangiectasia (Gutmann and Lemli, 1963). That these patients also manifest disordered immunological competence is indicated by the fact that they sometimes have a low serum IgA immunoglobulin and impairment of lymphocyte proliferation in response to stimuli (Oppenheim, Barlow, Waldmann, and Block, 1966).

The course of the disease is not significantly

influenced by treatment. Thrombocytopenia is not affected by the administration of ACTH or corticosteroids. Splenectomy has not been found to benefit the haemorrhagic manifestations, though a post-splenectomy rise in platelets has been documented, as was also noted in the brother of Case 1. A review of published reports shows that patients with the Wiskott-Aldrich syndrome, in whom a splenectomy had been performed, all died within one year of this operation. As this procedure of itself predisposes to serious pyogenic infections (King and Shumacker, 1952; Lowdon, Stewart, and Walker, 1966), it must be considered especially undesirable in the management of patients with the Wiskott-Aldrich syndrome.

The majority of patients die in early childhood. Case 2 is unusual in having survived to the age of 10 years. It is also notable that his cousin C.C. died at the age of 13 years. The cause of death in most cases is overwhelming infection or haemorrhage. Recently ten Bensel *et al.* (1966) have drawn attention to the increased incidence of malignant conditions in patients with the Wiskott-Aldrich syndrome. These authors reported the occurrence of malignancy involving the reticulo-endothelial system in 2 of 4 affected children in one family. They also referred to 7 other published cases which died from a malignant condition (3 from reticulo-endotheliosis, 2 from malignant lymphoma, 1 from myelogenous leukaemia, and 1 from a cerebral astrocytoma). These authors postulated that the neoplasia in this syndrome might derive from the chronic stimulatory effect of infections on the reticuloendothelial system, or perhaps directly from the immunological deficiencies.

In its typical form the Wiskott-Aldrich syndrome is extremely uncommon. It is possible, however, that isolated cases have been regarded as idiopathic thrombocytopenic purpura, as was so in W.S. (the brother of Case 1) and initially also in Case 2. This may also be true of a boy reported by Gofstein and Gellis (1956), who suffered from rectal bleeding and repeated episodes of infection from the age of 6 days. He failed to benefit from splenectomy. His blood group was O and he had a low titre of anti-A isoagglutinin and no anti-B isoagglutinin. Although neonatal thrombocytopenia may occur as a transient phenomenon from a variety of causes, true idiopathic thrombocytopenia purpura is rarely manifest before the age of 12 months, and thrombocytopenic purpura in a boy under 1 year should thus always suggest the possibility of the Wiskott-Aldrich syndrome. The presence of a low titre of blood group isoagglutinins is an important diagnostic feature.

Summary

Two patients of unrelated families with the Wiskott-Aldrich syndrome are described. The clinical and biochemical abnormalities are briefly discussed. It is suggested that this syndrome may not be as rare as the small number of reported patients would indicate. The diagnosis should always be considered whenever thrombocytopenic purpura is encountered in a boy of under 12 months. Occurrence of a low titre of blood group isoagglutinins in the Wiskott-Aldrich syndrome is a valuable diagnostic feature.

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