Constitutional aplastic anaemia: a family with a new X linked variety of amegakaryocytic thrombocytopenia

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SUMMARY A family is described in which three male members died in early infancy with severe thrombocytopenia and a fourth in adolescence with aplastic anaemia. One child was investigated in detail and shown to have amegakaryocytic thrombocytopenia, progressing to pancytopenia as a result of bone marrow hypoplasia. His associated congenital abnormalities differed from those described in Fanconi's aplastic anaemia, his chromosomes were normal, and the fetal haemoglobin level was 48%. Amegakaryocytic thrombocytopenia is itself rare and the index case appears unique. It is suggested that this family has a previously undescribed X linked variety of amegakaryocytic thrombocytopenia.

This paper describes a family in which four male members had constitutional aplastic anaemia. One child developed aplastic anaemia during adolescence, while the remaining three had a rapidly fatal form of amegakaryocytic thrombocytopenia, thought to be inherited in an X linked manner. The condition progressed in one of them, the index case, to aplastic anaemia. The clinical features of this latter child do not fit exactly into any of the syndromes described so far and he appears to be unique.

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Case report

The proband (VI.1, figure), an only child of healthy unrelated parents, was born uneventfully in April 1978, birthweight 2.502 kg. His mother worked during early pregnancy packing cordite in an ordnance factory. At 8 months both height and weight were below the 3rd centile. He had an odd, coarse facial appearance, rather suggestive of a mucopolysaccharidosis, and a short neck. The anterior fontanelle was fullish and the head circumference at 46 cm was on the 90th centile.

FIGURE Family pedigree.

There was a linear pigmented naevus on his chest, a dorsal scoliosis, and slight developmental delay.

At 1 year he developed a few small bruises on his legs and a petechial rash. No drugs had been given during the preceding 6 months. Investigations revealed: Hb 11.2 g/dl, WBC $15.1 \times 10^9/l$ (17% neutrophils, 76% lymphocytes, 7% monocytes), absolute neutrophil count $2567 \times 10^9/l$, platelets $23 \times 10^9/l$, and reticulocytes 2.5%. Hb F accounted for 45% of the total Hb. X-rays showed a dorsal scoliosis without hemivertebrae and rather thin parietal bones with wormian bones in the lambdoid suture. The forearms were normal. Two marrow aspirations showed normoblastic erythropoiesis and occasional atypical erythroblasts, for example, megaloblastoid forms and cells with polyploid nuclei. Myelopoiesis was normal. Only one megakaryocyte was seen with an unsegmented nucleus, but active in platelet production. Paraffin sections showed normal cellularity with extremely sparse megakaryocytes. The following investigations gave normal or negative results: thyroid function, serum calcium, phosphate, and alkaline phosphatase; blood and urine amino-acid chromatography; screening test for urinary mucopolysaccharides; Ham's test; cultures of blood, CSF, urine, and throat swab, toxoplasma, cytomegalovirus, and rubella titres; and immunoglobulins (IgG 6.58 g/l, IgM 0.98 g/l, IgA 0.15 g/l). Chromosome analysis on peripheral blood was normal (46,XY) with no abnormality in conventional G banded preparations. Cow's milk was withdrawn from his diet for 3 weeks without any improvement in his platelet count.

At 14 months further investigations were performed at the Department of Haematology, The Hospital for Sick Children, Great Ormond Street, London. His Hb was 9.29 g/dl, MCV 107, MCH 34, MCHC 32, reticulocytes 7.2%, platelets $2.0 \times 10^9/l$, WBC $8.9 \times 10^9/l$, neutrophils $0.712 \times 10^9/l$, and lymphocytes $8.0 \times 10^9/l$. Bone marrow and trephine showed hypoplasia with active erythropoiesis but macronormoblastic and dyserythropoietic features. Granulopoiesis was reduced and megakaryocytes were extremely scanty though morphologically normal. Iron stores were reduced and there was no increase in reticulin deposition. Bone marrow erythroid colony formation was reduced, although a normal range is not yet available: BFU E $0.2/10^5$ nucleated cells, CFU E $6/10^5$ nucleated cells. Haemoglobin electrophoresis showed Hb F 48.4% and no Hb A₂ was detected. Kleihauer stain showed homogeneous distribution of Hb F. The red cell enzyme pattern resembled that of fetal erythrocytes. Globin synthesis studies of blood, bone marrow, and erythroid colonies showed balanced α and non- α chain synthesis, with similar proportions of γ and β

chain production. The appearances were similar to that of cord blood. Deoxyuridine suppression test was normal at 4.3%. Serum iron was 16.1 $\mu\text{mol/l}$ (14 to 22 $\mu\text{mol/l}$), serum folate 32.0 $\mu\text{g/l}$ (6 to 21 $\mu\text{g/l}$), red cell folate 1204 $\mu\text{g/l}$ (150 to 650 $\mu\text{g/l}$), TIBC 73.2 $\mu\text{mol/l}$ (42 to 66 $\mu\text{mol/l}$), serum vitamin B₁₂ 1140 ng/l (150 to 1000 ng/l). Unsaturated B₁₂ binding capacity was 1378 ng/l. Transcobalamins I, II, and III were normal. Direct Coombs' test was negative and cold agglutinins were not raised. EB virus and hepatitis A were negative. Urinary mucopolysaccharides, glycosaminoglycans, and phenolic and organic acids were normal. There was generalised amino-aciduria and a positive test for reducing substances (lactose 1.0 $\mu\text{mol/l}$, galactose 0.5 $\mu\text{mol/l}$, glucose 0.5 $\mu\text{mol/l}$, and fructose 0.5 $\mu\text{mol/l}$). A skeletal survey showed slightly ovoid vertebral bodies in the lower dorsal and upper lumbar region with an infantile scoliosis.

In summary, the investigations revealed a pancytopenia resulting from bone marrow hypoplasia with platelet production most severely impaired. The raised MCV and fetal haemoglobin together with the red cell enzyme pattern and globin chain synthesis results fitted with a fetal pattern of erythropoiesis. There was also latent iron deficiency but no evidence of lack of folate or vitamin B₁₂. Oral iron was prescribed.

By 26 months he was severely anaemic, Hb 3.4 g/dl, with a platelet count consistently below $10 \times 10^9/l$ and an absolute neutrophil count of $0.672 \times 10^9/l$. Platelet and blood transfusions were started together with prednisolone and androgens, initially sublingual testosterone propionate and later oxymethalone, but he died aged 33 months after frequent episodes of haematuria and melaena.

Family history

Detailed physical examination of both parents was negative, with no physical abnormalities. There is no known consanguinity at any point in the family, but two first cousins of the mother, the second and third children of four sibs, both males, had died in infancy with thrombocytopenia.

V.9, born in October 1960, died at 16 days with severe thrombocytopenia (lowest platelet count 2000/cmm ($2 \times 10^9/l$)) and a cerebral haemorrhage was found at necropsy. The hospital notes did not state if there was evidence of disseminated intravascular coagulation or a history of idiopathic thrombocytopenic purpura in the mother, and neither was there information about drugs taken during the pregnancy.

V.10, born in June 1962, died at the age of 6 months following admission to hospital at 4 months.

A diagnosis of 'congenital idiopathic thrombocytopenic purpura with terminal haemorrhage' and a probable ventricular septal defect was made clinically. Bone marrow examination was not performed and necropsy was refused.

V.11, the third male maternal cousin, born in August 1963, is alive and as yet unaffected.

A distant relative with leukaemia (VI.9) later proved to be adopted and not truly related.

IV.2, a male relative of the father of the proband, was born in May 1964. In December 1980 he developed bruising, sore throat, pallor, and epistaxes. Investigations revealed Hb 5.1 g/dl, WBC $2.2 \times 10^9/l$, 10% neutrophils, 85% lymphocytes, 5% monocytes, platelets $15 \times 10^9/l$. Ham's test was negative. There was recent evidence of adenoviral infection. Bone marrow aspiration and trephine showed a severely hypocellular marrow consisting mainly of lymphocytes and plasma cells with very sparse megakaryocytes. Only occasional nests of erythroid and myeloid cells were identified. There was no physical congenital abnormality but x-rays of the radii, chromosome analysis, and haemoglobin F estimations were not performed. He died in March 1981 after a suspected cerebral haemorrhage, but necropsy was not undertaken.

Discussion

Only 16 cases of amegakaryocytic thrombocytopenia have been recorded.¹⁻⁶ Bloom *et al*² recorded two patients, both males without physical or chromosomal anomaly, and classified them as type II constitutional aplastic anaemia. O'Gormon Hughes⁴ reclassified constitutional aplastic anaemia in 1974 and recorded five males (type III) and two females (type IV) with amegakaryocytic thrombocytopenia, but only the females had associated congenital abnormalities or a positive family history.

In view of the very few patients reported it is difficult to ascertain whether amegakaryocytic thrombocytopenia is a distinct entity or merely the initial presentation of Fanconi's anaemia or a non-Fanconi's familial aplastic anaemia.

Several families have been described¹ where aplastic anaemia could not be attributed to Fanconi's anaemia. In five such families, however, no member had any associated congenital malformation.

Two males in the present family died of haemorrhage in infancy, almost certainly the result of amegakaryocytic thrombocytopenia, while the proband presented haematologically with amegakaryocytic thrombocytopenia but rapidly developed generalised bone marrow hypoplasia. His associated clinical features did not fit with either Fanconi's anaemia or the cases of familial aplastic

anaemia described so far. Although he was short with developmental delay, the skeletal deformities were confined to an infantile scoliosis, there was no abnormality of the thumbs, and the pigmented naevus was not typical of the diffuse mottled pigmentation or café-au-lait spots described in Fanconi's anaemia. There were no chromosomal breaks or rearrangements in peripheral blood lymphocytes, usually regarded as one of the most characteristic laboratory findings in Fanconi's anaemia and reported in 82% of the two largest series studied.⁷ Another notable feature was the fetal haemoglobin level of 48.4%, significantly higher than that recorded in Fanconi's anaemia (2.6 to 21.9%),⁴ constitutional aplastic anaemia (3 to 15%),⁸ or previously reported cases of amegakaryocytic thrombocytopenia (3.1 to 5.7%),⁴ (20.1%).⁶ Heterozygotes with hereditary persistence of high fetal haemoglobin have values of 20 to 30%, but no associated anaemia. However, as in the present case, there is an even distribution of fetal haemoglobin through the red cell population, in contrast to thalassaemia where a cell to cell variation occurs. The persistence of fetal erythropoiesis in association with aplastic anaemia supports the concept of abnormal stem cell function.^{1,6}

Most cases of constitutional aplastic anaemia demonstrate an autosomal recessive mode of inheritance, although one family with dominant inheritance has been described.⁹ A number of X linked disorders are associated with thrombocytopenia, including an X linked form of hereditary isolated thrombocytopenia, but this follows a benign course in the families reported. The X linked Wiskott-Aldrich syndrome and dyskeratosis congenita have distinctive clinical features.

The only satisfactory explanation of the genetics in the present family is that the aplastic anaemia of the adolescent child (IV.2) is quite unrelated to that of the index case and his two cousins. These latter three appear to have a previously undescribed X linked variety of amegakaryocytic thrombocytopenia, unique to this particular family.

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