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 15·1×10⁹/l (17% neutrophils, 76% lymphocytes, 7% monocytes), absolute neutrophil count 2567×10⁹/l, platelets 23×10⁹/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 narrow 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; Haematology, 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 (2×10⁹/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 x 10^9/l, 10% neutrophils, 85% lymphocytes, 5% monocytes, platelets 15 x 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 al2 recorded two patients, both males with physical or chromosomal anomaly, and classified them as type II constitutional aplastic anaemia. O'Gorman 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%), 5 or previously reported cases of amegakaryocytic thrombocytopenia (3.1 to 5.7%), 5 (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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