A new autosomal recessive syndrome

Early onset of pancytopenia, distinct facial features, growth retardation and developmental delay

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ABSTRACT

The association of dysmorphic features and failure of one or more bone marrow cell lines is well known. Examples are Fanconi's anemia and Diamond-Blackfan anemia. This report describes 3 similarly affected children from consanguineous parents, all showing low birth weight, severe growth retardation, distinct facial features, microcephaly, mental retardation and onset of severe pancytopenia in infancy without increased chromosomal breakage. We conclude that these cases represent a new familial autosomal recessive bone marrow failure syndrome.

Keywords: Aplastic, anemia, constitutional, familial.

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Several constitutional bone marrow failure syndromes are associated with dysmorphic features.[1] Aplasia of more than one cell line is part of Fanconi's anemia,[2] and dyskeratosis congenita[3] Schwachman Diamond syndrome[4] is occasionally associated with other syndromes like Seckel's dwarfism and Dubowitz syndrome.[5,6] Syndromes associated with single cell line aplasia are Diamond-Blackfan anemia,[7] Aase syndrome,[8] and thrombocytopenia with absent radii syndrome.[9] Furthermore, a number of families have been described with aplastic anemia associated with various abnormalities and different modes of inheritance.[1] In this paper we describe a new familial autosomal recessive bone marrow failure syndrome without increased chromosomal breakage, further characterized by low birth weight, growth retardation, distinct facial features, microcephaly, mental retardation and onset of pancytopenia during the first year of life.

Family history. The parents are first degree cousins both in their early 30s. They are healthy without any history of hematological problems. They have 3 affected children described in the case reports below. Their 4th child is 2 years old with normal facial features. The full blood count and the level of fetal hemoglobin (HbF) in the parents and the non-affected sibling are normal. There is no history of abortion or stillbirth. There is no history of blood diseases, growth problems or facial abnormalities in the extended family.

Case Report. ***Patient 1.*** The first child is a girl born at term after an unremarkable pregnancy and delivery. She was small for date, with a birth weight of 2.2kg. During the first 6 months of life she was breast fed and apparently well. At the age of 6 months she developed pallor and she was found to be anemic. Iron was prescribed, but there was no improvement. At the age of one year and a half she

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started to have skin bruises and gum bleeding. Apart from iron medication there was no history of drug ingestion and no history of a preceding infection or vaccination. There was no history of diarrhea, but there was developmental delay. She smiled at the age of 6 months, sat at the age of one year, walked at 2 years and used only single word speech at 2 years. At the age of 2 and a half years the child was referred to our hospital due to bleeding problems. On examination a very small, pale child was seen. The skin showed bruises all over the body, but no abnormal pigmentation. Her weight was 5.1kg (far below the 3rd centile), and height 60cm (far below the 3rd centile). The head circumference was 46cm (below 3rd centile). The facial features were remarkable with a high forehead, upsweeping of the anterior hairline, frontal bossing, downward slanted eyes, depressed nasal bridge and a wide nasal base (Figure 1). Liver and spleen were not enlarged. The extremities including the hands and external genitalia were normal. Investigations showed a white blood cell count (WBC) of 4.5 x 10^9/L with an absolute neutrophil count (ANC) of 0.2 x 10^9/L, lymphocytes 4.1 x 10^9/L and monocytes 0.2 x 10^9/L. The hemoglobin (Hb) was 3.7 mmol/L (6.0 g/dl) and the mean cellular volume 90 fentoliter. The reticulocytes were 1% with an absolute count of 41 x $l0^9$/L. The platelets were 16 x 10^9/L. The serum ferritin level was 821 microgram/L (normal 8-120). Vitamin B12 level was increased with 1487 pmol/L, the serum folate level was normal. Hemoglobin electrophoresis showed a normal HbA and HbA2, but a marginally increased HbF for age 2%. The level of serum immunoglobulins was lgG 9.0, IgA O.6 and lgM 0.5 gram/L (all values in the normal range). Lymphocyte subset analysis for CD3, CD4, CD8, CDI9, cD20 and DR showed normal percentages and absolute counts. Bone marrow aspiration and trephine bath showed hypocellular marrow with markedly reduced myelopoiesis, erythropoiesis and megakaryopoiesis and an increase of areas containing fat. Using standard cytogenetic techniques (550 band level) no numerical or structural chromosomal changes were noted. Chromosomal breakage after in vitro exposure to mitomycin and diepoxybutane was not increased. Serological studies for human immunodeficiency virus, cytomegalovirus, hepatitis, B virus, parvovirus, and Epstein Barr virus were negative. Screening for metabolic diseases was negative. Echocardiogram and ultrasound of the kidneys were normal. A skeletal survey including the limbs revealed no abnormalities. At this point the diagnosis of constitutional bone marrow failure syndrome was considered.

Following her initial presentation she required platelet transfusions every one to 2 weeks and transfusions of packed red blood cells every 2-3 weeks. At the age of 2 years and 6 months she was given a trial of oxymetholone 2mg/kg/day once daily plus a small dose of Prednisolone 5-10 milligram

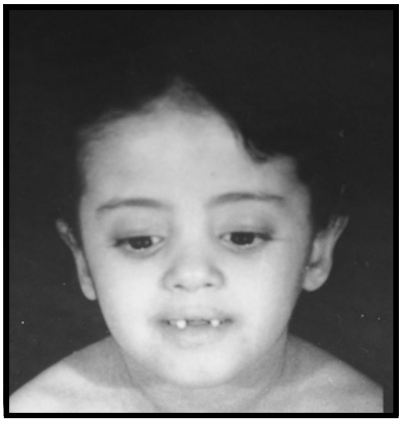

Figure 1 - (Patient 1) At the age of 5 years, showing frontal bossing, high forehead, upsweeping of frontal hairline, depressed nasal bridge, variable ear abnormalities and downward slanted eyes.

once daily. This medication was stopped after one year, as there was no response. At the age of 3 years and 6 months cyclosporine A at a dose of 6 mg/kg twice daily was given for 6 months and discontinued as there was no increase in cell counts or decrease in transfusion requirement. Three months after discontinuation of all therapy, at the age of 4 years and 3 months, her requirement for platelet and blood transfusion decreased and over the last 2 years no transfusions were given. Now, at the age of 7 years her Hb is 6.8 mmol/L (11 g/dl), reticulocytes 2.5%, WBC 10.1 x 10^9/L, and ANC 6.0 x 10^9/L. The platelets are still below 150 x 10^9/L, but always more than 50 x 10^9/L. Her facial features are unchanged. Her growth is retarded with a weight of 10.1kg, a height of 88cm and a head circumference of 48cm, all far below the 3rd percentile. She is an active, sociable child. She can make clear sentences of 2-4 words. Her intelligence quotient is 72 measured by the Stanford Bennet intelligence test.

Patient 2. The 2nd child is a boy, born after an unremarkable pregnancy and delivery. Like his sister he had a low birth weight of 2.3kg. He was breast feed, but was not growing well and showed marked developmental delay At the age of 9 months he presented in our hospital with complaints of gum bleeding and epistaxis. On examination a small, pale child was seen with multiple petechiae and ecchymoses. The height, weight, and head circumference were all far below the 3rd centile. He had similar, but more marked facial features than the first child with folded superior helixes and prominent antihelixes (Figure 2). Further examination was unremarkable.

Investigations showed a WBC of 1.5 x 10^9/L with an ANC of 0.1 x 10^9/L, lymphocytes 1.3 x 10^9/L and monocytes 0.1 x 10^9/L. The Hb was 4.3 mmol/L (7.0 g/dl) and the mean cellular volume 93 fentoliter. Reticulocytes were 1% with an absolute count of 56

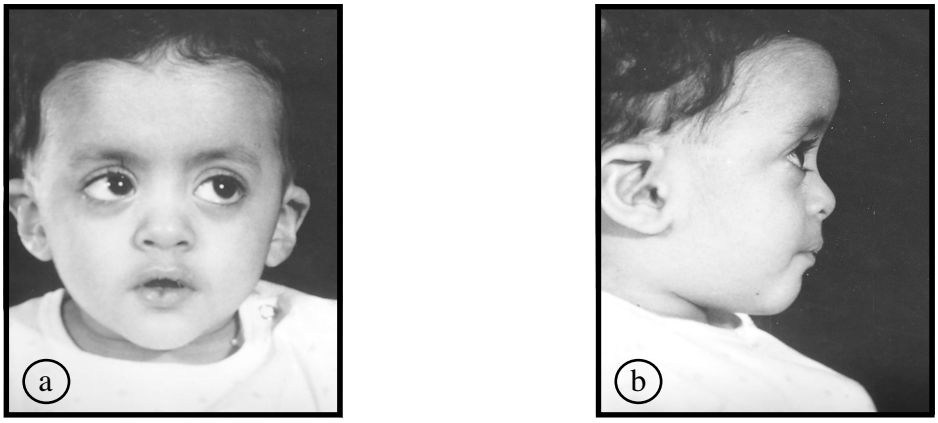

Figure 2 - Patient 2 at the age of one and a half years **(a)** Frontal view. **(b)** Side view, showing frontal bossing, high forehead, upsweeping of frontal hairline, depressed nasal bridge, variable ear abnormalities, and downward slanted eyes.

x 10^9/L. The platelets were 11 x 10^9/L. The vitamin B12 level was increased to 1500 pmol/L. The HbF was increased to 3%. Lymphocyte subsets and levels of serum immunoglobulins were normal. Findings of bone marrow aspiration and trephine were identical to Patient 1. Chromosomal breakage was not increased. Viral Screening was negative. Metabolic screening was negative. Following his presentation at the age of 9 months, he needed weekly platelet transfusions, and transfusions of packed red blood cells every 2-3 weeks. He was frequently admitted for treatment of skin infections and sepsis. He was given prednisolone 2mg/kg/day for 2 months, oxymetholone for 2 months and then granulocyte-macrophage colony stimulating factor at a dose of 10mg/kg/day for 2 months, but there was no improvement in cell counts, transfusion requirement or number of infections. The child died at the age of 2 and a half years from pneumonia.

Patient 3. The 3rd child was a girl, born after an unremarkable pregnancy and delivery. Like the other 2 children she had a low birth weight of 2.4kg. The facial features were similar to the first 2 children (Figure 3), She started to have gum bleeding and skin bruises at the age of 6 months. Also there was growth retardation, microcephaly and severe failure to thrive with a weight of only 3kg at the age of 5 months. Her developmental delay seemed more marked than in the first 2 children. She smiled at the age of 6 months, sat at one year and was not able to stand up alone at the age of 2 years and only able to say a single word. By now this family was known, with what seemed to be a familial bone marrow failure syndrome, the full blood count in this child was followed from birth. At birth the WBC was 13.0 x 10^9/L, the ANC 6.0 x 10^9/L, the Hb 9.9 mmol/L (16.0 g/dl) and the platelets 260 x 10^9/L. At the age of 4 months the WBC was 7.4 x 10^9/L, the ANC 1.6 x 10^9/L, the Hb 6.2 mmol/L (10.0 g/dl) and the platelets 150 x 10^9/L. At the age of 6 months the WBC was 2.0 x 10^9/L, ANC 0.4 x 10^9/L, the Hb 3.7 mmol/L (6.0 g/dl) and the platelets 40 x 10^9/L. The rest of the investigations were the same as in the first 2 children. Given the lack of response in the first 2 children to any form of treatment this child was given only transfusional support and treated for infections. She

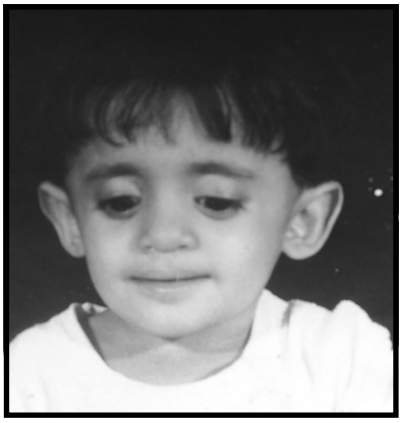

Figure 3 - Patient 3 at the age of 2 years showing frontal bossing, high forehead, upsweeping of frontal hairline, depressed nasal bridge, variable ear abnormalities and downward slanted eyes.

continued to have severe growth retardation and pancytopenia, and had moderate to severe developmental delay. At the age of 2 and a half years the child died of *pseudomonas* septicemia with extensive skin involvement.

Discussion. All 3 cases were small for date at birth and continued to have inadequate growth. They share similar facial features in the form of frontal bossing, high forehead with upsweeping of the anterior hairline, depressed nasal bridge, ear abnormalities, downward slanted eyes and mild to moderate developmental delay. In each case the onset of bone marrow failure happened in the 2nd half of the first year of life. The first child presented with pallor at the age of 6 month and bleeding tendency at 18 months the 2 other children presented with bleeding tendency between 6 and 9 months of age. Serial follow up of the blood picture in Patient 3 showed that the pancytopenia started between 4 and 6 months, supporting that the syndrome is characterized by a normal blood picture at birth and onset of pancytopenia by 6-9 months of age. Given the striking similarities in growth, physical features, laboratory results and natural history we conclude that these children suffer from the same clinical disorder. The mode of inheritance is most likely autosomal recessive given the consanguineous, but healthy parents, the presence of a normal sibling, absence of similar cases in the extended family, and the fact that both sexes are affected. Therapeutic intervention with different drugs like androgens, corticosteroids, G-CSF and cyclosporin A were unsuccessful. The lack of response to fresh frozen plasma or other blood products seems to exclude a missing serum factor as a possible etiology for the pancytopenia. The recovery from pancytopenia observed in Patient one is probably spontaneous, but a late response to cyclosporin A cannot be ruled out. Spontaneous recovery of cell counts could be part of this disorder, but the early death of the other 2 children does not allow a firmer conclusion. The first patient was less retarded, presented later with bleeding and had fewer infectious problems, suggesting some variability of clinical expression in this syndrome.

The described cases share some of the features of Fanconi's anemia such as short stature, microcephaly, and mental retardation, but the absence of major symptoms like skin pigmentation or skeletal abnormalities, the early onset of pancytopenia and its spontaneous recovery in one child, and the absence of increased chromosomal breakage exclude Fanconi's anemia.[2] The different facial features in our patients plus the absence of metaphysical dysplasia and exocrine pancreatic insufficiency rule out the possibility of Schwachman syndrome.[4] The absence of skin abnormalities and the early onset of pancytopenia do not fit with the diagnosis of dyskeratosis congenita.[3] The physical features in our patients are distinct from Seckel's dwarfism[5] or Dubowitz syndrome.[6] A small number of familial autosomal recessive syndromes combining bone marrow failure and other abnormalities have been reported. They are discussed below and compared to our patients. Two brothers were described with short stature and macrocytosis, but late onset of pancytopenia around 10 years of age.[10]

Congenital neurologic structural abnormalities are reported in 2 siblings who developed bone marrow hypoplasia also later in life.[11] The normal skeletal survey excludes Ghosal hemato-diaphyseal dysplasia.[12] A combination of albinism, which was not present in our cases, pancytopenia. microcephaly and minor anomalies were described in 2 related children).[13] Facial dysmorphia was described in 3 siblings, but unlike our cases they had increased skin folds, onset of pancytopenia at a later age and other birth defects.[14] Facial abnormalities, early onset of pancytopenia and growth retardation were seen in a sporadic case, but unlike our patients this child had a webbed neck, no microcephaly, normal developmental milestones and normal levels of vitamin B12 and HbF.[15] In a report of the international Fanconi Anemia Registry, 11 children are mentioned with dysmorphic features and aplastic anemia, but without increased chromosomal breakage.[2] These were mainly sporadic cases probably presenting a mixture of genetic and non-genetic entities and lack of clinical details precludes further comparison.

We conclude that these 3 cases represent a new familial autosomal recessive bone marrow failure syndrome. Hematologically it is characterized by onset of pancytopenia in infancy without increased chromosomal breakage and possibly spontaneous improvement later in childhood. The other features are low birth weight, short stature, distinct facial features, microcephaly and developmental delay. This new syndrome should be included in the differential diagnosis of children presenting with pancytopenia in infancy.

References

1. Alter BP, Young NS. The bone marrow failure syndromes. In: Nathan and Oski's hematology of infancy and childhood. Nathan DG, Orkin SH, editors. Philadelphia (PA): WB Saunders; 1998. p. 236-260.
2. Auerbach D, Rogartko A, Schroeder-Kurth TM. International Fanconi anemia registry: relation of clinical symptoms to diepoxybutane sensitivity. Blood 1989; 73: 391-396.
3. Drachtman RA, Alter BP. Dyskeratosis congenita: clinical and genetic heterogeneity. Report of a new case and review of the literature. Am J Pediatr Hematol Oncol 1992; 14: 297-304.
4. Smith OP, Hann IM, Chessells JM, Reeves BR, Milla P. Haematological abnormalities in Schwachman-Diamond syndrome: a review of twenty one patients. Br J Haematol 1996; 94: 279-284.

5. Butleter MG, Hall BD, McLean RN, Lozzio CB. Do some patients with Seckel's syndrome have hematological problems and/or chromosome breakage. Am J Med Genet 1987; 27: 645-649.
6. Kuster W, Majewski F. The Dubowitz syndrome. Eur J Pediatr 1986; 144: 574-578.
7. Bresters D, Bruin MCA, Van Dijken PJ. Congenitale hypoplastische anemie in Nederland (1963-1989). Ned T KG 1991; 59: 203-210.
8. Muis H, Beemer F, Van Dijken PJ, Klep-Pater N. The Aase syndrome: case report and review of the literature. Eur J Ped 1986; 145: 153-157.
9. Hedberg VA, Lipton JM. Thrombocytopenia with absent radii. A Review of 100 cases. Am J Pediatr Hematol Oncol 1988; 10: 51-64.
10. Abels D, Reed WB. Fanconi-like syndrome. Immunologic deficiency, pancytopenia and cutaneous malignancies. Arch Dermatol 1973; 107: 419-423.
11. Drachtman R, Weinblatt M, Sitarz A, Gold A, Kochen J. Marrow hypoplasia associated with neurologic anomalies in two siblings. Acta Paediatr Scand 1990; 79: 990-993.
12. Gumruh F, Besim A, Altay C. Gohsal haemato-diaphyseal dysplasia: a new disorder. Eur J Pediatr 1993; 152: 218-221.
13. Kotzot D, Richter K, Gierth-Fiebig K. Oculocutaneous albinism, immunodeficiency, hematological disorders, and minor anomalies: a new autosomal, recessive syndrome. Am J Med Genet 1994; 50: 224-227.
14. Stoll C, Alembik Y, Lutz P. A syndrome of facial dysmorphia, birth defects, myelodysplasia and immunodeficiency in three sibs of consanguineous parents. Genet Couns 1994; 5: 161-165.
15. Sacky K, Sakati N, Aur RJA, Shebib S, Sabbah RS, Rifai S. Multiple dysmorphic features and pancytopenia: a new syndrome. Clin Genet 1985; 27: 606-610.