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Fatal aplastic anaemia in a child with features of Dubowitz syndrome

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Abstract. We describe a boy with features of Dubowitz syndrome who developed anaemia, thrombocytopenia and granulocytopenia at 3 years of age. The family refused blood component transfusion and he died 6 months later from severe anaemia and pulmonary bleeding. This is the second case of bone marrow aplasia in 38 reported cases of Dubowitz syndrome. It is proposed that patients with Dubowitz syndrome need long-term follow up, including complete blood counts.

Key words: Dubowitz syndrome – Aplastic anaemia

Introduction

The Dubowitz syndrome was first described in 1965 as a rare autosomal recessive disorder characterized by intrauterine growth retardation, peculiar face, microcephaly with moderately impaired mental development, hyperactivity and eczematoid skin lesions. The typical cranio-facial features include sparse hair at the front of the head, broad nose, telecanthus, blepharophimosis and micrognathia. Patients with Dubowitz syndrome are at increased risk for malignancies such as non-Hodgkin lymphoma, lymphoblastic leukaemia and neuroblastoma [3, 13]. In 1985 Walters and Desposito [14] reported the development of aplastic anaemia responsive to oxymetholone in a 10-year-old girl with Dubowitz syndrome. We describe here a second case of a boy with features of Dubowitz syndrome first reported at 17 months by Nöll-Gröne and Fuhrmann [9]. The boy developed pancytopenia at the age of 3 years and died 6 months later of severe anaemia and pulmonary bleeding.

Case report

D. B. was the only child of unrelated parents. The mother was 163 cm tall, but four of her five siblings were short in stature (less than 150 cm). The 29-year-old father was 178 cm tall and had hypertension. His two sisters and both parents were reported to have renal disease and high blood pressure.

The boy was born at term with a weight of 2220 g, length of 45 cm and head circumference of 31 cm. He was hospitalized at 4 weeks of age for poor feeding, vomiting and diarrhoea. He had microcephaly, a wide-open fontanel with moderate internal hydrocephalus, telecanthus, broad nose, epicanthus, blepharophimosis and micrognathia. A high-pitched voice and hyperactive behaviour were already noticeable. With time it became more obvious that the hair at the front of the head was sparse. Hip dysplasia was treated conservatively. Micropenis and right cryptorchidism persisted throughout the 3rd year. Eczematoid skin lesions of the face were present only during infancy (Fig. 1).

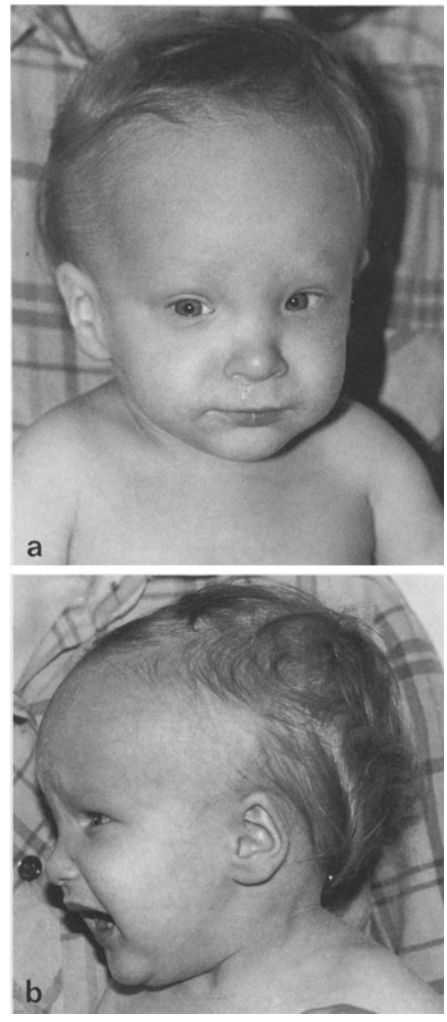

Fig. 1a, b. The patient at the age of 17 months

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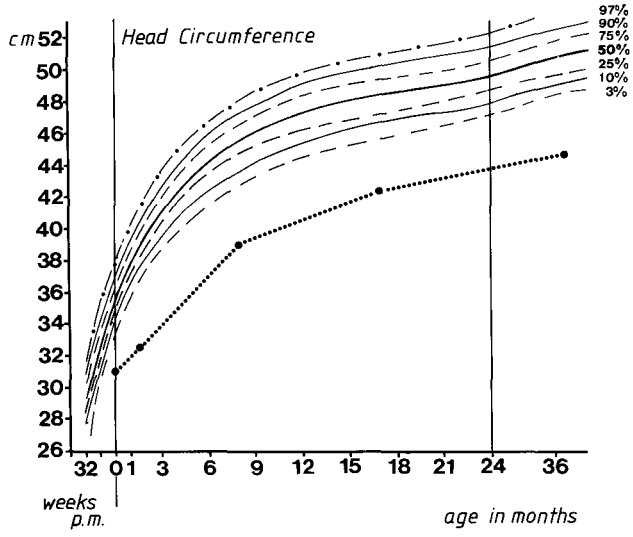

Fig. 2. Head circumference curve of the patient

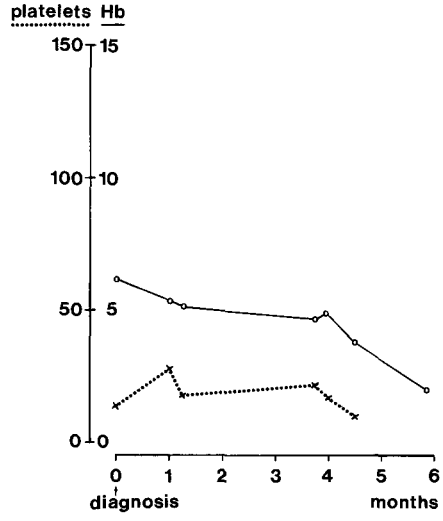

Fig. 3. Blood parameters during aplastic phase. Platelets/nl *(dotted line)*, haemoglobin (Hb) g/dl *(solid line)*. Granulocyte count remained stable around 1.0/nl

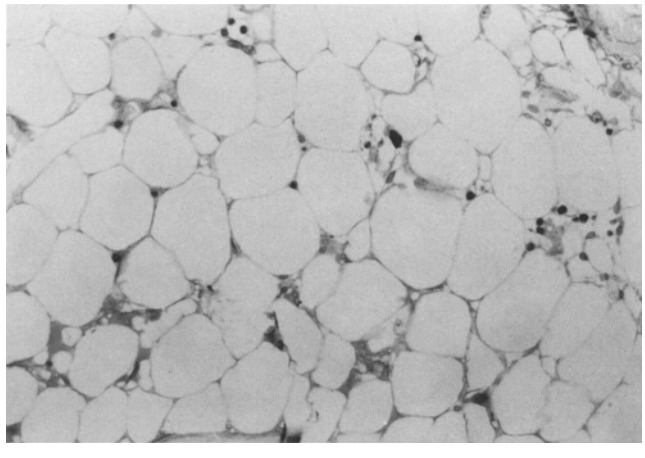

Fig. 4. Postmortem bone marrow samples showed marked reduction or absence of haematopoietic cells. Bone marrow is replaced by fat (Courtesy of Dr. Fritz, Institute of Pathology, University of Giessen)

Motor development was normal. Although mental development was difficult to ascertain in this hyperactive and anxious boy, some degree of retardation was assumed.

At the age of 3 years the patient presented with pronounced pallor, petechiae and microhaematuria. His blood counts showed a macrocytic anaemia (haemoglobin 6.2 g/dl, MCV 104 fl, MCH 36.3 ng, reticulocytes 0.6%) and severe thrombocytopenia (14/nl). Leucocytes were decreased (3.3/nl) with neutrophil granulocytes below 1.0/nl (13% bands, 13% seg). His cardiovascular condition was remarkably stable, suggesting a long adaptation process to the anaemia. He weighed 6 kg (5.8 kg below the third percentile), was 70.6 cm tall (20 cm below the third percentile) with a head circumference of 44.4 cm (4.0 cm below the third percentile) (Fig. 2). His bone age was delayed by 25 months (12 months vs. 37 m) and the large fontanel was still open at 3 years (1 × 1 cm). There was no hepatosplenomegaly, lymphadenopathy or bone tenderness. IgA, IgG and IgM were normal.

A bone marrow biopsy revealed general hypocellularity, with no megakaryocytes and markedly diminished red cell precursors. Granulopoiesis was relatively normal. Mean red cell survival time was slightly reduced to 22 days (normal range 26–32 days). No specific antibodies against platelets, red cells or leucocytes were detected in serum or on cell surfaces. T4/T8 ratio of T lymphocytes was normal. Chromosome analysis showed a normal 46 XY pattern and no signs of increased fragility (sister chromatid exchange, gaps, breaks) as described for Fanconi anaemia. Plasma vitamin B12 levels, folic acid and serum ferritin were in the normal range.

Both parents were members of the "Jehovah's Witnesses". They refused the transfusion of red blood cells and platelets on the basis of a doctrine of this sect. A compatible bone marrow donor was not available. Oral oxymetholone (4 mg/kg) had no effect, but compliance could not be verified. The haemoglobin and platelet count declined (Fig. 3) further over the next 6 months, probably representing the natural course of the patient's disease. He died at the age of 3.5 years during a mild respiratory infection with a haemoglobin level of 2.0 g/dl and terminal pulmonary bleeding. Postmortem examination of bone marrow confirmed earlier findings and demonstrated bone marrow failure (Fig. 4).

Discussion

In 1986 Küster and Majewski [7] summarized reports of 38 patients with Dubowitz syndrome, including our own case [1–4, 7–15]. As several cases were reported repeatedly as follow-up observations, one cannot be sure of the number of truly independent cases. Typical diagnostic criteria were intrauterine and postnatal growth retardation, microcephaly, mild mental retardation and developmental delay along with characteristic facial features: sparse blonde hair, telecanthus, epicanthic folds, commonly ptosis/blepharophimosis, broad tip of the nose, abnormal ears and retrogenia. Often described are a sloping forehead, shallow orbital ridge and a nasal bridge at about the same level as the forehead. Also common are eczema, hypogenitalism and hyperactivity, poor feeding, diarrhoea and vomiting.

Three patients with Dubowitz syndrome developed a malignant tumour: one lymphoma [13], one acute lymphoblastic leukaemia [3] and one neuroblastoma [13]. Two of these were associated with hypogammaglobulinaemia. Here

we report a patient who developed bone marrow failure at the age of 3 years and, unfortunately, died 6 months later. A similar patient with Dubowitz syndrome, originally described by Opitz et al. [10], who developed aplastic anaemia at 10 years of age, responded to oxymethalone therapy [14].

To summarize, the Dubowitz syndrome may be associated with an increased risk of bone marrow failure and with malignant disease. It is remarkable that out of 38 patients, 5 have demonstrated either malignancy or haematopoietic failure. Detailed study of Dubowitz syndrome patients may yield valuable clues as to the molecular basis of bone marrow failure.

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