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Osteopetrosis as a rare cause of anaemia in paediatric patients: a case report

Osteopetroza jako rzadka przyczyna niedokrwistości wieku rozwojowego – opis przypadku

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Abstract

Anaemia is a common manifestation in paediatric patients. The most common cause of anaemia is iron deficiency. In differential diagnosis not only the most common diseases resulting in haemoglobin decrease should be considered, but also those less common. In an outpatient care physician's practice, interview, physical examination and routine periodic preventative examinations play a very important role. They make it possible to detect chronic diseases, including congenital metabolic diseases. These include osteopetrosis, which manifests with impaired haematopoiesis. Osteopetrosis also causes stunted growth, bone deformation and neurological disorders. We present the case of a boy with diagnosed osteopetrosis, in whom anaemia was the first manifestation of the disease.

Keywords: anaemia, haematopoiesis, osteopetrosis, Albers-Schönberg disease, marble bone disease

Streszczenie

Niedokrwistość jest powszechnie spotykanym objawem u pacjentów pediatrycznych. Najczęstszą jej przyczynę stanowi niedobór żelaza. W diagnostyce różnicowej oprócz najpopularniejszych schorzeń powodujących obniżenie poziomu hemoglobiny warto wziąć pod uwagę również te mniej częste. W praktyce lekarza ambulatoryjnej opieki zdrowotnej niezwykle istotną rolę odgrywają wywiad, badanie przedmiotowe oraz okresowe badania bilansowe. Umożliwiają one wykrycie chorób przewlekłych, między innymi wrodzonych chorób metabolicznych. Jedną z nich jest osteopetroza, objawiająca się upośledzeniem hematopoezy. Powoduje również spowolnienie wzrastania, zniekształcenia kości, zaburzenia neurologiczne. W pracy przedstawiono opis przypadku chłopca z rozpoznaną osteopetrozą, u którego pierwszą manifestacją choroby była niedokrwistość.

Słowa kluczowe: niedokrwistość, hematopoeza, osteopetroza, choroba Albersa-Schönberga, marmurkowatość kości

INTRODUCTION

Anaemia in children, defined as a level of haemoglobin (Hb) below two standard deviations from the norm for a given age, is a sign of a large number of diseases.

In the paediatric population, anaemia is found in 42.6% of cases, while the prevalence of severe anaemia, which is associated with impaired cognitive functioning and increased mortality, is 0.9–1.5%[1]. In diagnostic investigation the distinction between different types of anaemia based on mean corpuscular volume (MCV) is important. Anaemia can by microcytic, normocytic and macrocytic.

In paediatric patients the most common type of anaemia is microcytic iron-deficiency anaemia[2]. Approximately 42% of cases of decreased Hb level in children are due to iron deficiency[1]. The peak prevalence of iron-deficiency anaemia is between the ages of 6 and 20 months and during puberty[3].

The coexistence of a decreased Hb level and a normal level of white blood cells (WBC) and platelets (PLT) may be a sign of selective red blood cell aplasia, excessive breakdown of red blood cells or anaemia associated with chronic diseases. Pancytopenia may indicate functional bone marrow abnormalities[4].

CASE REPORT

A boy with diagnosed anaemia observed from the age of 4.5 months (initially micro-, then normocytic), of unknown origin, who had been previously hospitalised at the Department of Infant Pathology, was referred to the Department of Paediatric Haematology, Oncology and Transplant Medicine at the age of 7 months for further diagnostic investigation. The family and perinatal history were unremarkable. The child was fed with a milk formula and its infant diet was being expanded; the boy had a good appetite and gained weight normally. His psychomotor development did not deviate from the norm. Upon admission to the Department

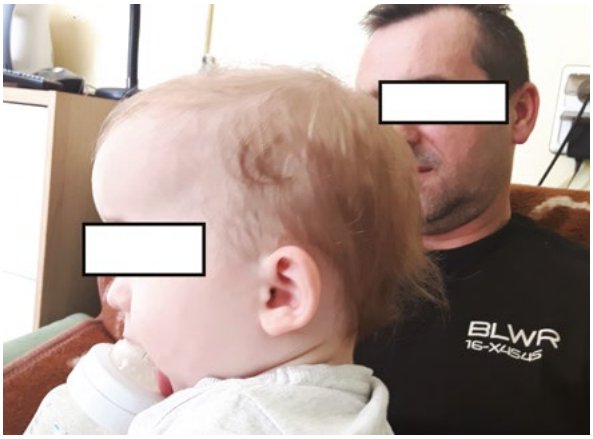

Fig. 1. Head shape of a child with osteopetrosis: macrocephaly, prominent frontal tubers

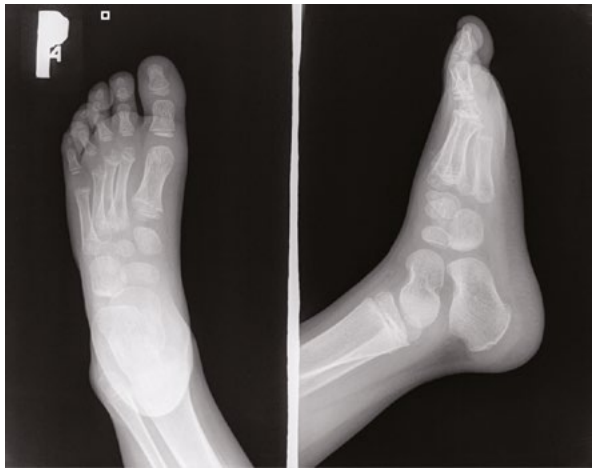

Fig. 2. Radiographic image of the right lower extremity: thickened metaphyses of long bones, increased bone mineral density

the child was in good general health, active in a normal way, with efficient circulation and respiration. On physical examination no abnormalities were found apart from a pale skin and single transmitted rhonchi audible over the lungs. In laboratory tests normocytic anaemia (Hb 8.8 g/dL, MCV 85.4 fl) and reticulocytosis (41‰) were found; WBC and PLT levels were within normal limits. Iron, vitamin B_{12} and folic acid deficiency and hypothyroidism were excluded. The results of tests for spherocytosis were negative.

Bone marrow aspiration biopsy was performed during another hospital stay. Technical difficulties during sample collection were noted: there was a problem inserting the biopsy needle to the medullary cavity.

Based on bone marrow analysis, red blood cell hypoplasia was diagnosed. Diamond–Blackfan anaemia (DBA) was suspected and oral steroid treatment with Encorton (ENC) was started at 2 mg/kg of body mass. Treatment tolerance was relatively good: a distinct, very good reaction to ENC was obtained; therefore, the dose was gradually reduced. The results of complete blood count performed during the diagnostic and treatment process are presented in Tab. 1.

	Hb (g/dL)	Ht (%)	MCV (fl)	WBC (×10³/µL)	PLT (×10³/µL)	Reti (‰)
Before ENC	8.8	28.6	85.4	12.54	254,000	41
ENC at 2 mg/kg of body mass/day	10.4	34.2	84.7	26.57	374,000	51
ENC at 0.9 mg/kg of body mass/day	14.3	44.1	83.1	21.83	481,000	9
After ENC discontinuation	9.6	30.2	77.6	8.26	293,000	23

ENC – Encorton; **Hb** – haemoglobin; **Ht** – haematocrit; **MCV** – mean corpuscular volume; **WBC** – white blood cells; **PLT** – platelets; **Reti** – reticulocytes.

Tab. 1. Complete blood count during ENC treatment

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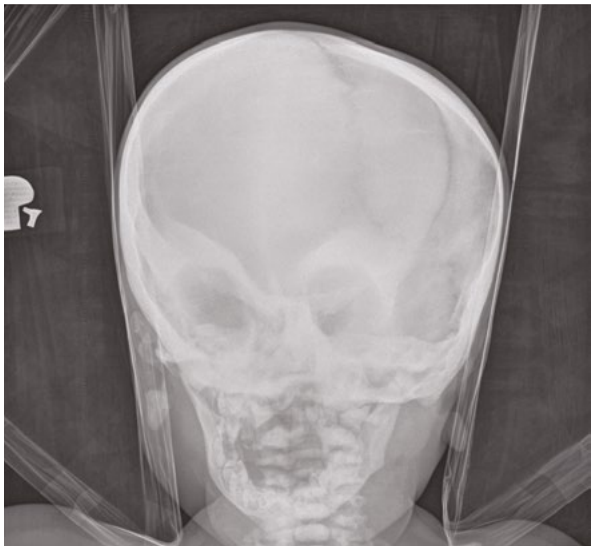

Fig. 3. Radiographic image of cranial bones, coronal plane: considerable enlargement of the neurocranium in relation to the viscerocranium, increased bitemporal diameter

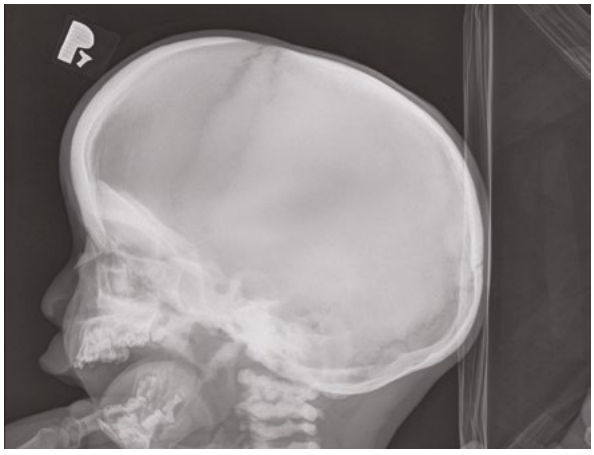

Fig. 4. Radiographic image of cranial bones, sagittal plane: considerable enlargement of the neurocranium in relation to the viscerocranium, increased occipitofrontal diameter, bright bones

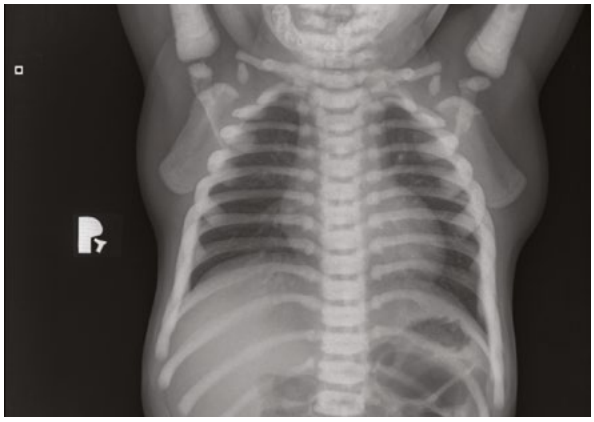

Fig. 5. Radiographic image of the chest, anteroposterior view: sclerotised vertebral bodies, central brightness in the vertebral bodies

In the second year of the boy's life his body proportions changed. The following were noted: prominent frontal tubers, increased bitemporal and occipitofrontal diameters and a disproportion between the viscerocranium and neurocranium with predominance of the neurocranium (Fig. 1). Bilateral hearing impairment and rotary nystagmus of the right eye were diagnosed. Radiographic images were taken of the bones, which revealed bone sclerotisation and thickening, particularly in the metaphyses of long bones (Figs. 2–4). Genetic testing for osteopetrosis (OP, Albers-Schönberg disease, marble bone disease) was conducted, which demonstrated the presence of a *TCIRG1* mutation associated with autosomal recessive osteopetrosis (ARO). In addition, hypogammaglobulinaemia was detected in the boy, which required intravenous administration of immunoglobulins.

The patient received allogeneic haematopoietic stem cell transplantation (allo-HSCT), which is currently the only available causal treatment for osteopetrosis.

DISCUSSION

Osteopetrosis is a genetic disease characterised by increased bone density, which results from impaired form and function of osteoclasts[5]. There are two varieties of the disease: autosomal dominant (adult) and autosomal recessive, known as malignant infantile osteopetrosis, which is discussed in the present paper.

There are a number of mutations causing ARO. Mutations in the genes *TCIRG1*, *CLCN7*, *OSTM1*, *SNX10* and *PLEKHM1* result in osteoclast-rich ARO (there is a high number of osteoclasts, but their resorptive ability is impaired), while mutations in the genes *TNFSF11* and *TNFRSF11A* result in osteoclast-poor ARO[5].

Paradoxically, increased bone density may weaken the bones, leading to pathological fractures and osteomyelitis. The growth of long bones is impaired, which results in short stature. Macrocephaly and prominent frontal tubers develop during the first year of life, which results in a characteristic facial appearance. Radiographic images show white, bright bones, deformed metaphyses of long bones resembling Erlenmeyer flask and unevenly sclerotised vertebral bodies called sandwich vertebrae (Figs. 2–5)[6].

Other symptoms of ARO are the result of obliterated medullary cavities and bone marrow dysfunction. This leads to life-threatening pancytopenia and secondary extramedullary haematopoiesis in the liver and spleen[6,7]. In addition, *TNFRSF11A* mutation is associated with defective maturation of B-cells, which leads to hypogammaglobulinaemia in individuals with ARO[8].

As a result of impaired bone resorption, cranial nerve canals become narrower and subsequently obliterated, which results in nystagmus, strabismus, vision loss and hearing loss. It is estimated that approximately 78% of patients with ARO have hearing loss[9].

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Anaemia is a frequently reported manifestation of OP, both the infantile and the autosomal dominant form. In children, anaemia often co-occurs with fever, hepatosplenomegaly and chronic fatigue; the affected patients are also short with macrocephaly[10–12].

CONCLUSION

It is worth bearing in mind that, apart from obvious causes such as iron and hematopoietic vitamin deficiencies, blood loss caused by e.g. menstrual periods, and a neoplastic process in the bone marrow, rare diseases may also be responsible for anaemia in children. A lack of improvement after treatment, exclusion of the most common diseases associated with a low Hb level and other concomitant symptoms which may suggest genetic origin indicate the need to perform further diagnostic tests and examinations at a specialist centre.

Conflict of interest

The authors do not report any financial or personal affiliations to persons or organisations that could adversely affect the content of or claim to have rights to this publication.

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