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Koray BODUROĞLU[1]
Ergül TUNÇBİLEK[1]
Turgay COŞKUN[2]
Canan UÇAR[1]

Infantile Galactosialidosis Associated With Vitamin D Deficiency Rickets

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Departments of [1]Clinical Genetics, [2]Nutrition and Metabolism, Hacettepe University, 06100 Sıhhiye, Ankara-Turkey

Abstract: Galactosialidosis is an autosomal recessive disease with combined deficiency of two lysosomal enzymes due to the lack of a protective protein. We report on a boy with infantile galactosialidosis who has an intermediate phenotype and vitamin D deficiency rickets. Due to the possible role of vitamin D deficiency in the pathogenesis of dysostosis multiplex we recommend that patients with lysosomal storage disease should be supplemented with vitamin D.

Key Words: Dysostosis multiplex, galactosialidosis, intermediate infantile form, vitamin D deficiency.

Introduction

Galactosialidosis is a lysosomal storage disease with a combined deficiency of two lysosomal enzymes; α-neuraminidase and β-galactosidase (1). Complementation studies have shown that this autosomal recessive disease is distinct from GM1 gangliosidosis (2) and sialidosis (3), in which only one of these two enzymes is defective. The basic deffect is the lack of a 32kD "protective protein" required for the aggregation of β-galactosidase monomers and activation of α-neuraminidase that forms a complex with β-galactosidase (4).

Different clinical phenotypes have been observed ranging from severe early infantile forms, to milder late infantile and juvenile/adult variants, presumably all allelic forms of the disorder (5, 6). Clinical findings of the early infantile form are coarse facial features, severeadema, ascites, skeletal dysplasia, ocular abnormalities including cherry-red spots and early death. In the late infantile form the onset is between 6-12 months and the main findings are dysostosis multiplex, visceromegaly, macular cherry-red spots and mild mental retardation (7, 8).

We report on a boy with galactosialidosis in the second month of life with vitamin D deficiency rickets.

Case Report

The 44-day-old male patients was the first child of consanguineous parents. The mother had had one abortion, previously. After an uncomplicated 40 week gestation he was born by Cesarean section due to breech presentation with a birth weight of 3700 g. During the first two weeks of life he required hospitalization due to respiratory insufficicency, feeding difficulties and hypoglycemia. After discharge feeding difficulties continued, edema and cyanotic attacks were noticed. On admission to our center his body weight was 3800 g, height 57 cm. and head circumference 36 cm. He had coarse facial features, puffy eyelids, a depressed nasal bridge and anteverted nostrils (Figure 1). Perioral cyanosis was manifest while crying. Physical examination revealed tight and thick skin, enlargement of the liver (5 cm below the costal margin) and spleen (2 cm below the costal margin), right inguinal and umbilical hernia, huge bilateral hydrocele and glandular hypospadias. There was a systolic murmur most prominent on the left sternal margin. Movements of elbow joints were limited bilaterally. Cherry-red spots were not present on ophthalmologic examination.

We noticed vacuolization in lymphocytes on the peripheral blood smear. Serum calcuim and phosphorus were both normal and alkaline phosphatase was slightly elevated. Serum and urine amino acid screening and urinary mucopolysaccharide excretion were normal. Urinary screening for oligosaccharides showed strong sialic acid containing bands revealing increased sialyloligosaccharides. Radiological evaluation did not show any finding consistent with rickets. Peripheral blood leukocytes karyotype analysis with G-banding technique was 46, XY.

Enzymological assay of leukocytes and fibrolasts demonstrated a lack of leukocyte β-galactosidase (13

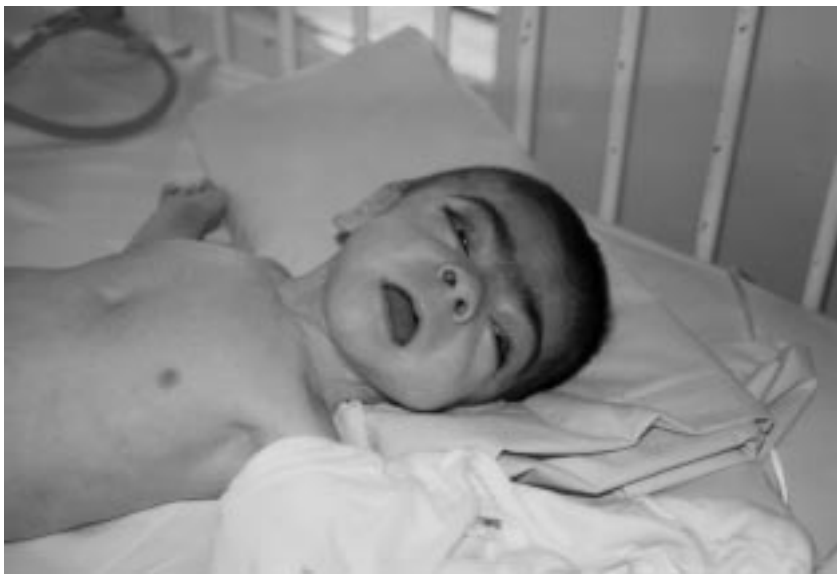

Figure 1. Facial appearance of the patient at the fourth month.

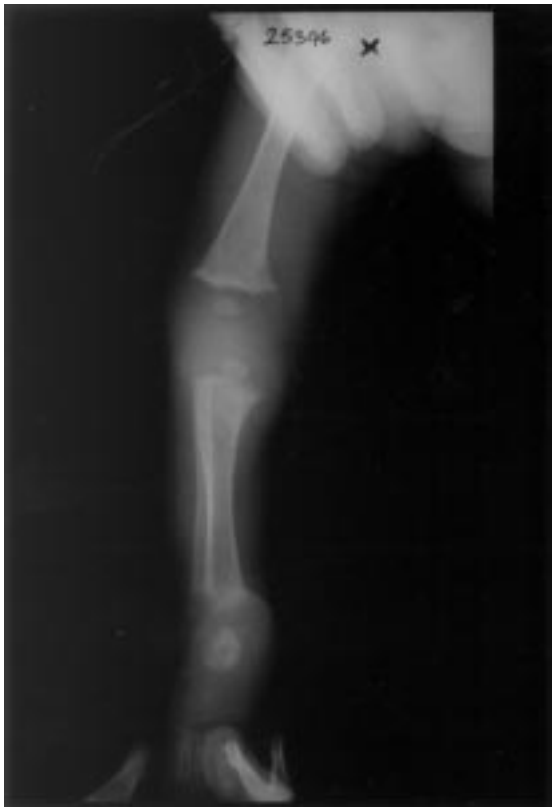

Figure 2. X-ray of the right lower extremity. Note decreased bone density and widened, irregular shaped metaphyses.

μmol/g.h, N:100-450) and fibrolast α-neuraminidase activity (0 μmol/g.h, N:38.4±5.4). These result confirmed the diagnosis of galactosialidosis.

Three months later he was admitted to the hospital with feeding difficulty, cyanosis, respiratory distress and failure to thrive. He required hospitalization due to pneumonia, heart failure and hypocalcemia. Physical examination revealed an increased coarsening of facial features, increased liver and spleen size (7 and 3.5 cm, respectively), enlarged hydrocele and crepitant rales on chest auscultation. The echocardiogram showed slight hypertrophy of the interventicular septum. Serum calcium, phosphorus and alkaline phosphatase were 4.5 mg/dl, 5.8 mg/dl, 2100 IU/L respectively. When the medical history was reevaluated we learned that in spite of prescription he was never given the vitamin D preparations. Radiological examination on this admission revealed generalized osteoporosis, widening of metaphyses, fraying of the epiphyseal borders (Figure 2), spatulate ribs and hypoplastic acetabulum which wereall consistent with dysostosis multiplex. Biochemical and radiological findings and lack of intake of vitamin D confirmed the diagnosis of rickets due to deficiency of vitamin D. After the vitamin D supplementation of 4500U/day for three weeks calcium and phosphorus levels were within the normal range with a significant decrease in alkaline phosphatase.

Discussion

Coarse facial features, visceromegaly and dysostosis multiplex were the most striking features in this patient. The term dysostosis multiplex is specifically applied to the group of radiological features collectively found in a number of specific metabolic disorders including the mucopolysaccharidoses, mucolipidosis, mannosidosis, fucosidosis and several other rarer conditions. Until Pazzaglia et al. (9) reported pathological findings in two

out of twelve cases in 1989, little was known about the underlying defect of dysostosis multiplex. In their study, inhibition of the growth plate cartilage calcification and rickets-like lesions were observed in the metaphyses. Enhanced subperiosteal remodelling and paratrabecular fibrosis were also evident in the diaphyses. High levels of parathormone were found in one case. The suggested that these findings supported the hypothesis that bone lesions might be secondary, at least in part, to damage in such viscera as the kidney and/or the liver and that they were mediated by vitamin D and parathormone. Our patient was also referred with a possible diagnosis of rickets. Despite normal calcium and phosphorus levels, alkaline phosphatase was elevated on first admission. Radiological appearence was normal. After a three month period without any vitamin D intake, laboratory data disclosed typical rickets due to vitamin D deficiency. Dysostosis multiplex was apparent, indicating a rapid course of deterioration with regard to the skeletal system. With treatment of vitamin D 4500 U/day and calcium lactate 75 mg/kg/day both calcium and phosphorus became within the normal range whereas alkaline phosphatase remained slightly elevated.

The disease had a rapid course in this patient. Enlargement of the liver and spleen, appearance of more characteristic facial features and hypertrophy of the heart muscle in three months are evidence for rapid progression. However the most striking change was in the skeletal system in this three months. Thus, we suggest that vitamin D deficiency has contributed to the radiological changes in this patient. To avoid rapid progression of skeletal involvement we recommend that all patients with dyostosis multiplex should be supplemented with vitamin D regardless of the underlying disease.

The patient did not have severe edema and ascites on first admission which arecharacteristic features of early infantile form but, on the other hand the onset was too early and the course was too accelerated for the late infantile form. He did not fulfill the criteria either for early, or late infantile forms. There are few cases decribed in the medical literature with such an inter mediate presentation. Those cases with intermediate presentation alsohad cardiomyopathy and lack of features such as cherry-red spots and corneal clouding. Our patient had similarities with those of previously reported cases. We suggest that a different mutation in the protective protein gene may be responsible for this intermediate form.

This patient with the clinically intermediate form of galactosialidosis shows the possible role of vitamin D metabolism in the development of skeletal changes (dysotosis multiplex) and the existence of a probable mutation responsible for a unique phenotype of galactosialidosis.

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