Fucosidosis with hypothyroidism: a case report

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Fucosidosis is a rare, autosomal recessive lysosomal storage disorder caused by a severe deficiency of α-L-fucosidase.

Here we present a 27-month-old male who was referred to us for evaluation of developmental delay, which was first detected at age six months. His past medical history was also remarkable for recurrent pulmonary infections and myoclonic seiures. His family history revealed that he was the first living child from a consanguineous marriage. He had a younger sister who died at five months of age from pneumonia who had facial resemblance to the proband, developmental delay and a congenital heart defect.

Physical examination revealed length: 81 cm (25-50p), weight: 10.2 kg (25-50p), and head circumference: 49 cm (50-75p). He had a coarse face, hepatomegaly and generalized spasticity.

His initial laboratory examination revealed negative urine screening column chromatography for mucopolysaccharidosis. His X-ray findings were consistent with mild form of dysostosis multiplex. Based on clinical and laboratory features, fucosidosis was suspected. Fucosidase enzyme activity was zero. In addition to fucosidosis, thyroid function tests indicated primary hypothyroidism.

This is, to the best of our knowledge, the fourth case of fucosidosis diagnosed in Turkey.

Key words: fucosidosis.

Fucosidosis is a rare, autosomal recessive disease caused by a severe deficiency of α-L-fucosidase and the accumulation of fucose-containing glycosphingolipids, glycopeptides and oligosaccharides in the lysosomes of the organs[1]. The α-fucosidase gene has been localized to chromosome 1 (FUCA 1 locus of the distal region of 1p34)[2]. Nearly 20 different mutations have been identified[1].

Two phenotypes have been described in this disorder: more severe infantile form (type I), and a milder form (type II). The clinical picture consists of progressive mental, motor and growth retardation, coarse face, recurrent infections, dysostosis multiplex and seizures[3]. Patients with type I have onset of clinical signs within the first year and type II within the second year of life. The major distinguishing features of the milder phenotype are the presence of angiokeratoma, longer survival and low sweat sodium chloride value[2].

The diagnosis is based on the enzymatic assay of α-L-fucosidase. Carrier detection studies and prenatal diagnosis are possible[2]. Moreover, it has been suggested that DNA analysis should be considered in families seeking prenatal diagnosis[2]. There is no specific therapy for this disease.

Case Report

A 20-month-old male was referred to our hospital for evaluation of his developmental delay, which was first detected at the age of six

months. He was born at term, after an uneventful pregnancy, via normal spontaneous vaginal delivery. His parents are first-degree cousins. He smiled to his mother at three months, sat with support at 12 months, and walked at 18 months. Afterwards his developmental delay became more obvious. Moreover, he developmentally regressed, losing his ability to walk. He never uttered any meaningful words. His past medical history was also remarkable for recurrent pulmonary infections and myoclonic seizures.

His family history revealed that he was the first living child of his parents. His mother had four prior miscarriages. He had a younger sister who died at five months of age from pneumonia. She was reported to have facial resemblance to the proband, developmental delay, a complex congenital heart defect, and agenesis of the corpus callosum.

On physical examination, his anthropometrics were as follows: length: 81 cm (10-25%), weight: 10.2 kg (10-25%) and head circumference: 49 cm (50-75%). He had a coarse face with strabismus, hypertelorism, macroglossia, and dental caries. His neck was short and abdomen was protuberant. Hepatomegaly and generalized hypertonia were the other clinical signs. There were no cutaneous lesions. Ocular examination and hearing were normal.

Laboratory investigations revealed normal urine and blood amino acid profile, and negative urine screening column chromatography for mucopolysaccharidosis. Thin layer chromatography had shown the increased levels of fucose containing glycoconjugates, and the activity of his leukocyte alpha L-fucosidase was zero, consistent with a diagnosis of fucosidosis.

In radiographic studies, all the bone structures appeared osteoporotic. Lower thoracic and lumbar vertebrae were rounded and there were small beaks on the anterior surfaces. Distal femoral and proximal tibial metaphyses were slightly flared and contained linear sclerotic lines (Figs. 1, 2). Chest X-ray revealed areas of

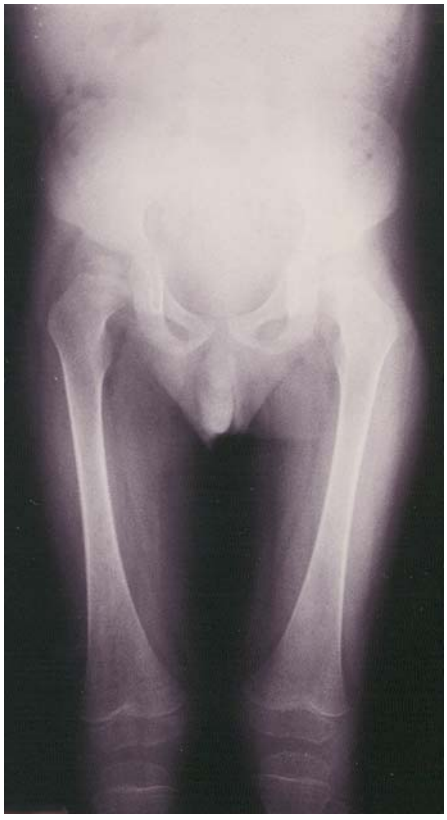

Fig. 1. X-ray of pelvis and lower extremities, showing slightly flared distal pemoral and proximal tibial metaphyses with linear sclerotic lines and osteoporosis.

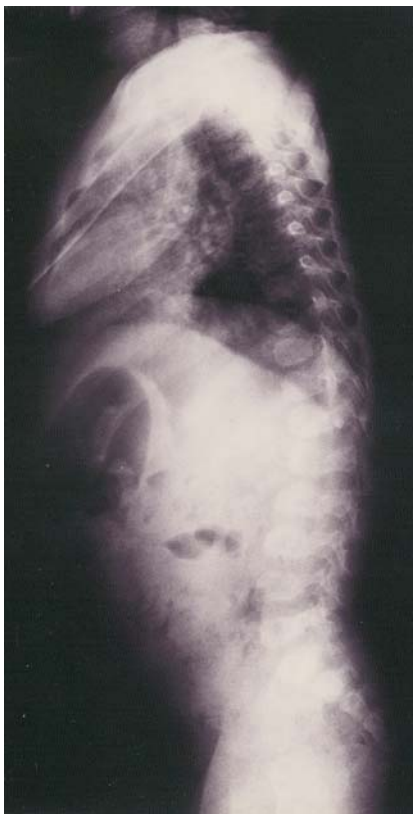

Fig. 2. Lateral X-ray of vertebrae showing rounded lower thoracic and lumbar vertebrae with small beaks on the anterior surfaces.

linear atelectasis in both lung bases and cardiomegaly. Echocardiography was normal. Computerized brain tomography appeared normal except for mild cortical atrophy. In addition to cortical atrophy, the cranial magnetic resonance imaging (MRI) showed focal nodular signal abnormalities in the brainstem on T2-weighted images (Fig. 3). The sodium chloride content of sweat was increased (70 mEq/L). Thyroid function tests indicated primary hypothyroidism (T_3: 50 ng/dl, T_4: 6 µg/dl, TSH: 14.8 µIU/ml, thyroid gland was normal in size but suppressed in the scan).

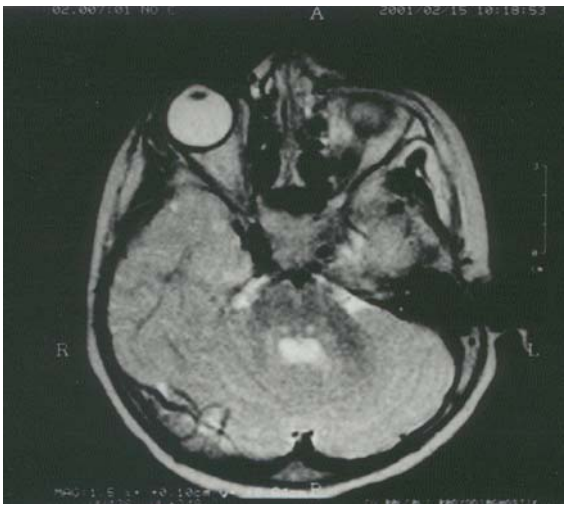

Fig. 3. Magnetic resonance imaging of the brain showing mild cortical atrophy and focal nodular signal abnormalities.

Discussion

Fucosidosis is a rare progressive neurodegenerative storage disorder first described by Durand[3] in 1969. To date, approximately 100 patients have been reported[2]. Although this disorder is panethnic, the majority of cases are from Italy and the United States of America[2]. This is, to the best of our knowledge, the fourth case of fucosidosis diagnosed in Turkey.

FUCA 1 gene mutations such as Q422X, G60D, E375X and P141fs have been demonstrated in more of the 70% of reported patients[4]. Eiberg et al.[5] have also shown a second locus (FUCA 2) that influences plasma fucosidase activity. This gene may involve a regulatory role rather than a structural gene[2]. It has been reported that establishing the genotype-phenotype correlation is difficult and that the clinical variability of the disease may not be explained by genetic heterogeneity[5,6]. We plan to study the mutation in our patient.

From the two phenotypes described for this disorder, the more severe infantile form type I fits our patient well, with early onset of disease (in first six months of life), more progressive course, absence of angiokeratoma, and a high sodium chloride content of sweat. İsmail et al.[9] reported a fucosidosis case with the features of both types I and type II[7].

Williems et al.[10] compared the data of 77 reported cases of fucosidosis. Individual clinical features were detected in the following proportions: mental retardation 95%, neurological deterioration 88%, coarse faces 79%, growth retardation 78%, recurrent infections 78%, kyphoscoliosis 66%, dysostosis multiplex 58%, angiokeratoma 52%, joint contractures 48%, seizures 38%, visceromegaly 30%, hearing loss 12%, hernia 9% and loss of visual activity 6%[8]. Our patient had mental and motor retardation, progressive neurological deterioration, coarse face, recurrent pulmonary infections, and a mild form of dysostosis multiplex, seizures, and hepatomegaly. In addition, our patient had primary hypothyroidism. Since no such association between fucosidosis and hypothyroidism has been reported previously, hypothyroidism in this case probably represents a chance association.

The skeletal findings in fucosidosis are those of mild dysostosis multiplex. Our patient had typical features of mild dysostosis multiplex. The mild cortical atrophy and intensity abnormalities seen in our patient have also been reported to a variable degree in other cases. The severest degree of cortical atrophy was seen in older patients; therefore, it appears that neuroradiological changes worsen with age. Furthermore, recent studies with MRI have shown a decreased intensity in deep white matter of brain on T_2-weighted images and especially localized in thalamus and globus pallidus, which were thought to be correlated with the neurological deterioration[9].

We plan to perform prenatal diagnosis for future pregnancies for this family by identifying the mutation and to await future developments in such areas as bone marrow transplantation and/or gene therapy.

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