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Case Report

A rare cause of opistotonus; fumaric aciduria: The first case presentation in Turkey

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Abstract

Fumaric aciduria is a rare autosomal recessive metabolic disease which is characterized with excessive fumaric acid exretion in urine. In the prenatal period, polyhydramniosis, intrauterine growth retardation, enlarged brain ventricles and brain anomalies are observed. Growth and development failure, hypotonia, seizures and brain atrophy are the common characteristics of patients with fumarase deficiency. On cranial imaging, the most common findings include polymicrogyria and ventriculomegaly. In our country where consanguineous marriages are common, the incidences of autosomal recessive diseases are expected to be high. In a patient who was born from a consanguineous marriage and referred to our hospital at the age of 45 days because of hyperamonemia and opistotonus, a diagnosis of fumaric aciduria was made with organic acid analysis performed considering metabolic diseases and this diagnosis was supported with radiological investigations. We thought this case was worth presenting, since there was no case of fumaric aciduria reported before in our country. (Türk Ped Arş 2014; 49: 74-6)

Key words: Fumaric aciduria, muscle hypertonicity, infant

Introduction

Fumaric aciduria is a rare congenital metabolic disorder characterized with increased fumaric acid which occurs as a result of deficiency of fumarase which is one of the enzymes included in the tricarcoxylic acid (Krebs) cycle. Fumarase deficiency was described by Zinn et al. (1) in 1986 for the first time in a case with increased excretion of fumaric acid in urine, hypotonia, microcephaly and lethargy (OMIM 136850). However, fumaric aciduria was reported by Whelan et al. (2) in 1983 for the first time in two children who were siblings.

Fumaric aciduria is characterized with excessive excretion of fumaric acid in urine. The main products of Krebs cycle, dicarcoxylic acids (suberic, adipic) and succinyl purine derivatives among other metabolites may be found in body fluids with different rates. The disease occurs rarely. Only 40 cases have been reported in the literature (3, 4).

Most of the patients have growth and developmental retardation. Serious neurological disorders including hypotonia, seizures and brain atrophy are common findings (5). The degree of neurological disorder is considerably variable. The disease can have a stable course in the first two years or may be fatal in this period. This may be related with enlarged brain ventricle and intrauterine polyhydramniosis (6). Clinical variance is not related with the level of enzyme activity or involvement of different tissues (7).

Our aim was to draw attention to fumaric aciduria in our country by presenting the first case of fumaric aciduria in Turkey.

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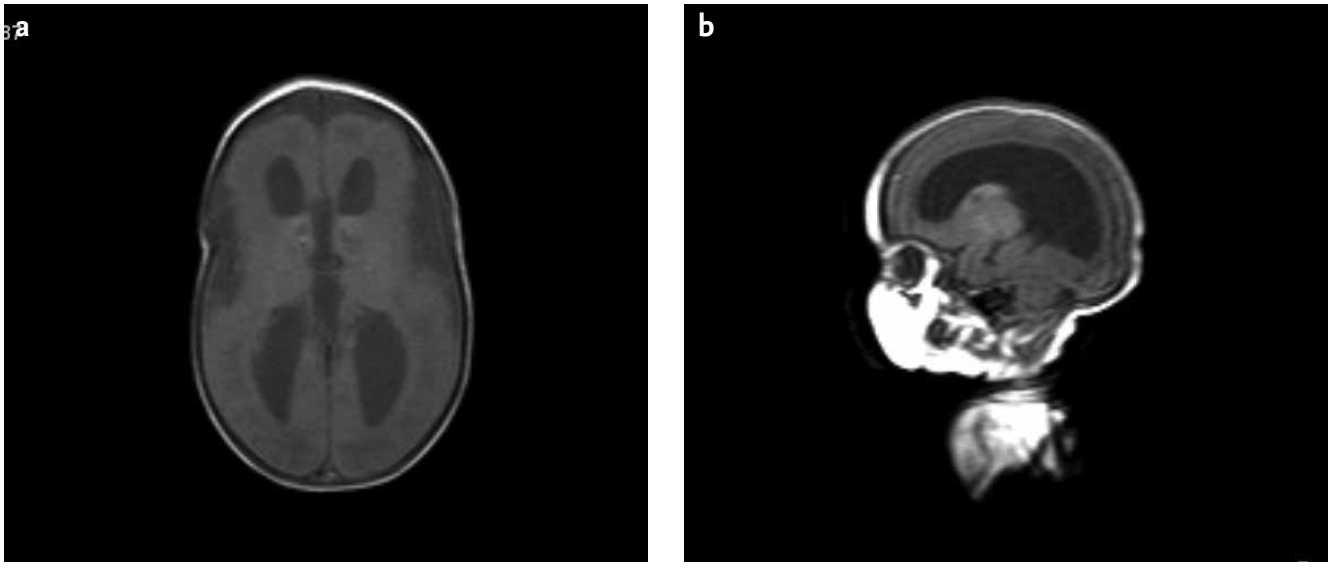

Figure 1. a, b. Polymicrogyria and ventricular enlargement on brain magnetic resonance imaging of the patient

Case

A male baby who was born in a hospital outside the province of Kayseri by cesarean section with a birth weight of 1730 g at the 32nd gestational week as the fourth live birth from the fourth pregnancy of a 30-year old mother who had polyhydramniosis during pregnancy was internalized in the neonatal intensive care unit because of respiratory distress. It was learned from his familial history that the mother and father were first cousins, two children of the family were healthy and one child was born at the 6.5th gestational month, lived for two hours and died. On the first physical examination, respiratory distress was present and lung sounds were found to be decreased. He was intubated and mechanical ventilation was started. A single dose of surfactant was administered and bicarbonat treatment was administered, since metabolic acidosis developed for three times after the 8th day. The patient was followed up with ventilatory support for a long time because of respiratory distress. Oral vitamin A and intravenous dexamethasone treatment was given in terms of chronic lung disease. On the 38th day, metabolic acidosis was considered because hyperamonemia [299 µmol/L (N:18-74 µmol/L)] developed and the patient was referred to our hospital on the 45th day. At presentation, he had opistotonus posture, decreased subcutaneous fat tissue, tachypnea and intercostal-subcotal retractions.

Biochemical values and blood gases at presentation were found to be normal. The value of ammonia was at the upper limit of normal [139 µmol/L (N:18-74 µmol/L)]. In urinary organic acid analyses, it was observed that urinary excretion of adipic acid, succinic acid, glutaric acid, glycolic acid, 4-OH phenylacetic acid and metylmalonic acid was normal, urinary excretion of 3-OH butiric acid, lactic acid and oxalic acid was slightly high and urinary excretion of fumaric acid was very high (Table 1).

On cranial magnetic resonance imaging, it was observed that the lateral ventricles were enlarged and polymicrogyria was present (Figure 1a, b).

Table 1. Urinary organic acid information of the patient

Urinary organic acids	Values of the patient	Normal values
Adipic acid	6 mg/g creatinine	< 140 mg/g creatinine
Succinic acid	148 mg/g creatinine	< 350 mg/g creatinine
Glutaric acid	6 mg/g creatinine	< 60 mg/g creatinine
Glycolic acid	4 mg/g creatinine	< 130 mg/g creatinine
4-OH phenylacetic acid	33 mg/g creatinine	< 250 mg/g creatinine
Metylmalonic acid	4 mg/g creatinine	< 50 mg/g creatinine
3-OH butiric acid	324 mg/g creatinine	< 50 mg/g creatinine
Lactic acid	460 mg/g creatinine	< 220 mg/g creatinine
Oxalic acid	67 mg/g creatinine	< 40 mg/g creatinine
Fumaric acid	2330 mg/g creatinine	< 100 mg/g creatinine

A diagnosis of fumaric aciduria was made with the clinical and laboratory findings. Low protein diet was started (1.5 g/kg/day). Enzyme and genetic studies could not be performed because of economical reasons. No convulsion occured in the follow-up. Opistotonus posture persisted.

The patient is 7 months old now and is still being followed up by the division of Pediatric Nutrition and Metabolism. In the follow-up, the amount of protein in the diet was gradually decreased up to 0.8 g/kg/day. However, no improvement occured in the level of fumaric acid in urinary organic acid analysis.

Discussion

Fumarase deficiency is inherited in an autosomal recessive pattern. It has two forms as cytosolic and mitochondrial fumarase deficiency. This gene is located in the first chormosome in humans (1, 3, 5, 6). On ultrasonographic examination of pregnan-

cies with fumarase deficiency in the fetus, polyhydramniosis, intrauterine growth retardation, enlarged brain ventricles and brain anomalies have been reported (5, 8).

Most newborns with fumarase deficiency display serious neurological anomalies including feeding difficulty, developmental retardation and hypotonia. In infants with early onset, encephalopathy, seizures and microcephaly and severe developmental retardation are common. In infants, spasms, hypertonic and dystonic posture in the extremities and truncal hypotonia, atetoid movements and autistic characterstics may be observed. In some cases, prominent facial characteristics have been reported (5, 8). It has been reported that the disease has no efficient treatment (9).

Keriggan et al. (3) evaluated 8 children born from consanguineous marriages in their study. They observed mental retardation, seizures, visual disturbance and optic nerve hypoplasia among neurological properties and dysmorphic structure, polystemia in the neonatal period, growth retardation, relative microcephaly and hypotonia among systemic properties. Polymicrogyria and enlarged ventricles which they observed on neuroradiological imaging in all their patients were also present in our patient. However, hypotonicity which they described in their patients was not present in ours. In contrast, our patient had opistotonus position (extensive extensor hypertonicity). Extensive extensor hypertonicity may occur with many metabolic and infectious causes which involve the brain. Brown et al. (10) analysed decerebrate rigidity in 64 patients and found intracranial hemorrhage in 30%, infection in 30%, hypoxia in 18%, metabolic disorder in 14% and other causes in 8% (birth trauma, congenital deformities, sagittal sinus injury).

Since fumaric acid is a metabolite which involves protein metabolism and synthesized in the mitochodrium, it was thought that low protein diet might decrease fumaric acid level and low protein diet (0.71 mg/kg/day) was administered in a 12-year old female patient who was being followed up with a diagnosis of fumaric aciduria. However, no positive response could be obtained similar to our patient (11).

Frequent consanguineous marriages in our country increase the prevalence of autosomal recessive diseases. Metabolic diseases can be missed with erroneous diagnoses. Enlarged brain ventricles and polyhydramniosis in the intrauterine follow-up of patients presenting with seizure, hypo or hypertonicity (opistotunus), microcephaly and growth retardation should suggest fumarase deficiency which is observed rarely.

We found it appropriate to present this case of fumaric aciduria because this is a rare metabolic disease, no such case has been published in our country before and we think that it can be missed with erroneous diagnoses.

Informed Consent: Written informed consent was obtained from patient who participated in this study.

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