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Case Report

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A two days old newborn with partial biotinidase deficiency presenting with treatment resistant convulsions

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ABSTRACT

Biotinidase deficiency (BD) is an autosomal recessive metabolic disorder characterized primarily by cutaneous and neurologic abnormalities (OMIM 253260). Symptoms usually appear by three months of age (minimum 12th day) with seizures as the most frequent initial symptom. We decided to present a patient with partial biotinidase deficiency since she presented with neurological findings as early as the second day of life in order to discuss the additional factors leading to such early signs. The baby was born via normal spontaneous delivery as the second child from nonconsanguineous healthy parents; a 33-year-old mother and 35-year-old father with a birth wieght was 3440 g. Her first clinical symptoms were cyanosis and tonic convulsions after feeding on the second day. Both her parents and her 17-month-old brother were healthy. On physical examination 1/6 pansistolic murmur was heard, diaper dermatites and sacral dimple was observed as well. She was admitted to Neonatal Intensive Care Unit (NICU) for the investigation and treatment of neonatal convulsion. Despite the use of phenobarbital and levetiracetam, apnea and generalized convulsions occurred thrice in the NICU. Biochemical evaluation during these convulsions revealed hypoglycemia (49 mg/dl) and hyperammonemia (150 mcmol/L); albeit her carnitine and aminoacid profile were nonspecific. Her further neurological evaluation by electroencephalography, and cranial magnetic resonance imaging was normal. Seizures were controlled with biotin and folate therapy. Final laboratorial evaluation showed a biotinidase activity of 2.60U/L, (3.5-13.80) and the genetic tests c.1330 G>C (p.Asp444His heterozygous) were related with biotinidase deficiency and A1298 C, C677T compound heterozygous mutations related to Methylene tetra hyrofolate deficiency (MTHFR). Both biotinidase deficiency and MTHFR may cause convulsions. However, the presence of neurologic symptoms as early as the second day of life has not been reported for both before. The coexistence of these diseases, which may cause similar neurological findings, should be investigated as a cause of early clinical findings. Until a satisfactory answer to this question is found, biotin and folate may be considered as a treatment option for early neonatal convulsions and coexistence of the biotinidase deficiency and MTHFR mutations should be investigated.

1. Introduction

Biotinidase, which is vital for the recycling of biotin, cleaves biotin from biocytin. Biotin acts as a prosthetic group in each of four carboxylases involved in the amino acid catabolism, fatty acid synthesis and gluconeogenesis. Biotinidase deficiency (BD) is an autosomal recessive disorder that is responsive to biotin treatment (OMIM 253260; Wolf et al., 1985; Wolf et

al., 2001). According to enzyme activity level, two types of BD are described: Less than 10% biotinidase activity is profound deficiency and 10-30% of mean normal activity is partial defficiency. Children with partial BD are at an increased risk of developing the same symptoms of profound deficiency. However, the appearance of symptoms seems to be associated with metabolic stressors (eg, illness, fever, fasting), and children may not be symptomatic until then (Swango et al., 1998). The spectrum of clinical signs and symptoms is variable. BD should be considered at presentation of intractable seizures, acidosis, rash, unexplained hearing or visual loss, spastic paraparesis, failure to thrive or sudden death (Burton et al., 1987; Hoffman et al., 2005). Patients usually present with lactic acidosis, hyperammonemia and a characteristic organic aciduria, in which lactic acid, 3-OH-isovaleric acid, methylcrotonylglycine, methylcitrate are the key metabolites. In children with BD, cerebral edema, low attenuation of white matter signal, cerebral atrophy, and compensatory ventricular enlargement can be observed in magnetic resonance imaging (MRI). Magnetic resonance spectroscopy (MR-S) also helps to determine the functional metabolism of the brain. Visual and hearing disturbances are investigated by Visual Evoked Potential (VEP), Electro Retinography (ERG) and Brain Stem Evoked Response Audiometry (BERA) (OMIM 253260; Burton et al., 1987; Dunkel et al., 1989; Wolf et al., 2001; Heller et al., 2002; Hoffman et al., 2005; Kalkanoğlu et al., 2007). Delay in the diagnosis of BD may lead to seizures, hypotonia, developmental delay, visual and hearing abnormalities, alopecia and skin rash, and eventually death. Contrarily, with treatment, patients have an excellent prognosis and potential for a normal lifestyle (Sweetman et al., 1986; Bousounis et al., 1993).

Folic acid is important for the metabolism of monocarbon compounds required in the synthesis of sulfur amino acids, nucleic acids and intermediate metabolites. Folic acid is not synthesized in the body, it is taken inactively with food. The conversion of dihydrofolate (DHF) in the body to active tetrahydrofolate (THF) requires the aid of the enzyme Methylenetetrahydrofolate Reductase (MTHFR). The monocarbon compounds (methyl, methylene, methyl, formyl) separated at the same time, convert homocysteine to methionine in sulfur amino acid metabolism; thymidylate (dTMP), formylglycinamide ribotide (FGAR), formylaminoimidazole carboxamide ribotide (FAICAR). Methylene THF suppresses the progression of folate and pyrimidine synthesis if it does not convert to methyl THF (Rosenblatt et at., 2016). MTHFR cannot be converted to methionine by adding methyl to homocysteine in the absence of quantity or function; homocysteine rises in the blood, and methionine falls. In 1995, Frost et al., described the relationship between temperature and function decline (thermolability) to genetics for the MTHFR C677T mutation. MTHFR C677T variant is seen in 8-15% of the population (Frost et al., 1996). The homozygous mutation of this enzyme deteriorates the stability of MTHFR by the increase in temperature, decreases enzyme activity by 50%. TT genotype has been shown to cause both maternal (50%) and fetal (80%) neural tube defects (NTD). Another common pathology A1298C mutation decreases the enzyme activity (Weisberg et al., 1998; Bloom et al., 2006). Both mutations alone or together lead to an increase in NTD frequency through folate metabolism (Ozer et al., 2011). MTHFR polymorphism in those with B12, folate deficiency increases homocysteine (Motulsky et al., 1996), which normalizes with folate supplementation. This effect is probably due to the stabilization of the thermolabile enzyme (Guttormsen et al., 1996) by folate at high blood level. If the serum folate level is above 15.4 nM, it may neutralize the C677T mutation (Jacques et al, 1996; Holm et al., 2007).

2. Case

Our patient was the second live child of a 33-year-old mother born at 39th gestational week, born by normal spontaneous vaginal route. The pregnancy history was uneventful. In the second day, she had cyanosis and tonic seizure was observed. The patient was referred to our hospital from the hospital where she was born. Her birth weight was 3440 g. On admission, her body weight was 3400 grams (75-90p), her height was 49.5 cm (50-75p) and her head circumference was 33.7 cm (25-50p). Skin examination revealed prominent diaper dermatitis and the sacral midline was deep (Fig. 1). Cardiovascular system examination revealed a 1/6 systolic murmur. Other systems were unremarkable. In the family history, there was no

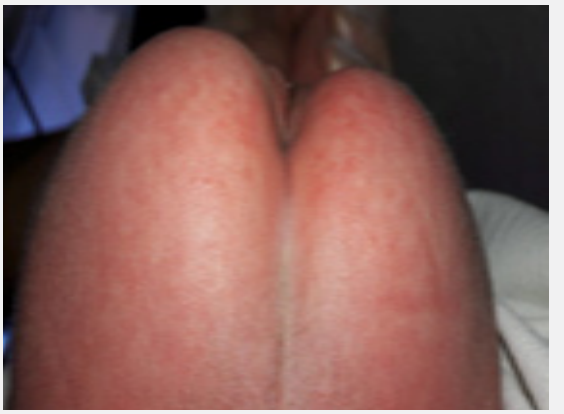

Fig. 1. Patient with prominent diaper dermatitis, deep sacral midline.

consanquinity between the 33-year-old mother and the 35-year-old father; her parents and 17-month-old sister were healthy. In the examinations of the patient, the patent foramen ovale associated with cardiac murmur was demonstrated by echocardiography. Direct laryngoscopic examination were normal.

On admission, biochemistry revealed a blood glucose level of 49 mg/dl; which did not recur. Simultaneously obtained insulin and C-peptide values were normal. Breastmilk was started as 8x10 cc, but she had three apnea attacks, causing desaturation. Oral feeding was stopped and intravenous dextrose support was increased to 8 mg/kg/minute. Transfontanel ultrasound and echocardiography were performed to explain the etiology of apnea; feature not found. A high ammonia level was detected during the evluation of hypoglycemia and she was consulted to the pediatric metabolism department. Oral feeding was discontinued for 2 days until metabolic tests were completed. Tandem mass with carnitine and aminoacid profile, urine organic acids by gas mass spectrophotometer and serum biotinidase activity by fluorimetric method, vitamin B12, folate, homocysteine, methylene tetra hydrofolate reductase mutation analysis was planned. During the clinical follow-up, the patient had seizures (cycling movements in four extremities) 3 times and phenobarbital was started. Brain magnetic resonance imaging (MRI) and electroencephalography (EEG) were ordered. Initial EEG and MRI were unremarkable. Epileptic activity was detected in the control EEG after 2 days; so levetiracetam was added to phenobarbital treatment by pediatric neurology department. Carnitine, biotin and folate were started by the pediatric metabolism department. Apnea attacks and seizures improved after biotine and folate supplementation. Breast milk was allowed since no specific pathology was oberved in metabolic basal tests. Nutritional tolerance was not a problem.

3. Results

Specific metabolic basal tests (serum ammonia, urine organic acids, plasma amino acids, urinary ketones, blood gases, biotinidase activity assey, carnitine, and acylcarnitine profiles) were demanded. Visual and hearing function were determinated by Visual Evoked Potential / Electroretinogram (VEP/ERG) and Brain Stem Evoked Response Audiometry (BERA); results were normal. Serum B12 level was 318 pg/ml (197-866), folate level was16.2 ng / ml (4.6-18.7); within the normal range; homocysteine was found at the upper limit: 12.47 mcmol / L (5-14). Final laboratorial evaluation showed that the patient's biotinidase activity was 2.60 U/L, (3.5-13.80) and her genetic evaluation revealed c.1330 G>C (p.Asp444His heterozygous) and MTHFR compound heterozygous mutations (Table 1).

Table 1. Pre treatment biochemical laboratory results of the patient

Test name and unit	Pretreatment results	References
Leucocyte/mm3	8690	4500-11000
Hemoglobine g/dl	16.1	11.5-14.5
Trombocyte /mm3	292,000	200-400 x103
Blood glocose mg/dl	49	60-100
Homocysteine mcmol / L	12.47	5-14
Urea mg/dl	6	<50
Creatinin	0.96	
Sodium mEq/L	134	134-146
Potassium Eq/L	4.89	3.5-5.2
Clor mEq/L	96.8	97-108
Phosphorus mg/dl	5.92	2.3-4.7
Calcium mg/dl	8.2	7.6-10.4
Magnesium mmol/L	0.83	0.7-1.05
Lactate mmol/L	2.41	5-14
25(OH) vitamin D3 mcg/L	9.23	30-80
Blood ammonia mcg/dl	150	18.7-86.9
Urine keton	Negative	
Blood pH	7.41	
Blood HCO3	23.1	
Serum B12 pg / ml	318	197-866
Folate ng / ml	16.2	4.6-18.7
Biotinidase activity U/L	2.60	3.5-13.80

4. Discussion

In Turkey both MTHFR and biotinidase deficiencies are more frequent when compared to other countries. Therefore, the probability of these two disorders, occuring in the same patient is higher in our country. The incidence of partial and profound deficiencies is 1 per 60,000 population in the world (Wolf et al., 1991), but 1/11.144 in Istanbul, Turkey (Baykal et al., 2005). Neonatal screening that was determined by Heard and colleagues is cost effective (Heard et al., 1986). Now screening for biotinidase deficiency is performed routinely in several countries around the world (Wolf et al., 1991), including Turkey.

Both biotinidase deficiency and MTHFR might lead to convulsions. However, neither of them had an early onset of neurological symptoms as early as the second postnatal day. The median age of clinical onset of BD is 3 months, but it can occur as late as 10 years of age. Initial symptoms have been reported as early as twelfth day of life (Baumgartner et al., 1985). This asemptomatic period allows sufficient time for early diagnosis and treatment and is important for neonatal screening programme.

Generalized convulsion, hypoglycemia, seizures, severe apnea requiring respiratory support and severe diaper dermatitis on the second postnatal day are reported for the first time in our patient. Intrauterine folate and B12 deficiency may cause perinatal convulsions. The mother does not have any nutritional habits or diseases that may lead to serious vitamin deficiency during pregnancy. On the contrary, she had used folic acid regularly during pregnancy and there was no problem in the intrauterine period.

Pisani et al., reported that the incidence of neonatal seizures was inversely related to gestational age and birth weight (Pisani et al., 2018).

We argue that two diseases, through different mechanisms, increased the risk of convulsions in our patient. Addition of the stress of labor caused the clinical findings to present very early. The rapid positive response to biotin and folate suplementation, especially the cessation of seizures and apnea attacks of the baby stands for this theory.

In conclusion; when BD and MTHFR deficiency, which may cause similar neurological symptoms, come together, the question of whether an early clinical finding occurs should be investigated. Until the satisfactory answer to this question is found, it is recommended to consider BD and MTHFR coexistence in the presence of early neonatal convulsions. We advice the addition of biotin and folate to the standard empirical neonatal convulsion treatment options.

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