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Case study

A girl with spastic tetraparesis associated with biotinidase deficiency☆

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ABSTRACT

Biotinidase deficiency is a disorder of biotin metabolism that manifests with cutaneous, ophthalmological and neurologyical symptoms in childhood. Spinal cord involvement has rarely been reported and all of the reported cases are spastic paraparesis. A 3 year-old girl with biotinidase deficiency was admitted to our clinic with hyperventilation, hair loss and spastic tetraparesis. To our knowledge, our case is the first reported tetraparesis associated with biotinidase deficiency. She was treated with oral biotin and benefited significantly from this therapy.

1. Introduction

Biotinidase deficiency is a form of multiple carboxylase deficiency which affects the endogenous recycling of biotin and it is inherited in an autosomal recessive manner. The prevalence is 1 in 60 000 births.[1] The age at onset of symptoms can range from several months to several years. Biotinidase deficiency is associated with a wide spectrum of clinical manifestations including skin rash, eczema, glossitis, hair loss, intractable seizures, ataxia, hypotonia, developmental delay and hearing loss. Spinal cord impairment is a rare complication of this disease and is frequently unrecognized.[2] Herein, we present a 3 year-old girl with biotinidase deficiency, spastic tetraparesis and hyperventilation who showed a marked clinical improvement following biotin administration.

2. Case report

A 3 year-old girl was referred to our hospital with complaints of upper-lower limb weakness, inability to sit and upper respiratory tract infection in the previous week. The patient's medical history was unremarkable. Her attainment of developmental milestones had been normal. Her parents were first-degree cousins and she had two healthy siblings.

Physical examination results showed full eye movements. Her pupils were equal, round and reactive to light. Extraocular muscles were intact. Facial movements were symmetric with normal strength. Her gag reflex was intact and her tongue was midline. She had motor weakness; muscle strength was 2/5 in the arms and 1/5 in the lower extremities. Muscle tone was decreased and deep tendon reflexes were brisk in all extremities. Babinski sign was negative and no clonus was elicited.

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Laboratory investigations showed normal electrolyte, urea, creatinine, alanine aminotransferase and aspartate aminotransferase levels. Cerebrospinal fluid showed normal cellular and biochemical markers. Blood and cerebrospinal fluid cultures were negative. Motor and sensory nerve conduction velocities and F response latencies were normal in electromyography. Needle electromyography showed normal MUAP's and no denervation on M.Tibialis anterior, M.Vastus medialis, M.Abductor pollicis brevis, M.Biceps brachii and M.Deltoideus. Paraspinal needle electromyography was not performed. Visual evoked potentials were normal. The spinal sagittal and axial T2-weighted magnetic resonance image (MRI) revealed diffuse edema and abnormal signal between the cervicomedullary junction and the 5th thoracic vertebra (Fig. 1a,b). Transverse myelitis was diagnosed according to these clinical and laboratory findings, and pulse steroids (30 mg/kg) were given for 5 days. After the completion of pulse steroid treatment intravenous immunoglobulin (IVIG) 1 gr/kg daily for 2 days was given to the patient. Despite the treatment, her clinical findings did not show any improvement. Also her parents were first-degree cousins. Therefore tandem mass spectroscopy and urine organic acid analysis were planned to exclude metabolic disorders. But we couldn't get the result of these analyses during the hospitalization period. Following the completion of IVIG and pulse methylprednisolone therapy, patient was discharged with 1 mg/kg/day oral methylprednisolone treatment.

One month later, the patient was admitted to our hospital again with complaints of hyperventilation, respiratory difficulty, hair loss, inability to sit and upper-lower limb weakness. In physical examination hyperventilation, hair loss, vomiting and stridor were noted. Similar findings to the previous admittance were noted in her neurological examination. Laboratory investigations, including electrolyte, urea, creatinine, alanine aminotransferase, aspartate aminotransferase levels, were normal. Compensated metabolic acidosis (pH 7.51, bicarbonate 13, carbon dioxide partial pressure 16.5, base excess −10) was observed. Serum lactate levels were elevated, 32.4 mg/dl (10–18). The results of tandem mass spectroscopy and urine organic acid samples, which were sent during the first admission, were obtained. Tandem mass spectroscopy revealed elevated levels of C5O6 (3–OH isovaleryl carnitine) and C3 (propionyl carnitine), urinary organic acid analysis revealed elevated levels of methylmalonic acid and 3-hydroxy isovaleric acid. By clinical and laboratory findings, biotinidase deficiency was diagnosed and serum biotinidase activity was found to be 0.13 U/L (4.4–12 U/L) by the colorimetric assay. Oral biotin at a dose of 10 mg twice daily was initiated. The patient showed a gradual clinical improvement in 1 month following the initiation of biotin therapy. She was able to walk independently and her hair grew back in 6 months of treatment.

3. Discussion

Biotin is a B-complex vitamin which acts as a coenzyme in four carboxylation reactions in human. Three of these enzymes, which are pyruvate carboxylase, propionyl-CoA carboxylase, 3-methylcrotonyl CoA-carboxylase, are located in the mitochondrion while acetyl-CoA carboxylase is in the cytosol. These four enzymes are essential in gluconeogenesis, fatty acid synthesis and amino acid catabolism. Numerous proteolytic enzymes degrade the holocarboxylase to form biocytin in the lysosomes, which, in turn, is hydrolyzed by biotinidase to form biotin and lysine. Failure of this process due to biotinidase deficiency leads to reduced biotin uptake and impaired carboxylase function.[1–3]

The incidence of biotinidase deficiency is 1:60,000 newborns in Western countries.[1] In Turkey, the incidence is 1:14,800 newborns. As consanguinity is known to be high in Turkey, the reported incidence appears to be underestimated. Researchers indicate that, biotinidase deficiency is most frequently seen in Turkey.[4] The parents of our patient were first-degree cousins.

Biotinidase deficiency presents in the first few years of life and is associated with a wide spectrum of neurological, dermatological and ophthalmological manifestations. Dermatological lesions such as eczema, perioral or facial rash, glossitis and alopecia are major features of biotinidase

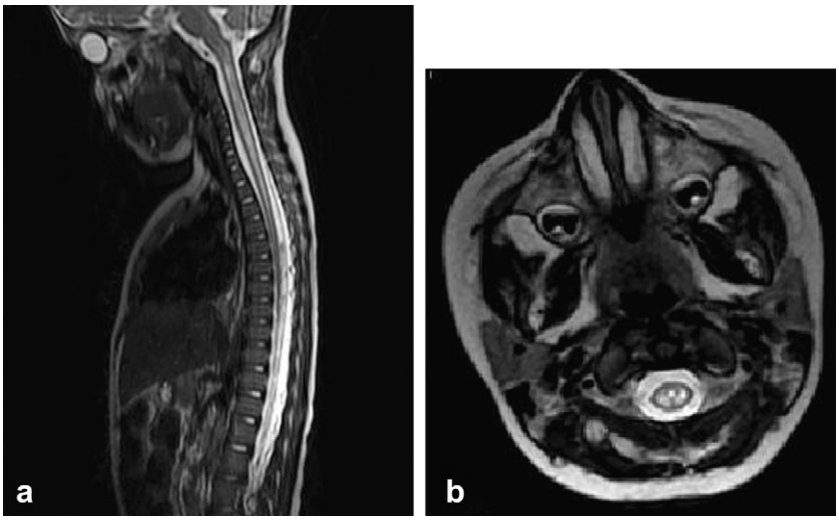

Fig. 1 – The spinal (a) sagittal and (b) axial T2-weighted MRI revealed diffuse edema and abnormal signal between the cervicomedullary junction and the 5th thoracic vertebra.

deficiency.[1,2] In our case, except hair loss no dermatological findings were noted. Ophthalmological abnormalities, including optic atrophy, are rare.[5] Our patient had no abnormal ophthalmological findings.

The neurological manifestations of biotinidase deficiency largely vary. Seizure is the most common symptom. Other neurological symptoms include hypotonia, developmental delay, ataxia, optic atrophy, hearing loss and spastic paraparesis.[1,2,5] Spinal cord involvement has rarely been reported and the cases reported are spastic paraparesis. Motor weakness was evident in our patient and spastic tetraparesis was detected. To our knowledge, our case is the first reported tetraparesis associated with biotinidase deficiency. We suppose that tetraparesis observed in our patient is due to the marked involvement of the cervicomedullary junction and the spinal cord.

Children with delayed onset biotinidase deficiency have symptoms of spinal cord involvement and that is an uncommon condition, with only a few cases reported in the literature.[6–8] While the cases reported until today were spastic paraparesis, our case had spastic tetraparesis. Our patient presented with inability to sit and upper-lower limb weakness. Muscle strength was 2/5 in the arms and 1/5 in the lower extremities. Muscle tone was decreased and deep tendon reflexes were brisk in all extremities. The first case was reported in 1992 by Hanovar et al. and he reported the postmortem findings in a patient with biotinidase deficiency and noted neurological disorder including spinal cord involvement. Pathological examination revealed necrotizing lesions and severe focal edema in the deep grey matter of the cerebral hemispheres, the brain stem and the spinal cord.[9] A few number of cases with biotinidase deficiency complicated with spastic paraparesis were reported. Age of paraparesis onset was reported as 18 months to 12 years.[10,11] In the most recent report, Mc Sweenay et al. described two cases with unusual presentations and symmetrical changes in MRI scans in the medial thalamus, dorsal brainstem, medulla and spinal cord. In our case, MRI of the spinal cord showed diffuse edema and abnormal signal in the white matter of the spinal cord between the cervicomedullary junction and the 5th thoracic vertebra. But we were unable to explain how cervicomedullary junction involvement led to tetraparesis, although MRI findings were similar with the previous reports. The severe involvement in the cervical spinal cord detected in our patient may have affected the innervation of the upper limbs.

Respiratory difficulty was reported in some cases of biotinidase deficiency. In our patient, hyperventilation and dyspnea were present in her second application. A metabolic disorder was considered according to this unusual clinical presentation, metabolic acidosis and respiratory difficulty.[12] Subsequently, tandem mass spectroscopy, urinary organic acid analysis and clinical findings led us to the diagnosis of biotinidase deficiency, and serum biotinidase activity was found to be 0.13 U/L (4.4–12 U/L) by the colorimetric assay.

In the treatment of biotinidase deficiency, high dose oral biotin is given. While dermatological and neurological manifestations resolve easily, ophthalmological and hearing impairments are more resistant to therapy.[6–8] Our patient had significant benefits from biotin 10 mg twice daily treatment. Six months after initiation of biotin therapy, the patient was able to walk independently.

As a result, biotinidase deficiency should be kept in mind in patients with spinal cord involvement and a clinical picture of biotinidase deficiency. In the absence of cutaneous findings and acidosis, acutely developed tetra- or paraparesis may lead to misdiagnosis. Increased awareness of biotinidase deficiency may enable the earlier diagnosis of this treatable condition.[13] Therefore recently, neonatal screening for biotinidase deficiency has been started to be performed routinely in some countries. In our country, neonatal screening has been started in early 2010.

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Conflicts of interest

None.

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