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Case Report

Biotinidase Deficiency Presenting as Recurrent Myelopathy in a 7-Year-Old Boy and a Review of the Literature

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ABSTRACT

Biotinidase deficiency may produce variable neurologic manifestations. Brainstem and spinal cord disease comprises an uncommon presentation of biotinidase deficiency. We describe a 7-year old boy with subacute progressive quadriplegia and "sighing" respirations. Severe biotinidase deficiency was established, and the patient demonstrated complete recovery with biotin supplementation. Genetic studies revealed presence of homozygous mutation in the *BTD* gene [c.133C>T (p.H447Y)]. Biotinidase deficiency should be considered in the differential diagnosis for subacute, long segment myelopathy, particularly with brainstem involvement. This entity is treatable; a high index of suspicion can be life-saving. We also review the literature on biotinidase deficiency presenting as spinal cord demyelinating disease.

Introduction

Biotin or vitamin H is required as a catalyst for the function of various carboxylases [1]. Biotin is covalently bound to these enzymes, and undergoes proteolytic metabolism to biocytin [1,2]. The cleavage of breakdown products results in a restoration of free biotin, and biotinidase is required for this cleavage [1,2]. Hence, biotinidase deficiency leads to a deficiency of free biotin and the dysfunction of carboxylases [1,2]. Biotinidase deficiency may present with neurologic manifestations such as seizures, hearing loss, developmental delay, or multiple nonneurologic manifestations, including alopecia and skin rashes [2].

Case Report

History

A 7-year-old boy presented at our Pediatric Neurology Clinic with progressive weakness in all four limbs, and with difficulties in breathing and swallowing. His complaints had begun 2 months earlier, with frequent falls and intermittent "sighing" respirations. During this time he had become quadriplegic, with the lower limbs more prominently affected. He demonstrated grade 0 power (according to the grading system of the Medical Research Council of the United Kingdom) in his lower limbs. He also manifested proximal upper limb weakness. He presented significant difficulty with swallowing, and had stopped accepting oral feeds. Examination revealed a normal sensorium, hypophonic speech, bulbar palsy, and spastic quadriplegia. He did not manifest hearing impairment, skin rashes, or alopecia. His birth and developmental history were unremarkable. He was born of a nonconsanguineous union.

His history included a similar illness at age 5 years, when he was evaluated elsewhere. He had developed respiratory problems, which had been investigated with computed tomography of the chest and bronchoscopy, with negative findings. Simultaneously he had developed progressive quadriparesis. His illness had not responded to immunotherapy (intravenous immunoglobulin) and steroids. He then received multiple vitamins, including thiamine, biotin, and riboflavin. He recovered after 1 month, and all medications were discontinued. No definite diagnosis was rendered at the time.

He was admitted and evaluated for a second episode of progressive bulbar palsy with quadriplegia. Clinically he demonstrated no evidence of infection, and investigations involving a hemogram and blood culture were normal. His arterial blood gas was normal. A routine examination of cerebrospinal fluid produced normal results. However, his cerebrospinal fluid lactate levels were significantly elevated (at 77.7 mg/dL; normal range, 10.8-18.9 mg/dL).

Multiplanar, multi-echo plain and contrast magnetic resonance imaging scans of the brain and spine were performed, including single and three-dimensional multivoxel spectroscopy. Magnetic resonance imaging indicated diffuse T_2 hyperintensity, with involvement of the septum pellucidum, the posterior part of the corpus callosum, and fornix in the midline, with bilateral symmetric lesions in the medial thalamus, dorsal midbrain, periaqueductal gray matter, dorsal pons, and medulla (Fig 1). His optic tracts and optic chiasm also demonstrated signal changes. Diffusion-weighted imaging revealed restricted diffusion at the septum pellucidum, medial thalamus, and fornix. Spinal cord lesions extended from the medulla up to the T_{12} vertebral level (Fig 2). Magnetic resonance spectroscopy through the lesions demonstrated a mild reduction in the *N*-acetyl aspartate peak, with the presence of a lactate peak. Moreover, the spectra through the ventricles and basal ganglia indicated a lactate peak. Nerve conduction studies demonstrated borderline slow lower limb conduction velocities.

Because he presented with definite evidence of a Leigh-like syndrome with a past history of possible response to biotin, biotinidase deficiency was considered a likely diagnosis. His biotinidase levels were significantly low (1.0 nmol of PABA liberated/minute/mL; normal range, 12-17 nmol of PABA liberated/minute/mL).

He was treated with supplements of oral biotin, 20 mg daily. In about 1 week, bulbar signs showed evidence of resolution, and after 1 month of treatment, he

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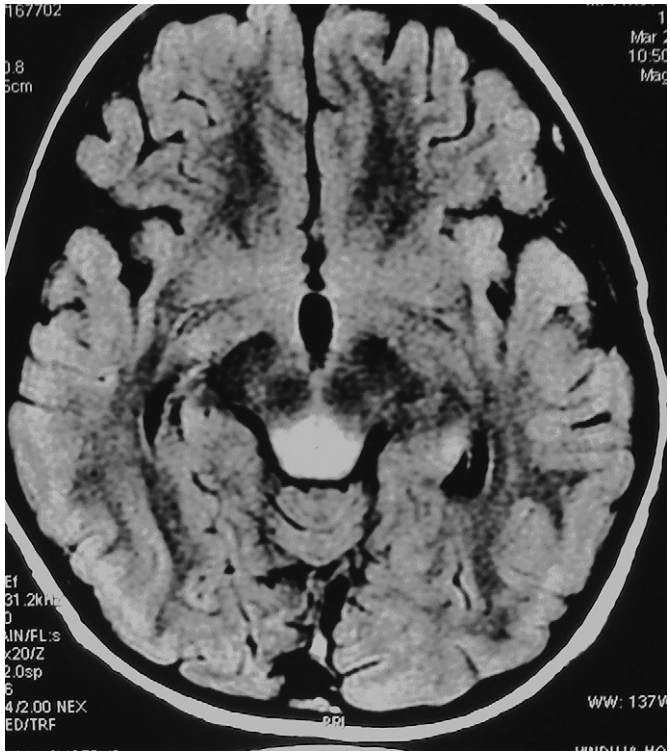

Figure 1. Magnetic resonance imaging-fluid attenuated inversion recovery axial image demonstrating involvement of the periaqueductal gray matter in a 7-year-old boy with biotinidase deficiency.

regained ambulation. At follow-up after 3 months of treatment, the only evident abnormality was residual spasticity of the bilateral triceps surae muscles.

Mutation analysis

Genomic DNA was extracted for mutation analysis. A homozygous mutation was present in the *BTD* gene on 3p25, c.133C>T (p.H447Y). He was not born of a consanguineous union. His parents were revealed to be heterozygous for this mutation.

Discussion

Biotinidase is an enzyme vital for the recycling of biotin. Biotin cannot be endogenously synthesized, and is obtained from dietary sources. Because biotin is required as a catalyst for carboxylases, including pyruvate carboxylase, significant variability occurs in the clinical presentation of biotin deficiency. Holocarboxylase synthetase deficiency presents in the neonatal period, and this enzyme is responsible for covalently binding biotin to apocarboxylases. Children with biotinidase deficiency usually present at age 2-5 months. However, presentations up to age 5 years were reported [3,4]. Patients usually exhibit hypotonia, seizures, ataxia, skin rash, alopecia, hearing loss, optic atrophy, breathing problems, and developmental delay [3,4]. Older children may present with involvement of the spinal cord and optic nerve [3,5].

Clinical and radiologic findings

Our patient manifested recurrent, progressive involvement of the brainstem and spinal cord. There was clinical and radiologic evidence for two episodes of similar illness. These illnesses appeared to be demyelinating in nature, involving the dorsal brainstem and periaqueductal gray matter in particular. The clinical syndrome was suggestive of a Leigh-like illness.

Profoundly low biotinidase levels and homozygous mutation in the *BTD* gene established biotinidase deficiency as the cause of Leigh-like syndrome in this patient. The high cerebrospinal fluid lactate values and the presence of a lactate peak on magnetic resonance spectroscopy are secondary to pyruvate carboxylase deficiency [2]. Treatment with oral biotin at doses of 5-20 mg/day is recommended for biotinidase deficiency [2]. Spinal cord demyelination as a manifestation of biotinidase deficiency has been infrequently described [3,5-7].

Wolf et al. described four children in 1998 with late onset biotinidase deficiency, all of whom manifested spastic paraparesis. Observations were based on analyses of cross-reacting materials to anti-biotinidase and on mutation analysis [3]. Myelography was not performed in three patients, and one patient manifested no abnormality [3].

Table 1 provides a review of literature on patients with biotinidase deficiency and spinal cord involvement. Five out of 10 patients had significant respiratory problems along with clinical or

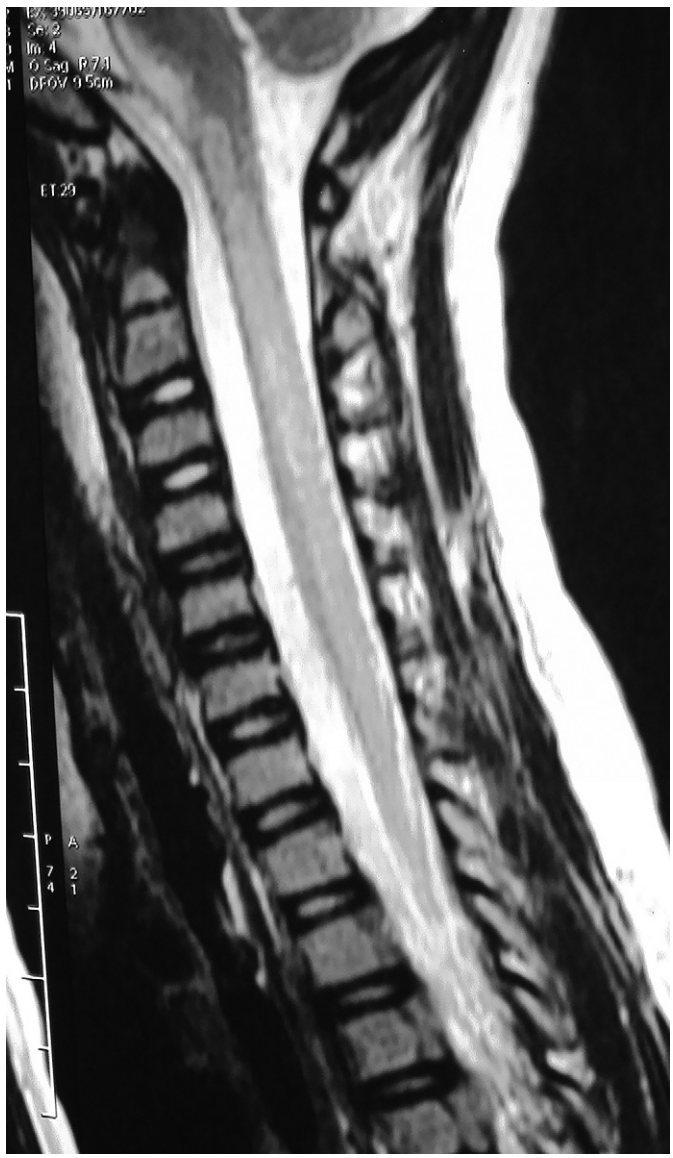

Figure 2. Magnetic resonance imaging indicates diffuse T_2 hyperintensity with involvement of the dorsal brainstem and spinal cord with lesions extending from the medulla up to the T_{12} vertebral level in a 7-year-old boy with recurrent myelopathy secondary to biotinidase deficiency.

Table 1. Review of clinical and laboratory findings in the literature of patients with biotinidase deficiency with involvement of the spinal cord

	Our Patient	Aziza et al. [5]	Yang et al. [6]			Wiznitzer and Bangert [8]	Wolf et al. [3]			
			1	2	3		1	2	3	4
Clinical features										
Age of onset	5 yr	3 yr	7 yr, 4 mo	5 yr	1 yr	1 yr, 6 mo	Adolescent	Adolescent	2 yr	2 yr
Duration of illness	2 yr	2 mo	8 mo	7 yr	2 yr	Since birth	–	–	–	–
Gait difficulty	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Lethargy/fatigue	Y	Y	Y	Y	Y	–	Y	Y	Y	Y
Spasticity	Y	Y	N	Y	N	Y	Y	Y	Y	Y
Hypotonia	N	N	Y	N	Y	Y	N	N	Y	N
Quadri/paraparesis	Y	Y	N	Y	Y?	N	Y	Y	Y	Y
Ataxia/dysmetria	N	N	N	Y	–	Y	N	N	N	Y
Respiratory problems	Y	Y	N	N	Y	N	N	N	Y	Y
Feeding/speech abnormalities	Y	–	N	N	–	Dysarthria	–	–	–	–
Other findings										
Peripheral neuropathy	N	N	Reduced conduction velocity	N	–	–	–	–	–	–
Visual impairment	Y	N	N	Y	–	–	Y	Y	Y	–
Hearing impairment	N	Unilateral	Increased I-III IPL in BAEP	–	–	–	N	N	Y	Y
Alopecia/skin rash	N	Sparse hair	Dermatitis	Both	Alopecia	Both	Rash	N	Rash	Both
Past history										
Developmental delay	N	Speech delay	N	N	N	N	–	–	–	–
Similar illness	Y	N	N	Y	Y	Rashes	–	–	–	–
MRI										
Spinal cord	C, T	C, T	C, T	C	C	Entire cord	–	–	–	–
Brainstem	Dorsal brainstem	Midbrain	N	N	Medulla	Medulla	–	–	–	–
Optic nerve/chiasm/tract	Chiasm	N	N	Optic nerve	N	–	–	–	–	–
Mutation analysis	c.133C>T(p.H447Y).	C>T1339;H447Y	–	–	–	–	G1369>A	C643>T; T1186>C	C1612>T	G98d7i3; C643>T

Abbreviations:
BAEP = Brainstem auditory evoked potential
C = Cervical cord
IPL = Interpeak latency
mo = Months
MRI = Magnetic resonance imaging
N = No
T = Thoracic cord
Y = Yes
yr = Years
– = Information not available

radiological evidence of spinal cord disease. Brain stem lesions were present in four patients. All six patients whose neuroimaging findings were available presented evidence of long segment spinal cord involvement.

Biotinidase deficiency should be included in the differential diagnosis of children presenting with demyelinating spinal cord disease, particularly with involvement of the optic pathway. The most common diagnosis in patients with this clinical presentation is usually neuromyelitis optica or multiple sclerosis with involvement of the spinal cord [3,7]. The criteria for a diagnosis of neuromyelitis optica include optic neuritis with myelitis in the presence of contiguous spinal cord lesions [9]. Our patient presented evidence for an involvement of the optic tract and chiasm, in addition to the long segment spinal cord lesions, and hence his signs clinically and neuroradiologically overlapped with those of neuromyelitis optica.

Genetic findings

A single case report from India describes genetically proved biotinidase deficiency. Rathi and Rathi reported on a 3.5-month-old child with a homozygous *7D3I* mutation, who presented with seizures and regression [10]. No details about corresponding molecular changes were mentioned [10]. Our report involves the first proven case from the Indian subcontinent of delayed-onset biotinidase deficiency with a mutation of the *BTD* gene.

A mutation of the *BTD* gene was observed in one patient during a meta-analysis of more than 150 mutations detected in genes of the nuclear genome that were responsible for Leigh-like syndrome [11].

Late-onset or juvenile-onset multiple carboxylase deficiency was described as early as 1971, and is secondary to biotinidase deficiency [12]. It constitutes an autosomal recessive disorder, and the *BTD* gene is localized to chromosome 3p25 [13].

More than 100 mutations responsible for biotinidase deficiency have been identified [14]. The *BTD* gene mutation c.133C>T (p.H447Y) is not the most commonly known mutation in cases of biotinidase deficiency, although it was previously reported [5]. Of the 10 patients with spastic paraparesis, two of them manifested this mutation.

Patients homozygous for missense mutations were hypothesized to involve late presentations and no hearing loss, whereas those homozygous for null mutations present early and do manifest hearing impairment [15].

Neonatal screening programs can identify profound (<10%) and partial (10-30%) biotinidase deficiencies. Most states in India do not offer neonatal screening for this disorder [2].

Conclusion

Late-onset biotinidase deficiency may present as myelopathy and may involve the brainstem and optic pathways. In countries

without neonatal screening for biotinidase deficiency, the recognition of this entity can be life-saving. The clinical syndrome overlaps with acquired demyelinating white matter disorders such as neuromyelitis optica and metabolic syndromes such as Leigh's.

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References

[1] Frank Y, Ashwal S. Neurologic disorders associated with gastrointestinal diseases, nutritional deficiencies and fluid-electrolyte disorders. In: Swaiman K, Ashwal S, Ferriero D, editors. Pediatric neurology: Principles and practice. 4th ed. Philadelphia: Elsevier; 2006. p. 2317.
[2] Enns G, Cowan T, Klein O, Packman S. Aminoacidemias and organic acidemias. In: Swaiman K, Ashwal S, Ferriero D, editors. Pediatric neurology: Principles and practice. 4th ed. Philadelphia: Elsevier; 2006. p. 590–1.
[3] Wolf B, Pompino R, Norrgard K, Lott I. Delayed onset profound Biotinidase deficiency. J Pediatr 1998;132:362–5.
[4] Wolf B, Grier RE, Allen RJ, et al. Phenotypic variation in biotinidase deficiency. J Pediatr 1983;103:233–7.
[5] Aziza K, Chedrawi A, Ali A, et al. Profound biotinidase deficiency in a child with predominantly spinal cord disease. J Child Neurol 2008;23:1043–8.
[6] Yang Y, Choayang L, Zhaoyue Q, et al. Spinal cord demyelination associated with biotinidase deficiency in three Chinese patients. J Child Neurol 2007;22:156–60.
[7] Tokath A, Coskun T, Ozalp I. Biotinidase deficiency with neurological features resembling multiple sclerosis. J Inherit Metab Dis 1997;20:707–8.
[8] Wiznitzer M, Bangert B. Biotinidase deficiency: Clinical and MRI findings consistent with myelopathy. Pediatr Neurol 2003;29:56–8.
[9] Wingerchuk DM, Lennon VA, Pittock SJ, Lucchinetti CF, Weinshenker BG. Revised diagnostic criteria for neuromyelitis optica. Neurology 2006;66:1485–9.
[10] Rathi N, Rathi M. Biotinidase deficiency with hypertonia as unusual feature. Indian Pediatr 2009;46:65–7.
[11] Finsterer J. Leigh and Leigh-like syndrome in children and adults. Pediatr Neurol 2008;39:223–35.
[12] Online Mendelian Inheritance in Man. MIM number 253260: 9/15/2009. Baltimore: John Hopkins University, URL: http://www.ncbi.nlm.nih.gov/omim/.
[13] Hymes J, Stanley C, Wolf B. Mutation in *BTD* causing biotinidase deficiency. Hum Mutat 2001;18:375–381.
[14] Wolf B, Jensen K, Barshop B, et al. Biotinidase deficiency: Novel mutations and their biochemical and clinical correlates. Hum Mutat 2005;25:413.
[15] Sevri HS, Genc GA, Tokatli A, et al. Hearing loss in biotinidase deficiency: Genotype-phenotype correlation. J Pediatr 2007;150:439–42.