Biotinidase Deficiency: A Treatable Neurological Inborn Error of Metabolism

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Biotinidase deficiency is a rare inborn error of biotin metabolism with autosomal recessive inheritance. Biotinidase is responsible for the recycling of biotin, an essential co-factor for the normal function of four human enzymatic carboxylases. Complete deficiency of biotinidase is caused by bi-allelic mutations in the *BTD* gene encoding this key enzyme and results mainly in progressive neurological impairment and dermatological manifestations. The clinical symptoms of the disease develop gradually in early infancy and are often non-specific, thus presenting a significant diagnostic challenge for the pediatrician since a delay in diagnosis will result in irreversible neurological deficits [1].

We describe a 2-month-old male who presented with new-onset seizures and hypotonia. Metabolic investigations that included analysis of organic acids and acylcarnitine profile suggested the diagnosis of biotinidase deficiency, enabling early initiation of oral biotin that resulted in complete reversal of the neurologic symptoms.

PATIENT DESCRIPTION

The male patient is the first offspring of consanguineous parents of Arab Muslim descent living in a village in the Nazareth region. Pregnancy and delivery were uneventful.

He presented initially at the age of 2 months with jerky movements of both upper and lower limbs and up-rolling eyes consistent with seizures. On examination he had normal vital signs, but neurological examination displayed marked head lag, truncal hypotonia, combined with generalized hyper-reflexia and clonus. In addition, he exhibited abnormal eye contact, lack of eye pursuit, and lack of social smiling. Laboratory investigations showed normal levels of serum electrolytes, glucose, calcium, magnesium, ammonia, renal function studies, liver transaminases, and arterial blood gases. Serum lactate levels were moderately elevated (4.15 mmol/L, normal value < 2.78 mmol/L). Cerebrospinal fluid (CSF) levels were mildly elevated (2.71 mmol/L, normal value < 2.20 mmol/L) Sepsis workup including blood, urine and CSF cultures were normal, as was initial CSF analysis. His brain ultrasound was normal. Initial electroencephalogram (EEG) showed an abnormal pattern consistent with burst suppression.

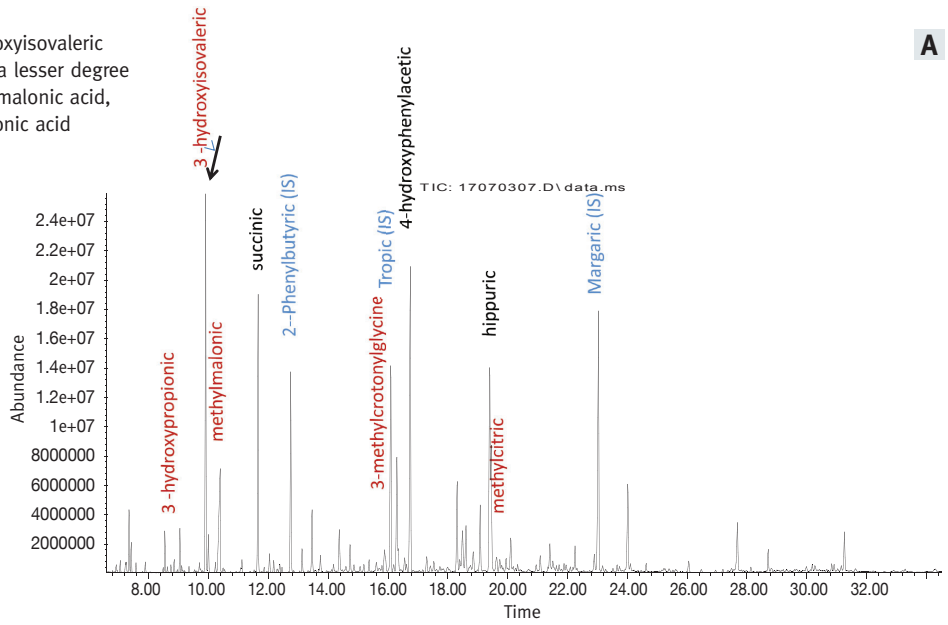
Therapy with phenobarbital was started, but seizure activity continued. Metabolic investigations were obtained, and his urinary organic acid analysis using gas chromatography-mass spectrometry showed significant excretion of 3-hydroxyisovaleric acid (3HIA) as well as slightly increased levels of 3-methylcrotonoylglycine, methylcitric and 3-hydroxypropionic acids. A minor elevation of methylmalonic acid was also noticed (23 mmol/mol creatinine, normal value < 12 mmol/mol creatinine for age) but was absent on repeated urinary organic acid test [Figure 1A]. Blood-spot acylcarnitine profile measured by UPLC-MS/MS (ultra-performance liquid chromatography–tandem mass spectrometry) showed elevated levels of C5OH carnitine, and of propionylcarnitine (0.78 mmol/L, normal range 0–0.47), and of methylmalonylcarnitine (3.96 mmol/L, normal range 0–1.15).

These findings suggested biotinidase deficiency, and the analysis of biotinidase enzyme activity in serum revealed almost absent enzyme activity (0.1 nmol/min/ml serum, normal range 3–8 nmol/min/ml serum). The diagnosis was further confirmed by genetic analysis of the *BTD* gene, which identified a homozygous frameshift mutation c.393delC that is predicted to result in early truncation of the protein (p.Phe131Leufs28*). The infant was started on oral biotin 10 mg daily and within a few days showed remarkable improvement with cessation of seizures, complete resolution of truncal hypotonia and limb hypertonia, and improvement in eye contact and communication. Repeated tests of organic acids showed normalization of all biochemical abnormali-

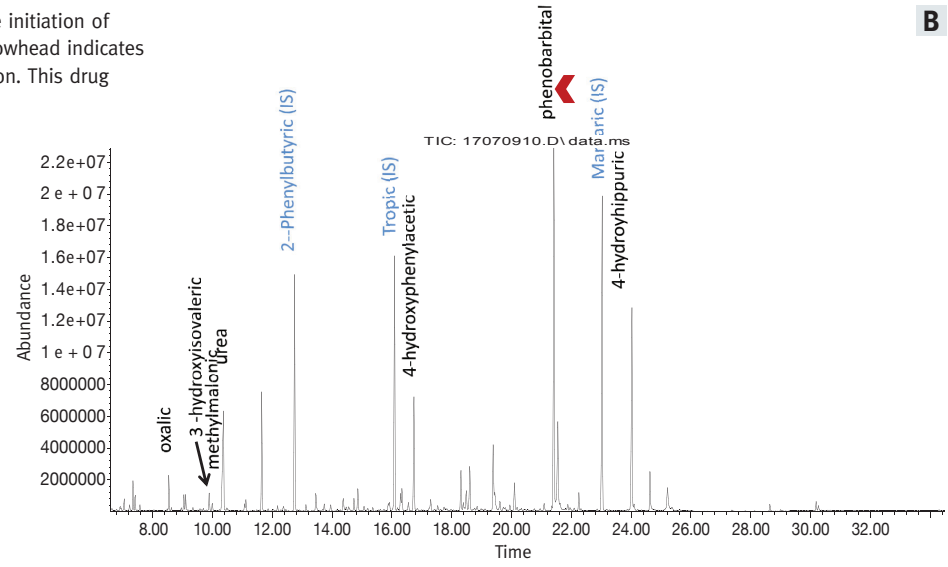
*The first two authors contributed equally to this study

Figure 1. Urinary organic acids analysis using gas chromatography-mass spectrometry

[A] Increased excretion of 3-hydroxyisovaleric acid (3HIA) (black arrow) and to a lesser degree 3-methylcrotonoylglycine, methylmalonic acid, methylcitric acid, 3-hydroxypropionic acid



[B] 3HIA normalized following the initiation of oral biotin (black arrow). The arrowhead indicates the urinary phenobarbital excretion. This drug was later discontinued



GC-MS: Agilent GC 7890A/ MS 5975, **Column:** Agilent HP-5MS (30 m, 0.25mmX 0.25µm), **Internal standards:** 2-Phenylbutyric, Tropic, Margaric

ties [Figure 1B]. At age 10 months he demonstrates normal growth and development, no dermatologic abnormalities, and normal hearing as confirmed by brainstem evoked response audiometry

COMMENT

Profound biotinidase deficiency is caused by almost complete deficiency (< 10%) of biotinidase enzyme activity and is associated with the most severe presentation of infantile or childhood onset of neurological impairment, including new-onset seizures, evolving hypotonia, ataxia, and developmental deterioration, as well as non-neurological symptoms such as skin rashes, alopecia, hearing loss, and ophthalmologic abnormalities. The disease is easily prevented by early administration of pharmacologic doses of oral biotin, which compensates for the unavailable recycled biotin. Moreover, neurological symptoms that already appeared can be completely reversed upon early diagnosis and timely biotin administration.

Since neurological abnormalities are non-specific and can develop gradually without being correctly diagnosed, many countries include this disorder in their newborn screening panel [2]. In Israel, biotinidase deficiency is not included in the national newborn screening, posing a major challenge for pediatricians in timely diagnosing infants with non-specific neurological symptoms. Rapid initial metabolic investigations are therefore crucial and should be performed in consultation with metabolic experts. The laboratory diagnostic clues include elevated serum and/or CSF lactate, elevated propionylcarnitine (C3), hydroxyisovalerylcarnitine (C5OH) on blood-spot acylcarnitine profile, and increased 3HIA excretion in urine. Upon initial suspicion, oral biotin should be initiated and biotinidase activity assessed.

The mutation identified in our patient was previously described in two patients from the Nazareth region and in another patient from Turkey [3]. Notably, in Nazareth and the surrounding villages, we already know of three different deleterious mutations associated with profound biotinidase deficiency including the current c.393delG, in addition to c.100G>A [4] and c.1613G>A. Of note, the significantly high carrier state of the c.100G>A mutation in one specific village with high inbreeding permitted the inclusion of this mutation into the Israeli genetic prenatal couple screening program. According to national health authorities, the successful implementation of the c.100G>A mutation in this program significantly decreased the birth rate of undiagnosed babies with biotinidase deficiency. Furthermore, based on Israeli Ministry of Health data, only two cases (including the current patient) of biotinidase deficiency were clinically diagnosed in the last 5 years. Nevertheless, in agreement with the genetic variability of biotinidase deficiency in the Israeli (mainly the non-Jewish) population and the successful, simple and available treatment, we strongly recommend reconsidering the incorporation of this disorder into the current Israeli newborn screening, as was done for other treatable disorders [5].

In conclusion, biotinidase deficiency is a rare inborn error of metabolism with neurological sequelae that can be completely prevented by early recognition and appropriate treatment. This case report highlights the importance of timely diagnosis and treatment of this disorder. A high index of suspicion is crucial in any child presenting with unexplained neurological deterioration.

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References

1. Wolf B. Biotinidase deficiency. In: Pagon R, Bird T, Dolan C, eds. *GeneReviews*. University of Washington, Seattle, 2000 (updated9 June 2016) https://www.ncbi.nlm.nih.gov/books/NBK1322/.
2. Wolf B. Successful outcomes of older adolescents and adults with profound biotinidase deficiency identified by newborn screening. *Genet Med* 2017; 19: 396-402.
3. Wolf B, Jensen K, Hüner G, Demirkol M, et al. Seventeen novel mutations that cause profound biotinidase deficiency. *Mol Genet Metab* 2002; 77: 108-11.
4. Pomponio RJ, Reynolds TR, Mandel H, et al. Profound biotinidase deficiency caused by a point mutation that creates a downstream cryptic 3' splice acceptor site within an exon of the human biotinidase gene. *Hum Mol Genet* 1997; 6 (5): 739-45.
5. Somech R, Lev A, Simon AJ, et al. Newborn screening for severe T and B cell immunodeficiency in Israel: a pilot study. *IMAJ* 2013; 15 (8): 404-9.

Capsule

Integrative states within the brain

The brain constantly integrates enormous amounts of information. While dynamically synthesizing cognitive processes as a function of an everchanging environment, the brain must stay flexible enough to adapt to continuous challenges. **Shine** et al. used a sophisticated computational framework to analyze functional magnetic resonance imaging data obtained during a wide range of cognitive tasks. They found a large integrative core of interconnected brain regions that processes information and optimizes cognitive performance and that also correlates with fluid intelligence. When the brain needs to work on more specific tasks, this integrative network segregates into more-specialized, regional brain activity. Altering neurotransmitter activity by pharmacological manipulation or disease could modulate these dynamics and affect cognitive performance.

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Eitan Israeli

"Whatever you can do, or dream, you can begin it. Boldness has genius, power and magic in it"

Goethe (1749–1832), German poet, novelist, and playwright. His works include novels, epic and lyric poetry, prose and verse dramas, memoirs, an autobiography, literary and esthetic criticism, and treatises on botany, anatomy, and color. His novel *The Sorrows of Young Werther* is said to have prompted a wave of suicides among young men. He was an early participant in the Sturm und Drang literary movement.

"Bad officials are elected by good citizens who do not vote"

George Jean Nathan (1882–1958), American author, editor, drama critic, and magazine editor