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RESEARCH REPORT

Irreversibility of Symptoms with Biotin Therapy in an Adult with Profound Biotinidase Deficiency

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Abstract We report a 36-year-old woman who exhibited progressive optic atrophy at 13 years old, then stroke-like episodes and spastic diplegia in her 20s. Biotinidase deficiency was not readily considered in the differential diagnosis, and the definitive diagnosis was not made until pathological variants of the biotinidase gene (*BTD*) were found by exome sequencing. Profound biotinidase deficiency was confirmed by enzyme analysis. Unfortunately, her symptoms did not resolve or improve with biotin treatment. Biotin therapy is essential for all individuals with profound biotinidase deficiency and for preventing further damage in those who already exhibit irreversible neurological damage. Newborn screening for the disorder would have avoided years of clinical symptoms that now appear to be irreversible with biotin treatment.

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Introduction

Biotinidase (EC 3.5.1.12) is the enzyme responsible for cleaving and recycling the vitamin biotin from biocytin and from dietary protein-bound sources (Pispa 1965; Wolf 2001). Profound biotinidase deficiency (<10% of mean normal serum activity) (OMIM #253260) is an autosomal recessively inherited metabolic disorder (Wolf 2012). Individuals with profound biotinidase deficiency, if untreated, usually exhibit seizures, hypotonia, skin rash, alopecia, vision problems, hearing loss, and developmental delay with accompanying ketolactic acidosis, and organic aciduria, usually in infancy or early childhood (Wolf 2001, 2012). Symptoms of the disorder can be successfully improved or prevented with pharmacological doses of oral biotin. However, if vision and hearing problems and developmental delay occur in an untreated individual, they are usually irreversible (Wolf 2012). Delayed-onset biotinidase deficiency presents with myelopathy with or without vision problems in adolescence or adulthood (Wolf et al. 1998; Wolf 2015a). All states in the United States and many countries screen their newborns for the disorder, although some countries do not (Wolf 2015b).

We report the case of a 36-year-old woman who had late, atypical clinical, and metabolic features, despite having profound biotinidase deficiency, and which resulted in a greatly delayed diagnosis and irreversible disability. It exemplifies the clinical variability of this potentially treatable disorder and the need to consider it in the differential diagnosis of diverse, even adult clinical presentations.

Case Report

A 27-year-old woman was referred to the inherited metabolic disease service at the Alberta Children's Hospital for further investigation of progressive optic atrophy and paraplegia. She had been healthy with normal development in infancy and childhood, except for a febrile seizure. At 13 years of age, her vision, which had previously been documented at 20/20, started to deteriorate, and she was diagnosed with optic atrophy. Her vision was adequate for reasonably normal functioning until about 19 years of age, when she experienced deterioration in her mid-20s when she became legally blind. From about 18 years of age, she experienced progressive leg weakness, balance difficulties, and severe pain in her abdomen, back, and legs but remained ambulatory until age 24 when she developed acute worsening associated with situational emotional stress. Since that time, she has not been able to walk. Significant pain in her legs has been her most concerning symptom, likely due to her spastic diplegia. Hearing was reported normal. She completed a Bachelor of Arts degree. Past surgeries included cholecystectomy, tonsillectomy, and a Caesarian section. Previous investigations did not reveal a cause for her problems, including a normal MRI of the brain and spinal cord, an EMG and nerve conduction, a muscle biopsy, an audiological evaluation and normal molecular testing for Leber hereditary optic neuropathy, spinal cerebellar ataxia, and Friedreich ataxia. Her parents are of Native American, Cree ancestry, but are not known to be consanguineous. She has two healthy siblings. She had three pregnancies, a son with type 1 diabetes diagnosed at 4 years, a daughter with multiple anomalies consistent with VACTERL association, and an early miscarriage. There is no other known family history of neurologic or neuromuscular disorders, blindness, or deafness.

Significant features on physical examination were obesity, left esotropia, spasticity, muscle weakness, brisk deep tendon reflexes, up-going plantar responses, and clonus in the legs and normal power, tone, and reflexes in her arms.

Further investigations included normal CBC, coagulation profile, urinalysis, electrolytes, glucose, liver function tests, lactate, plasma amino acids, plasma methylmalonic acid, plasma and urinary 3-methylglutaconic and 3-methylglutaric acids, and oxypurines. Plasma-free and total carnitine, and an acylcarnitine profile were normal (3-hydroxyisovaleryl carnitine was 0.09 μmol/L; normal <2 μmol/L); organic acids were normal except for a borderline elevated 3-hydroxyisovalerate at 2.01 mmol/mol creatinine (normal <2 mmol/mol creatinine). Molecular testing for the common mitochondrial DNA deletion for MELAS (mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes) and Charcot-Marie-Tooth, types 1A and 1B were all negative.

Plasma homocysteine concentration was elevated at 57.7 μmol/L (normal = 4.7–10.8 μmol/L). She was found to be a homozygote for the *MTHFR* 677C>T mutation. Further investigations revealed normal vitamin B12 and folate concentrations. Molecular analysis of the CBS gene for cystathionine beta-synthase was negative. Because this was not an adequate explanation for the degree of hyperhomocysteinemia, further detailed studies were performed on cultured fibroblasts (courtesy of Dr. David Rosenblatt, McGill University). [^{14}C]-propionate incorporation was slightly low, but higher than that seen in the methylmalonic acidurias, and [^{14}C]-methyltetrahydrofolate was normal. The uptake of [^{57}Co]-cyanocobalamin was low, but there was adequate synthesis of adenosylcobalamin and methylcobalamin. However, the specific activity of methylenetetrahydrofolate reductase was low at 5.4 compared to 16.5 nmol CHO/mg protein/h in extracts from a control cell line. Subsequent complete sequencing of the *MTHFR* gene did not reveal any other deleterious mutations.

She was prescribed betaine (3 g t.i.d), folate (5 mg/d), and vitamin B12 (0.5 μg b.i.d). Her other medications included baclofen, Elavil, ranitidine, ASA, and nitrazepam. Plasma homocysteine concentration decreased to 15.5 μmol/L, but compliance was inconsistent with later values in the 30–40 μmol/L range. There was no obvious clinical benefit from this regimen; in fact, there was some deterioration over about 8 years of subsequent follow-up evaluations. She had several sudden episodes of muscular spasm or stroke-like episodes, associated with vomiting and diarrhea, and accompanied by hemiparesis on one occasion and sensory loss in her lower extremity with facial palsy. Five months prior to her diagnosis, she woke up with right-sided facial weakness. This was followed by a severe headache in the right temporal and mastoid region and weakness of her right leg and arm. She also had an intermittent skin rash with the appearance of folliculitis pilaris and fragile nails, but her hair was normal with no alopecia. On two occasions, she had mildly abnormal organic acid analyses with moderate elevations of isovaleric acid, 3-methylglutaconic acid, and traces of methylcrotonylglycine and tiglylglycine and plasma acylcarnitines with a mild elevation of isovaleryl carnitine (1.48 and 1.19 μmol/L).

After appropriate counseling and informed consent, she was enrolled in the "Care4Rare" exome sequencing research program, through which she was discovered to have biallelic pathogenic mutations in the biotinidase (*BTD*) gene: c.511G>A;1330G>C; p.Ala171Thr;Asp444His and c.98_104delinsTCC; p.Cys33Phefs*36. This combination is known to cause profound biotinidase deficiency (Wolf et al. 1985) and was subsequently confirmed with serum biotinidase activity of <1.0 IU/L (normal 5.8–14.6 IU/L).

Biotin treatment, 16 mg for 2 weeks and then increased to 24 mg, over 3 months failed to improve any of the symptoms. Because there were no clinical improvements, she stopped her biotin after 3 months. However, biotin was

restarted after she developed significant pain in her posterior left thigh. She has had no further stoke-like episodes to date.

Discussion

This individual had an unusual, late, and confusing presentation of biotinidase deficiency. There apparently were no significant problems in childhood, and optic atrophy was the first issue developing in adolescence, followed by progressive muscle weakness, balance difficulties, and spastic paraplegia in early adult life and then by subsequent stroke-like episodes. In retrospect, her clinical picture is compatible with the diagnosis of biotinidase deficiency. Hyperhomocysteinemia at first appeared to be a diagnostic clue, but retrospectively turned out to be irrelevant, and diverted attention away from other possible diagnoses. Metabolic abnormalities in acylcarnitines and organic acids were unfortunately only borderline abnormal and disregarded because they were not consistent or not considered particularly significant in her clinical context. As a result, she underwent an unfruitful extensive diagnostic odyssey, only finally to be resolved by exome sequencing.

The phenotype of adolescents and adults with profound biotinidase deficiency is different from that of younger children (Wolf et al. 1998). These older untreated individuals with delayed-onset biotinidase deficiency exhibit diplegia/myelopathy with or without vision abnormalities (Wolf 2015a). There are multiple reports of older symptomatic individuals who have been diagnosed with various other disorders before the correct diagnosis was made and biotin therapy begun (Bottin et al. 2015; Wolf 2015a) However, when identified relatively rapidly, the symptoms can be ameliorated with therapy. The individual reported here is the oldest reported symptomatic individual to have been diagnosed with profound biotinidase deficiency and fails to demonstrate any improvement of symptoms with pharmacological doses of biotin. If diagnosis and treatment are delayed, the symptoms in adults may be irreversible, as they can be in older enzyme-deficient children. There has always been some improvement in symptoms, even complete resolution, in affected adolescents and other adults with biotin treatment, although not in the individual reported here (Wolf 2015a).

Based on previous experience, we expected to see some or significant clinical improvement after 3 months of biotin therapy. However, no improvement was observed. There is always the question of compliance, although she reported that she took the biotin during this initial 3-month period. If the clinical features are allowed to continue without a definitive diagnosis and the institution of biotin therapy, as in this case, they may become irreversible. Although subsequent biotin therapy will likely prevent new neurological problems from developing, many or most symptoms may have become permanent if sufficient time has passed before the diagnosis and biotin therapy has begun.

This individual appears to have some abnormality of homocysteine metabolism with an increased plasma homocysteine concentration and decreased MTHFR activity. Although the homozygous 677C>T alteration in *MFTHR* is known to be benign, in the presence of an elevated plasma homocysteine, we cannot entirely exclude that this individual is at increased risk for a thromboembolic or "stroke-like" event from her hyperhomocysteinemia. However, the major neurological symptoms of visual abnormalities and spastic diplegia seen in this individual are consistent with those seen in other symptomatic adults with profound biotinidase deficiency (Bottin et al. 2015; Wolf 2015a).

This case report emphasizes the following important points:

1. If a symptomatic adult with biotinidase deficiency is unrecognized for a sufficient length of time before being diagnosed and treated, the clinical symptoms may be irreversible with biotin therapy.
2. Biotin therapy is essential for all individuals with profound biotinidase deficiency and for preventing further damage in those who already exhibit irreversible neurological damage.
3. Exome or whole-genome sequencing was important in definitively establishing a diagnosis.
4. The importance of paying attention to abnormal results, even if seemingly minor and inconsistent, and at the same time not to be distracted by abnormal results that may lead to blind alleys.
5. Neonatal screening for biotinidase deficiency is important. At the date of her birth, biotinidase newborn screening had not yet been introduced in the Province of Alberta. If it had, early diagnosis and treatment would have significantly changed the patient's medical course.

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Contributions of the Authors

- Dr. Ferreira is a treating physician and helped write the manuscript.
- Dr. Chan is a treating physician and helped write the manuscript.
- Dr. Wolf planned, organized and wrote the manuscript.

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References

Bottin L, Prud'hon S, Guey S, Giannesini C, Wolf B, Pindoliua K, Stankoff B (2015) Biotinidase deficiency mimicking neuromyelitis optica: initially exhibiting symptoms in adulthood. Mult Scler J 21:1604–1607

Pispa J (1965) Animal biotinidase. Ann Med Exp Biol Fenn 43 (Suppl.5):1–39

Wolf B (2001) Disorders of biotin metabolism. In: Scriver CR, Beaudet AL, Sly WS, Valle D (eds) The metabolic and molecular bases of inherited disease. McGraw-Hill, New York, pp 3935–3962

Wolf B (2012) Biotinidase deficiency: if you have to have an inherited metabolic disease, this is the one to have. Gend Med 14:565–575

Wolf B (2015a) Biotinidase deficiency should be considered in individuals exhibiting myelopathy with or without vision loss. Mol Genet Metab 116:113–118

Wolf B (2015b) Why perform newborn screening for profound and partial biotinidase deficiency? Mol Genet Metab 114:382–387

Wolf B, Heard GS, Weissbecker KA, Secor McVoy JR, Grier RE, Leshner RT (1985) Biotinidase deficiency: initial clinical features and rapid diagnosis. Ann Neurol 18:614–617

Wolf B, Pomponio RJ, Norrgard KJ, Lott IT, Baumgartner ER, Suormala T, Raemaekers VT, Coskun T, Tokatli A, Ozalp I, Hymes J (1998) Delayed-onset profound biotinidase deficiency. J Pediatr 132:362–365