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Case Report

Biotinidase deficiency is a rare, potentially treatable cause of peripheral neuropathy with or without optic neuropathy in adults

Elizabeth Kellom [a,c,*], Kimberly Stepien [a], Gregory Rice [b,c], Barry Wolf [d]

[a] University of Wisconsin, Madison Department of Ophthalmology and Visual Sciences, United States of America
[b] Department of Pediatrics, University of Wisconsin School of Medicine and Public Health, United States of America
[c] Waisman Center, University of Wisconsin School of Medicine and Public Health, United States of America
[d] Ann and Robert H. Lurie Children's Hospital of Chicago and Northwestern Feinberg School of Medicine, Chicago, IL, United States of America

A B S T R A C T

Background: We describe two adult brothers with lower limb neuropathy and one with progressive optic neuropathy. One brother was found to have profound biotinidase deficiency by identifying biallelic pathogenic variants of the *BTD* gene by whole exome sequencing, which was confirmed by markedly decreased serum biotinidase activity.

Case report and methods: The first brother had progressive optic atrophy and vision loss over 10 years and progressive peripheral neuropathy with weakness, pain, and fatigue for 20 years. Profound biotinidase deficiency was also identified in an older brother, who exhibited peripheral neuropathy since four years of age, but had no vision loss.

Results: The first brother's vision loss and neuropathy improved markedly with biotin in six months. However, the neuropathy of the other brother did not improve with 16 months of biotin therapy.

Conclusions: The first brother's neurological issues partially reversed with biotin. However, the longer-term symptoms of the other brother were irreversible. These cases emphasize the importance of considering biotinidase deficiency in the differential diagnosis of adolescents and adults with peripheral neuropathy with or without optic neuropathy/atrophy before symptoms become irreversible. Although WES initially identified the disorder in this family, measuring serum biotinidase activity was a necessary confirmatory step after WES and is less expensive than performing whole exome sequencing.

1. Introduction

Biotinidase deficiency is an autosomal recessive metabolic disorder that usually presents in early-childhood [1] Deficiency of biotinidase prevents the body from recycling biotin and usually results in neurological features, such as seizures, hypotonia, ataxia, hearing and vision loss, and developmental delay, and cutaneous features, such as dermatitis, alopecia, and conjunctivitis [2]. When identified early, treatment with pharmacological doses of biotin prevents onset and progression of symptoms [2,3]. For this reason, the United States and many countries have implemented newborn screening programs with biotinidase deficiency so therapy can be implemented before symptoms occur [4,5].It is more difficult to recognize the late-onset form of this condition in adolescents and adults that primarily results in peripheral neuropathy, such as myelopathy or spastic paraparesis, with or without optic neuropathy [6–10].

2. Case reports and results

We report two adult brothers with biotinidase deficiency as the two oldest affected individuals with variable onset and nature of symptoms with discordant response to biotin supplementation.

Brother A was referred to Genetics at 49 years old to identify the etiology of his bilateral, progressive optic atrophy which begun 10 years earlier. Whole exome sequencing was performed and identified three pathogenic mutations in the *BTD* gene [11]. He was compound heterozygous for the c.98_104delinsTCC variant and the combination c.[511G > A;1330G > C] (p.[A171T;D444H]) variant. These two variants are both common pathogenic variants for profound biotinidase deficiency [12].His serum biotinidase activity was markedly reduced (0.3 nmol PABA formed /mL/min; Normal: >5.0), confirming his diagnosis of profound biotinidase deficiency. Improvement of his vision has been previously documented [11].

In addition to his ophthalmological findings, he experienced approximately 20 years of numbness, pruritus, and pain in his limbs. He also experienced persistent upper extremity dysesthesia leading to

* Corresponding author at: Waisman Center, University of Wisconsin School of Medicine and Public Health, United States of America.
E-mail address: ekellom@wisc.edu (E. Kellom).

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carpal tunnel surgery in his early 30s that did not improve his symptoms. Intermittent dysesthesia of his lower extremities was brought on by flexion of his hips. Neurological examination noted diminished sensation over left lateral calf and lateral malleolus with normal, symmetric strength and patellar reflexes. Numbness of both legs radiate down his calves, greater on the left. Evaluation included lumbar x-rays that showed relatively normal preservation of the intradisc spaces.

These symptoms continued to progress over 15 years with complaints of worsening balance and severe pruritic sensations in his arms and back. Neurological examination at the age of 45 demonstrated normal strength, muscle tone, and bulk with deep tendon reflex of +1 and preserved ankle jerks. At that time, diminished sense of touch on both feet was noted, with left worse than right. His gait was slow and antalgic. Evaluation for multiple sclerosis and related disorders showed no oligoclonal bands in the cerebrospinal fluid and normal IgG synthesis rate, vitamin B_{12}, and thyroid-stimulating hormone.

Upon diagnosis, he took 10 mg of oral biotin daily which led to rapid improvement of both visual and systemic symptoms. After 16 months of treatment, his activity normalized with near resolution of tingling and numbness other than mild persistence on the balls of his feet and toes. The pruritus completely resolved. Brother A was the only one of his four siblings to experience progressive vision loss. Enzyme testing for all siblings was recommended due to the variability of the onset of symptoms in Brother A. Of his siblings, 54-year-old Brother B was also found to have markedly low biotinidase activity (<1 nmol PABA formed /mL/min; consistent with profound biotinidase deficiency.

Brother B's history of peripheral neuropathy was significantly longer, but without associated vision loss. He reported nerve pain as early as 4 years of age with itching sensations of his hands and thighs at 12 years old. In his early 40s, he began to experience burning and itching in his hands and feet which evolved to numbness. Neuralgias began in his arms and legs 10 years later. Neurological examination identified normal deep tendon reflexes throughout and graded pinprick sensory loss was found bilaterally in upper and lower extremities. Gait, muscle bulk, and coordination were normal without balance concerns. Nerve conduction velocity studies revealed bilaterally, decreased conduction velocity of the median nerve; reduced amplitude of the tibial motor nerve; prolonged distal onset latency and decreased conduction velocity of the ulnar motor nerve; and prolonged distal peak latency, reduced amplitude, and abnormal peak latency difference of median in the hands.

His electromyelogram revealed bilateral mild axonal peripheral neuropathic process involving the left lower extremity suggesting mild motor neuropathy and moderate left median nerve compromise at or near the wrist/carpal tunnel affecting the sensory components. This was interpreted as a demyelinating process. He was diagnosed with idiopathic progressive peripheral neuropathy. A diagnosis of multiple sclerosis was considered, although evaluation was negative.

3. After 14 months of biotin therapy, there was no improvement in his symptoms

The brothers in this report are the oldest symptomatic individuals to be diagnosed with biotinidase deficiency. As seen in other late-onset individuals, our brothers presented with limb neuropathy with or without optic neuropathy. Similar to others, demyelinating disorders were considered in the differential diagnosis. Brother A's symptoms were more severe, but over a shorter period than Brother B. A previous report of a 36-year-old woman with the same genotype also exhibited no improvement on biotin (13). We propose that in cases without improvement with therapy, too much time has elapsed between onset of symptoms and initiation of treatment.

4. Discussion

Biotinidase deficiency is a readily treatable inherited disorder of metabolism. In childhood, the untreated disorder usually exhibits various neurological and cutaneous abnormalities [14]. However, the phenotype of the disorder is different in adolescence or adulthood [6,15]. Affected adults usually exhibit neuropathy/myelopathy with or without optic neuropathy.

The brothers in this report are the oldest symptomatic individuals to be diagnosed with biotinidase deficiency. As in other later-onset individuals with biotinidase deficiency, our brothers presented with limb neuropathy with or without optic neuropathy/atrophy. Similar to that of others, they were initially considered to have multiple sclerosis or disorders such as neuromyelitis optica or transverse myelitis [6,9].

Brother A is the oldest to exhibit partial reversal of symptoms. Brother B has milder symptoms than in his younger brother, but he has had symptoms for a longer period. His peripheral neuropathy did not improve with months of biotin therapy. A previous report of a 36-year-old woman with the exact same genotype as these brothers also exhibited no improvement in her symptoms with biotin [13]. In both cases, it is likely too much time had elapsed before they were diagnosed and treated resulting in irreversibility of the symptoms.

Both brothers have complained of itching, probably neuropathic pruritus, prior to developing numbness and burning; all of these are symptoms of paresthesia. The pruritus completed resolved with biotin therapy in Brother A, but not in Brother B.

The neuropathy in Brother B was likely due to biotinidase deficiency because of the similarity in symptoms to those of Brother A: progressive, painful and itching with similar distribution and characteristics.

We propose that this discrepancy is due to the length of time each brother experienced symptoms and indicates the need for prompt diagnosis and treatment in adults in order to reverse the effects of peripheral neuropathy and/or optic neuropathy. In addition, family members should be tested whether or not they are symptomatic.

Although biotinidase deficiency is included in all newborn screening programs in the United States and in many countries, the date of initiation for these newborn screening programs varies. Therefore, many adults and some adolescents have not been screened for the disorder. Although Brother A was diagnosed initially through WES, this testing is not readily available to all individuals, especially because of lack of insurance coverage, particularly in adults. Depending on the laboratory used, measuring serum biotinidase activity is generally the most rapid and least expensive method for definitively diagnosing biotinidase deficiency, whereas sequencing the *BTD* gene is usually more expensive and takes longer to obtain the results. Both of these methods are less expensive than performing WES. Importantly, measuring serum biotinidase activity is a necessary confirmatory step even with suggestive molecular results, especially when there variants of unknown significance or if phase undetermined.

Measuring serum biotinidase activity is a comparatively rapid and inexpensive test compared to WES for screening for and diagnosing this treatable disorder in adults with limb neuropathy with or without optic neuropathy. This is not to discount the utility of WES and broad-based genetic testing in these situations, but to highlight the importance of considering biotinidase deficiency when determining a testing strategy. In addition, if an individual is diagnosed with biotinidase deficiency, all immediate family members should be screened.

Brother A's vision loss and peripheral neuropathy was significantly reversed with biotin therapy and demonstrates the treatability and reversibility of symptoms even into adulthood. The clinical scenarios of these brothers highlight the importance of testing for biotinidase activity in older individuals with peripheral neuropathy with or without optic neuropathy, particularly if a definitive etiology has not been determined. However, if the disorder is not included in the differential diagnosis, an affected individual may develop symptoms that ultimately are irreversible with biotin therapy. Therefore, biotinidase deficiency should be added to the differential diagnosis of any individuals with peripheral neuropathy with or without optic neuropathy, especially if the diagnosis of multiple sclerosis, is being considered.

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