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Biotinidase deficiency should be considered in individuals thought to have multiple sclerosis and related disorders

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ABSTRACT

Background: Multiple sclerosis is a disorder of the central and peripheral nervous system of young and old adults that is characterized by muscle, coordination and vision abnormalities. Multiple sclerosis is likely due to numerous causes.
Methods: Recently, adolescents and adults with ophthalmological and or neurological findings have been diagnosed with biotinidase deficiency. These individuals have exhibited myelopathy, paresis and/or spastic diplegia/tetraplegia with or without optic neuropathy/vision loss. These older individuals with biotinidase deficiency were considered initially to have multiple sclerosis or similar disorders before they were determined to have biotinidase deficiency.
Results: If a symptomatic individual with biotinidase deficiency is treated with biotin early enough, the symptoms markedly improve or completely resolve, but if treatment is delayed, the symptoms may be irreversible.
Conclusion: Therefore, although biotinidase deficiency is rare relative to that of multiple sclerosis, the disorder should be included in the differential diagnosis of individuals thought to have multiple sclerosis or related disorders. Biotinidase deficiency should be considered in individuals thought to have multiple sclerosis or related disorders.

1. Introduction

Multiple sclerosis (MS) is a demyelinating disorder of the central and peripheral nervous system. Individuals with MS can exhibit a variety of physical and mental problems, including vison problems, double vision, blindness, optic muscle weakness, problems with sensation, and/or coordination (Goldenberg, 2012; Reich et al., 2018). MS can occur in relapsing attacks or in progressive forms. Symptoms may abate or the neurological symptoms may continue and progress. MS is a relatively common neurological disorder that usually begins between ages of 20 and 50 years.

Biotinidase (EC 3.5.1.12) is the enzyme that cleaves and recycles free, unbound biotin from biotin bound to protein (Wolf et al., 1983). Biotinidase deficiency is an autosomal recessively inherited disorder caused by deficient activity of biotinidase (Wolf, 2016). Young children with profound biotinidase deficiency (less than 10% of mean normal activity in serum), if untreated, may exhibit neurological and cutaneous symptoms, including seizures, hypotonia, ataxia, developmental delay, conjunctivitis, hearing loss, and visual problems, including optic atrophy, skin rash, and alopecia (Wolf, 2012). Symptomatic children may exhibit metabolic ketoacidosis, organic aciduria and hyperammonemia. If left untreated, some individuals develop severe metabolic compromise that can result in coma or death. Children with profound biotinidase deficiency can be effectively treated with pharmacological doses of biotin (5–10 mg/d). Early treatment will prevent the development of symptoms. Biotinidase deficiency meets the criteria for inclusion in many newborn screening programs throughout the world (Wolf, 1991).

Recently, multiple adolescents and adults with neurological and ophthalmological findings have been diagnosed with biotinidase deficiency. These individuals have exhibited myelopathy, paresis and/or spastic diplegia/tetraplegia with or without optic neuropathy/vision loss (Wolf, 2015). If treated early enough, the symptoms of biotinidase deficiency improve or completely resolve (Table 1), but if treated too late, the symptoms may be irreversible (Ferreira et al., 2017). Several of these individuals were initially thought to have multiple sclerosis or similar disorders (Wolf, 2015). Although biotinidase deficiency is rare relative to multiple sclerosis, because of biotinidase deficiency's ease of diagnosis and treatment, it should be included in the differential diagnosis of individuals thought to have multiple sclerosis or related

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Table 1
Clinical and diagnostic imaging features and enzymatic and mutational analysis of adolescent and adults with biotinidase deficiency with features of MS or related disorders (in the order of the age of diagnosis).

Age of diagnosis	Initial neurological symptoms	Initial ophthalmological symptoms/VEP	Other symptoms	MRI/CT of the Head	MRI/CT of the Spine	EMG/NCV	Auditory/ BAEP issues	Neurological outcome after biotin therapy	Biotinidase activity (Units/ml serum) or % of mean normal	Mutation	Reference	Author
14 years	Limb weakness	Progressive vision loss		Bilateral symmetric high T2 signal intensity and contrast enhancement at tectal plate, optic nerve and optic chiasm	High T2 signal intensity and contrast at cervical spinal cord (1–6 cervical vertebrae		NT	Vison normalized; Limb weakness became normal	8%	c.98_104del/insTCC; p.C33Ffs*36/ c.1369G > A ;p.V457M	Yilmaz et al. (2017)	Yilmaz
15 years	Fatigue, hypotonia, limb weakness, spastic paraparesis with clonus	Optic atrophy, ABN VEP		Normal	NT	NT	ABN	Resolution of scotomas, but some residual limb weakness	0.1	c.1612C.T; p.R538C/ c.1612C.T; p.R538C	Wolf et al. (1998)	Wolf
15 years	Difficulty walking and stiffness of lower extremities. Spasticity of the lower limbs.hyperreflexia, blateral plantar reflexes were extensor	Some residual ambulation difficulties, loss of vision, optic atrophy		NT	T2 Hyperintensities in the anterior, lateral and posteriror columns of the entire spinal cord.	NT	NT	Residual visual problems	0.1	NT	Bhat et al. (2015)	Bhat
18 years	Limb hyperreflexia, muscle weakness, paraparesis	Bilateral progressive optic atrophy, scotoma		T2-weighted hyperintensities of both optic nerves and chiasm without Gadolinium enhancement	Bilateral longitudinally extensive high T2-signal intensities of anterior part of the spinal cord		Normal	Vision improved, but bilateral distal leg weakness	<10%	c.695T > G; p.F232C /c.1319T > C, p.L440P	Deschamps et al. (2017)	Deschamps
22 years	Progressive spasticity of all four limbs	Loss of vision, optic atrophy, bilateral central scotoma		T2 hyper-intensity involving the spinal cord, the optic nerves, the fornix and the mammillar bodies	Hyperintensity on T2 from cervico-medulllary junction to T12. Swelling of cervical aspect. Hypersignal of the columns of the fornix and mammaliar bodies and optic nerves	NT	NT	Some residual spasticity and proximal deficits of the lower limbs, some residual loss of visual acuity.	~4%	c.1318C > A;p.A439N/ c.1318C > A;p.A439N	Bottin et al. (2015)	Bottin
25 years		Progressive central scotoma		Normal			Normal	Vison improved to normal	<10%	c.1368A > C, p.Q456H/ c.1612C > CT, p.R538C	Deschamps et al. (2017)	Deschamps
31 years		Vision loss	Pneumonia, respiratory failure, respiratory acidosis, , lactic acidemia, weakness, alopecia, gait difficulty since birth, tchypnea, hyperventilation	NT	NT		Hearing loss	Normal	1.47%	NT	Demirturk et al. (2016)	Demirtürk
36 years				Normal	Normal	Normal			<10%			Ferriera

(*continued on next page*)

Table 1 (*continued*)

Age of diagnosis	Initial neurological symptoms	Initial ophthalmological symptoms/VEP	Other symptoms	MRI/CT of the Head	MRI/CT of the Spine	EMG/NCV	Auditory/ BAEP issues	Neurological outcome after biotin therapy	Biotinidase activity (Units/ml serum) or % of mean normal	Mutation	Reference	Author
	Spastic diplegia, paraplegia, balance difficulties, leg weakness, myelopathy, hearing loss	Progressive optic atrophy, esotropia						No improvement on biotin		c.511G > A;1330G > C; p.Ala171Thr;D444H/	Ferreira et al. (2017)	

VEP: Visual evoked potential studies, BAEP: Brainstem auditory evoked response studies, ABN: Abnormal, NT: Not tested.

disorders. If an individual is found to have biotinidase deficiency, there will not be a delay in instituting appropriate biotin therapy, and the individual will be less likely to develop irreversible clinical problems.

2. Subjects and results

Multiple adolescents and adults ultimately found to have biotinidase deficiency initially exhibited signs and symptoms that were considered consistent with multiple sclerosis or similar disorders (Ferreira et al., 2017; Yilmaz et al., 2017; Wolf et al., 1998; Bhat et al., 2015; Deschamps et al., 2017; Demirturk et al., 2016) (Table 1). The neurological and ophthalmological abnormalities of these individuals are summarized in Table 1. The abnormalities found on imaging studies and vision assessments overlap with those seen in some individuals diagnosed with MS. These individuals were initially diagnosed with multiple sclerosis or related disorders and failed to respond to the therapies directed at these diagnoses. Eventually the correct diagnosis of biotinidase deficiency was made for a variety of reasons, and they were treated with biotin. Most of these individuals improved with biotin therapy, several continued to exhibit some residual problems, and only one had no improvement, probably because the treatment was initiated too late and the symptoms were irreversible.

3. Discussion

The cause(s) of MS are uncertain, but may be abnormalities of the immune system, due to environmental factors, such as viral infection, or due to a genetic predisposition. Although there are no known cures of MS, there are various medications used to ameliorate the condition (Reich et al., 2018).

Clinical criteria alone are not usually sufficient to make the diagnosis of MS. Contrast neuroimaging is the most commonly used diagnostic test often showing demyelination. In addition, the cerebrospinal fluid is analyzed for evidence of chronic inflammation, including oligoclonal bands of IgG on electrophoresis. Individuals with MS also often have abnormalities in visual- and sensory-evoked potentials.

The phenotype of biotinidase deficiency in adolescents and adults usually presents with myelopathy with or without optic neuropathy (Wolf, 2015). Demyelination of the brain and spine, inferred from MRIs, is commonly seen in symptomatic individuals with biotinidase deficiency (Wolf, 2011). The clinical symptoms, optic neuropathy and/or myelopathy, in these individuals can occur gradually over weeks to months or suddenly. This variability in presentation does not appear to correlate with specific mutations.

The older individuals identified to have biotinidase deficiency were ascertained because their physicians performed organic acid analysis showing the metabolites indicative of multiple carboxylase deficiency or performed whole exome sequencing finding two pathogenic mutations in the biotinidase gene (BTD). In a several instances, the physicians actually included biotinidase deficiency in their differential diagnosis and confirmed the diagnosis by enzymatic measurement. As discussed, these individuals were initially thought to have multiple sclerosis or a similar disorder. This method of ascertainment obviously was dependent upon a fortunate event or testing or because of the physician's awareness that biotinidase deficiency can exhibit similar findings. Obviously, this method of ascertainment does not allow determination of the frequency of individuals with biotinidase deficiency within the group thought to have multiple sclerosis or related diseases.

One of the individuals with biotinidase deficiency have had elevated oligoclonal bands and immunoglobulin G concentrations in their cerebral spinal fluid (Yang et al., 2007). The presence of oligoclonal bands and elevated immunoglobulin G concentrations in cerebrospinal fluid have been used as markers for certain immunological disorders, such as MS, transverse myelitis and neuromyelitis optica. Individuals with these latter disorders are commonly treated with steroids and intravenous immunoglobulins (Cabasson and Rivera, 2015; Chedrawi et al., 2008;

Bottin et al., 2015; Hill, 1997; Komur et al., 2011). None of these individuals ultimately shown to have biotinidase deficiency improved while on these therapies, which often took days to weeks to assess their ineffectiveness. These ineffective therapies delayed arriving at a correct diagnosis.

Initially, the adolescents and adults with biotinidase deficiency were considered as having a variety of disorders, including MS. Only when the treatment of these disorders failed to improve the clinical status of the individual, did the differential extend to other possibilities, such as biotinidase deficiency. Because biotinidase deficiency is so easy to diagnose definitively and the treatment potentially can result in such marked clinical improvement, we recommended that biotinidase deficiency should be added to the differential diagnosis of individuals who exhibit myelopathy with vision abnormalities (Wolf, 2015).

All the symptomatic adolescents and adults with biotinidase deficiency had profound biotinidase deficiency (Wolf, 2015). Of the individuals who have had mutation analysis, all have had missense mutations with some residual enzymatic activity (Wolf et al., 1998; Chedrawi et al., 2008; Raha and Udani, 2011). It is possible that having some residual enzymatic activity is responsible for the later-onset of symptoms. Symptoms may be precipitated in these individuals when they experience a specific stress, such as an infection or surgery. We have not identified a specific genotype-phenotype correlation for individuals with untreated biotinidase deficiency who develop later-onset myelopathy.

Biotinidase deficiency is incorporated in many newborn screening programs throughout the world. However, there are still multiple countries, notably the United Kingdom and France, that still do not screen their newborns for the disorder. There is a gap time between when some countires began newborn screening for biotinidase deficiency and when adolescents or adults may develop symptoms of MS. In those countries that do not perform newborn screening for biotinidase deficiency, there is an increased chance of identifying adolescents or adults with symptoms of MS who actual have biotinidase deficiency.

Obviously, the number of individuals with biotinidase deficiency is small relative to the number of individuals who are thought to have multiple sclerosis. Biotinidase deficiency is readily diagnosed by performing a simple test of biotinidase activity in the individual's serum or plasma for biotinidase activity (Wolf et al., 1983). All the individuals described in this report have had profound biotinidase deficiency or less than 10% of mean normal serum activity. This further indicates why it is unlikely to miss an affected individual through testing. Further confirmation of the diagnosis can be also be performed by mutation analysis of the individual's DNA (Pomponio et al., 1997). The enzymatic testing can be performed when the diagnosis of multiple sclerosis is considered. This testing is irrelatively inexpensive, usually less than one hundred USD, and is performed by essentially all commercial laboratories. If the diagnosis of biotinidase deficiency is made, the individual can be treated immediately with pharmacological doses of biotin.

There is variability in the clinical presentation and findings of late-onset biotinidase deficiency and there is variability in the presentation and clinical findings in multiple sclerosis and related disorders. Biotinidase deficiency is a disorder due to mutations within a single gene, whereas the cause(s) of multiple sclerosis are, yet, unknown and are likely due to multiple etiologies. Nevertheless, there is considerable overlap of clinical features, even though some have been considered more typical of multiple sclerosis, such as segmental spinal cord lesions and oligoclonal bands. Many physicians still make the diagnosis of multiple sclerosis in the absence of these more distinctive features. The ophthalmological findings observed in late-onset biotinidase deficiency are also variable, may be the only feature or may be absent, yet they can occur in individuals diagnosed with multiple sclerosis or a related disorder. However, because the presentation symptoms of late-onset biotinidase deficiency are variable and most physicians are unaware of the phenotype of this disorder in adults or adolescents, the disorder is usually not included in the differential diagnosis of individuals thought to have multiple sclerosis. It would be a mistake to miss this diagnosis and fail to initiate biotin treatment in an individual with the enzyme deficiency. The testing for biotinidase deficiency can be performed while considering other more common, but less easily treatable, disorders. Individuals who exhibit clinical symptoms suggestive of multiple sclerosis or related disorders should have biotinidase deficiency excluded, especially if they fail to respond to known therapies.

4. Conclusion

Rapid recognition that an individual with myelopathy and/or neuropathy/vision loss has biotinidase deficiency will facilitate prompt treatment, thereby, increasing the possibility of complete recovery and avoidance of permanent neurological issues. The vision loss or scotomata are usually reversible. The spastic paraparesis are also usually reversible, but it can take weeks to months for near or complete resolution. It is important that biotinidase deficiency be included in the differential diagnosis of individuals with myelopathy and vision problems, because the disorder may be readily treatable before the symptoms are irreversible. If an individual is determined to have biotinidase deficiency, biotin treatment can be initiated immediately, thereby preventing misdiagnosis, a delay in instituting appropriate therapy and the possible development of irreversible clinical problems. Biotinidase deficiency should be tested in individuals thought to have multiple sclerosis or related disorders.

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