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# Biotinidase deficiency should be considered in individuals exhibiting myelopathy with or without and vision loss

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ABSTRACT

Multiple symptomatic children with biotinidase deficiency have exhibited spastic para- or tetraplegia due to myelopathy with and without vision loss. Although this has been a feature of what has been designated as delayed onset-biotinidase deficiency, myelopathy is likely also on the continuum of clinical features seen in younger children who have had these features attributed to dysfunction of the upper brain rather than of the spinal cord. Because many countries are still not screening their newborns for biotinidase deficiency, the disorder should be included in the differential diagnosis of individuals with myelopathic symptoms. Many of these children have gone weeks to months before they were correctly diagnosed with biotinidase deficiency. Rapid recognition that a child with myelopathy with and without vision loss has biotinidase deficiency will undoubtedly facilitate prompt treatment, increase the possibility of complete recovery and avoid potential residual permanent neurological damage. Newborn screening for biotinidase deficiency would avoid the delay in the diagnosis and treatment of individuals who otherwise may present with myelopathic or other neurological symptoms.



**Contents**



Since 1982, almost all individuals with the juvenile or late-onset form of multiple carboxylase deficiency have been shown to have biotinidase deficiency [1]. Biotinidase deficiency is an autosomal recessively inherited disorder in which the vitamin biotin is ineffectively recycled, resulting in secondary biotin deficiency which in turn causes multiple carboxylase deficiency [2,3]. Fortunately, the disorder can be effectively treated by administering these individuals' pharmacological doses of oral biotin. Although the symptoms can markedly improve, some, such as optic atrophy, hearing loss and some aspects of cognitive disabilities, may be irreversible. For this reason, newborn screening of biotinidase deficiency has been incorporated into the newborn screening programs of all the states in the United States and in many countries [4,5]. Outcome evidence supports that identification of children with the enzyme deficiency at birth and their treatment with biotin prior to the development of symptoms, does, in fact, prevent these children from developing symptoms [6,7].

There is, however, a disadvantage when there is a relatively short time from the discovery of a disorder to its incorporation into newborn screening programs; there is a lack of information about the long-term natural history of the disorder. Because there are still countries that have chosen not to screen their newborns for biotinidase deficiency,

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**Table 1**
Clinical, biochemical, molecular and imaging features of individuals with profound biotinidase deficiency exhibiting myelopathy (ordered by age of diagnosis).

| Age of first symptoms | Age of diagnosis | Neurological symptoms | Head MRI/CT | Spinal findings/MRI | EMG/NCV | Ophthalmological symptoms/VEP | Auditory/BAEP issues | Residual neurological damage after biotin therapy | Enzyme activity (units/ml serum) or % of mean normal | Mutation | Reference |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 16 months | 19 months | Hypotonia, proximal weakness, bulbar problems, stridor, swallowing issues, choking | N | Necrotizing lesions in posterior columns. Edema in white matter of the anterior columns. Astrocytosis in the anterior horns of cord. | NT | Finer pigmentation of the retinae, optic atrophy, abnormal VEP | NT | Died | Parents consistent with heterozygotes | NT | [11] |
| 22 months | 22 months | Spastic paresis, neuropathic bladder | ABN | Abnormal signal in the inferior brainstem and upper cervical, abnormal signal extending down through the medulla down to the spinal cord to the conus | N | Aptic atrophy/ABN VEP | ABN | Walking with residual speech and cognitive impairment and hearing loss | 0.5 | NT | [14] |
| 1 year | 3 years | Lethargy, fatigue, abnormal gait, hypotonia | NT | Medulla and cervical spinal edema and demyelination | NT | N | NT | Mild developmental delays | 0.1 | NT | [20] |
| 3 years | 3 years | Abnormal gait, fatigue, ascending weakness, hypotonia, decreased strength in the lower extremities, muscle atrophy, hyperreflexia, decreased responsive to pain and ankle clonus | ABN | Intramedullary nonenhancing cervicothoracic cord lesion and abnormal intensity in the cervicothoracic spinal cord | NT | Normal VEP | ABN | Residual spasticity in the lower limbs with improvement of spinal lesions | 0 | p.1339C>T; p.H447Y/ p.1339C>T; p.H447Y | [13] |
| 1 1/2 years | 3 years | Hypotonia, truncal and head titubations, dysmetria of the extremities, ataxia, brisk reflexes | NT | Diffuse abnormal signal in the white matter from the cervicomedullary junction to the conus and mild cervical cord enlargement. | N | NT | NT | Mild paraparesis | 0.09 | NT | [12] |
| 3 years | 3 years | Upper and lower extremity weakness, brisk reflexes, stridor | NT | Diffuse edema and abnormal signal between the cervicomedullary junction and the 5th thoracic vertebra. | NT | Normal VEP | NT | Improvement, but short-term follow-up | 0.13 | NT | [15] |
| 4 years | 4 years | Slurred speech, hyperventilation, difficulty walking, ataxia, spastic tetraparesis, brisk reflexes | N | Cervical spinal cord was enlarged with hyperintense central T2-weighted signal | NT | Conjunctivitis | ABN | Cervical spine normalized, but slight right arm weakness and brisk tendon reflexes, bilateral hearing loss | 0 | NT | [16] |
| 4 1/2 years | 4 1/2 years | Spastic paraparesis, motor weakness, ankle clonus, dyspnea | ? | Spinal cord edema, T2-hyperintensity of the posterior pons and medulla | NT | Normal optic disks | NT | Walked independently after 6 weeks and abnormal BAEP | 0% | NT | [18] |
| 5 years | 7 years | Abnormal gait, fatigue, quadraplegia, predominantly the lower extremities, no strength in the lower limbs, proximal upper | ABN | Hyperintensity of the dorsal brainstem and spinal cord to the lower thoracic vertebra | ABN | ABN | N | Residual spasticity | 6.8% | c.133C>T; p.H447Y/ c.133C>T; p.H447Y | [19] |