Adult-onset biotinidase deficiency

Biotinidase is the enzyme that recycles the water-soluble vitamin, biotin, which is the coenzyme for four carboxylases that are involved in gluconeogenesis, fatty acid synthesis, and in the catabolism of several branch-chain amino acids. Biotinidase deficiency (BD) is a rare (worldwide is incidence is 1:60,000), autosomal recessively inherited disorder. Individuals with profound BD usually exhibit symptoms during early childhood with neurological features, such as hypotonia, developmental delay, seizures, optic atrophy, hearing loss, and/or non-neurological findings, including metabolic acidosis, respiratory problems, alopecia, skin rash, that may progress to coma or death, if untreated.

In 2015, the first case of adult-onset BD (AOBD) was reported in a 22-year-old, French-born man. He had a progressive tetraparesis and bilateral optic neuropathy (ON). After 8 weeks, he was bedridden and nearly blind. MRI showed an extensive lesion of the spinal cord and optic nerve involvement. Exhaustive biological screenings were negative, but urinary organic acid analysis was suggestive of multiple carboxylase deficiency, and subsequent testing indicated that his serum biotinidase activity was markedly deficient. Oral biotin therapy was initiated and his condition improved. At his last follow-up examination, he was fully ambulatory, but he had marked visual impairment with visual acuity (VA) 20/200 in the right eye (OD) and 20/320 in the left eye (OS). More recently, we reported two other individuals, both born in France, with severe bilateral ON related to AOBD. The first was an 18-year-old man with a 7-month history of bilateral progressive severe visual loss (VA of both eyes was less than 20/200). He also had flaccid distal paraparesis of the legs. MRI of the brain and spine showed involvement of both optic nerves, chiasm and the anterior portion of the entire spinal cord and an electromyelogram demonstrated predominantly motor axonal polyneuropathy. The second individual, a previously healthy 25-year-old man, exhibited visual loss that deteriorated sequentially over four months. On admission, his VA was 20/200 OD and 20/32 OS. MRI showed involvement of both optic nerves. For these two individuals, biotinidase activity markedly decreased. Both individuals resolved their symptoms with oral biotin.

BD is a severe disease and when symptoms occur, delays in diagnosis and treatment may result in irreversible neurological disability. If the disorder is treated before symptoms develop, the symptoms can be prevented. Because of this, neonatal screening for BD is performed in multiple countries around the world, with the notable exceptions of France and the United Kingdom. Consequently, symptomatic individuals with BD are regularly described in countries that do not screen their newborns. It is likely that this rare disorder is not well recognized. Therefore, it is likely underdiagnosed in these countries, especially in adults, and in countries that do screen their newborns, but the adults were not screened. Genetic variability, residual biotinidase activity, and/or dietary differences may explain why some individuals with profound BD do not exhibit symptoms until adulthood. These recently reported French cases support the inclusion of BD into the newborn screening program in our country.

In conclusion, physicians must have a heightened awareness about BD in adults and its

association with bilateral ON and/or extensive myelopathy. Determination of serum biotinidase activity is simple and definitive. Oral biotin is an inexpensive therapy, with no known side effects and is highly effective when initiated early. BD should be including in newborn screening programs to identify affected infants so they can be treated with biotin and the clinical problems associated with the disorder, as children or adults, can be prevented.

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