CASE REPORT

Biotinidase Deficiency, Bilateral Optic Atrophy, and a Visual Field Defect

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ABSTRACT

We present an update on the ophthalmic status of a female patient with biotinidase deficiency who has attended our clinic for over 30 years. She is the only reported case of juvenile-onset glaucoma associated with biotinidase deficiency. Her intraocular pressure, optic nerve appearance, and visual field defect have, however, remained stable throughout her follow-up. We feel that this patient's visual field defect is a result of optic atrophy due to biotinidase deficiency in early life rather than glaucomatous damage.

Keywords: Biotinidase deficiency, juvenile-onset glaucoma, optic atrophy

CASE REPORT

A 39-year-old lady with a diagnosis of biotinidase deficiency has attended our ophthalmic clinic from the age of 6 years. She was the first child of second cousins who was born at full term by normal delivery, weighing 3300 g. Her development was deemed normal in early infancy, but at aged 5 months she was treated for a respiratory tract infection and her parents noted that her respiratory rate was increased. At 8 months she developed weakness and floppiness. On examination she was found to be profoundly hypotonic. She was also noted to have rolling eye movements at that time. Her arterial blood gas was found to be acidotic with a pH of 7.43, pointing to a metabolic cause for her condition. Analysis of her urine found elevated amounts of breakdown products of leucine. This was initially thought to be due to impaired activity of 3-methylcrotonyl coenzyme A carboxylase, but some years later she was found to have undetectable biotinidase activity. She was treated with a daily dose of 10 mg of biotin. Within 1 week her respiratory rate had normalised and her hypotonia had significantly improved.¹ At aged 2½ years she was found to have delayed speech and profound neurosensory deafness.

At 6 years she was found to have decreased vision with Snellen acuities of 6/24 in the right eye and 6/36 in the left eye. She was documented to have atrophic optic nerves bilaterally (Figure 1). Her intraocular pressure was measured to be slightly elevated at 27 mm Hg in both eyes on two occasions with Perkins tonometry under ketamine anaesthesia. As her optic nerves were already damaged, their appearance could not be used to assess progression to glaucoma, so she proceeded to have bilateral nasal goniotomies and a right trabeculectomy to ensure her intraocular pressure was within normal range. Her pressures quickly stabilised at less than 18 mm Hg in both eyes and have been checked at least yearly since then. At 9 years of age she was documented to have a bitemporal hemianopia on confrontational testing. She began doing 24/2 Humphrey visual field testing at the age of 27 and this has demonstrated 12 years of no objective change (Figure 2). Her pituitary fossa was found to be normal on neuroimaging. Her most recent refraction was right: +1.50/−0.50 × 180, left: +2.00/−0.50 × 180. The appearance of her optic nerve, visual acuity, intraocular pressure, and field defect has remained stable for over 30 years.

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FIGURE 1 Right and left optic nerves showing generalised atrophy, a large cup but no focal thinning or notching at the age of 36.

FIGURE 2 (A) Left and right 24/2 Humphrey visual field done at the age of 27 showing bitemporal hemianopia. (B) Left and right 24/2 Humphrey visual field done at the age of 39 showing no progression of visual field defect.

DISCUSSION

The incidence of biotinidase deficiency is 1 in 60,000.² Biotin is a water-soluble B complex vitamin and is a coenzyme in carboxylation and is essential in gluconeogenesis and fatty acid and branched-chain amino acids synthesis. Biotinidase breaks down biocytin to free biotin and lysine. If biotin is not recycled, it results in deficient activities in the biotin-dependant carboxylases, causing an accumulation of abnormal quantities of organic acids. This results in keto and lactic acidosis and hyperammonaemia. Individuals with biotinidase deficiency can only use a molecule of biotin once, as it cannot be recycled. Biotinidase deficiency is inherited in an autosomal recessive pattern. The gene *BTD* that encodes for biotinidase is located on chromosome 3p25. Over 140 mutations have been found in the *BTD* gene.

Children with profound biotinidase deficiency (enzyme activity of less than 10%) usually present between 2 and 5 months of age with hypotonia, seizures, rash, and alopecia. If untreated, patients may develop severe metabolic acidosis, which can result in coma and death. Some may also have developmental delay, hearing loss, and optic atrophy. Although the hypotonia recovers quickly once biotin replacement is started, hearing loss, optic atrophy and developmental delay usually does not improve. There is a great variation in the phenotype. Those with partial biotinidase deficiency (10–30% enzyme function) usually only develop signs during times of metabolic stress, such as infection. Biotinidase deficiency is currently not part of neonatal screening in the United Kingdom but is screened in some states in the United States and in some European countries.

Salbert et al. reviewed the ophthalmic findings in 78 symptomatic children with profound biotinidase deficiency.³ Half of patients had ophthalmic findings. The most common association was eye infections, including conjunctivitis, blepharitis, fungal infections, and corneal ulceration (30%). Optic atrophy was found in 19% and ocular motility abnormalities, including nystagmus and strabismus, in 12%. Our case is the only reported association of juvenile-onset glaucoma in the literature. The retinal ganglion

cells are particularly sensitive to intracellular metabolic defects because of their long course and high energy demands. Defects in energy metabolism can result in decreased myelin production, cell death, and ultimately optic atrophy.⁴ Optic atrophy is felt to be non-reversible, particularly in profound biotinidase deficiency, resulting in lifelong decreased vision and visual field defects. Caeco-central and peripheral scotoma have been previously described in optic atrophy associated with biotinidase deficiency.⁵ Bitemporal hemianopia has not been reported previously in biotinidase deficiency but has been documented in other causes of optic atrophy.⁶

In the authors' opinion, the patient's stable bitemporal hemianopia is due to optic atrophy caused by biotinidase deficiency early in life and not glaucoma as previously suggested. This case highlights the importance of ophthalmic review of such patients and early commencement of treatment to prevent permanent loss of vision.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

Note: Figure 1 of this case report appears in colour online at informahealthcare.com/oph.

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