Case Report

Biotinidase Deficiency in the Second Decade with Atypical Neuroimaging Findings

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Abstract

Biotinidase deficiency is a rare autosomal recessive neurometabolic disorder resulting in biotin deficiency. Our patient presented with seizures and developmental delay since infancy and was started on megavitamin supplements. At 14 years, she presented with motor regression with encephalopathy after discontinuation of vitamins. There were no skin and hair changes. Magnetic resonance imaging (MRI) of the brain showed bilateral symmetrical posterior putamen signal changes. Tandem mass spectroscopy showed increased methyl malonyl carnitine and 3-OH isovaleryl carnitine. There was a low biotinidase level, and a pathogenic variant in the *BTD* gene in the next-generation sequencing was identified. Special importance is placed on the unusual symmetric posterior putamen involvement seen in MRI of the brain.

Keywords: Biotin, biotinidase deficiency, BTD gene variants, enzyme activity, neonatal screening

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Introduction

Biotinidase deficiency is a rare genetic disorder inherited in an autosomal recessive fashion. It is caused due to the deficiency of the enzyme biotinidase. The resulting biotin deficiency leads to reduced activity of multiple carboxylase enzymes. The incidence is estimated to be about 1 in 60,000.[1] It presents with developmental delay, ataxia, and seizures. Hair and skin changes like alopecia, atopic dermatitis, and eczema are commonly seen. Some patients develop long-term complications such as hearing loss and optic atrophy. Neuroimaging usually shows cerebral atrophy and patchy signal in cerebral white matter. The symmetric involvement of posterior putamen as seen in this case is unusual, hence, we are reporting this atypical case.

Case Report

A 14-year-old girl born to third-degree consanguineous marriage with a normal birth history presented with global developmental delay and seizures. The child had the first episode of seizure at two months of age. At nine months of age, she was admitted with an episode of metabolic acidosis. Tandem mass spectrometry had shown elevated methyl malonyl carnitine and 3-OH isovaleryl carnitine. She was on carnitine, vitamin-B12, and biotin on and off. She has poor cognition, difficulty in daily activities, poor school performance, and visual difficulty. She developed motor regression with unable to walk, lethargy, and drowsiness for the past six months after discontinuation of megavitamins.

On examination, the weight of 43 kg, and head circumference of 49 cm. Neurological examination showed a Glasgow coma scale of 12/15, dystonia [Figure 1a], depressed deep tendon reflexes in bilateral lower limbs, strabismus [Figure 1b], and optic atrophy. Arterial blood gas analysis showed pH of 7.34, serum bicarbonate of 11.5 mEq/L, pCO_2 of 15.8 mmHg, and base excess of −9.1 mmol/L indicative of compensated

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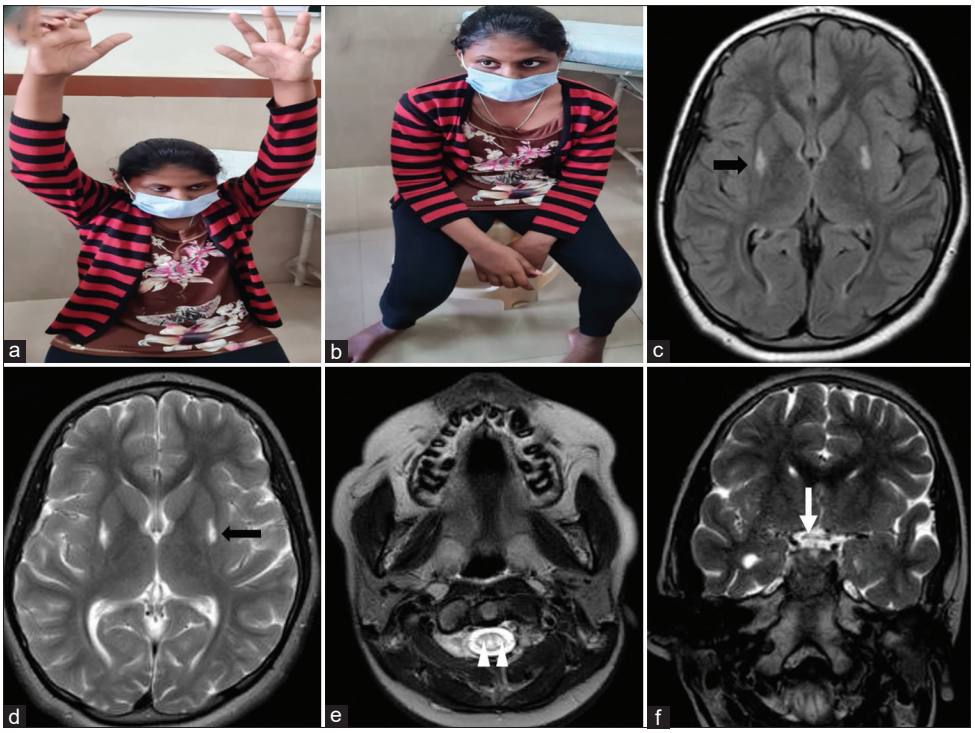

Figure 1: Clinical picture showing dystonia in the bilateral upper limbs (a), and strabismus (b). MRI of the brain showing, symmetrical hyperintense areas in bilateral posterior putamen (arrows-c) on FLAIR, T2 Weighted sequences (arrows -d), hyperintense areas in the upper cervical spinal cord suggestive of myelomalacia (arrowheads-e) in axial T2 W images, thinning of optic chiasma with hyperintensity suggesting atrophy (arrow- f)

metabolic acidosis. The serum lactate of 41.98 mg/dL (normal: 4.5–19.8 mg/dL) and Vitamin B12 of more than 2,000 pg/mL (normal: 160–950 pg/mL) levels were increased. Magnetic resonance imaging (MRI) of the brain revealed symmetric posterior putamen changes [Figure 1c] on FLAIR, T2-weighted sequences [Figure 1d], hyperintense areas in the upper cervical spinal cord suggestive of myelomalacia [Figure 1e] in axial T2 W images, thinning of optic chiasma with hyperintensity suggesting atrophy [Figure 1f]. The biotinidase enzyme levels were low at −5.03 units (normal ≥40 units). Whole-exome sequencing detected a pathogenic variant of the *BTD* gene (ENST00000643237.3): c.1553G>A(p. Arg518His) in exon 4 in the homozygous state. The child was started on biotin tablets of 20 mg per day and is improving on follow-up after three months.

Discussion

We describe an adolescent girl with infantile-onset global developmental delay with adolescent-onset motor regression and encephalopathy without unique involvement of posterior putamen in neuroimaging.

Karimzadeh *et al.*,[2] studied 16 patients with 10 showing cutaneous manifestations, 8 having alopecia, and 12 patients having abnormal neuroimaging with one patient having abnormal signal changes in basal ganglia. Desai *et al.*,[3] studied 4 patients, all of whom had hypopigmentation, sparse hair, and abnormal brain MRI with one showing focal hyperintense lesion in bilateral caudate nuclei, and the caudothalamic groove involvement. Fallah *et al.*,[4] reported severe degeneration of the putamen and caudate nucleus in a 10-year-old girl. Sweeney *et al.*,[5] studied two cases, one showed sparse hair and the other had no skin or hair changes. MRI showed symmetrical involvement of the medial thalamus and extending caudally into the tectum and periaqueductal grey in one and medial thalamic nuclei in the second patient. Schulz *et al.*,[6] reported a case of basal ganglia calcification in biotinidase deficiency. Bousounis *et al.*,[7] reported gradual hair loss in one patient and extensive eczema in the other with both showing diffuse brain atrophy. Viyannan *et al.*,[8] reported skin peeling, alopecia, and loss of brain volume with symmetric involvement of frontoparietal regions, cerebellar white matter, and vermis. Gowda *et al.*,[9] found a 6-year-old with skin changes and alopecia with MRI brain showing changes in periaqueductal Gray, dorsal midbrain, pons and medulla, and cervical spinal cord. Gowda *et al.*,[10] in a retrospective review of diagnosed cases of BD showed partial alopecia, subtle dermatitis with demyelinating leukoencephalopathy, and subcortical cysts on MRI in three infants. Our case has no skin and hair changes probably due to the child being on biotin treatment earlier. MRI changes of posterior putamen involvement alone have not been described in the literature.

The variant is a nonsynonymous variant c.1553G>A which causes a change in amino acid from arginine to histidine at position 518 in the BTD protein sequence. According to ACMG criteria[11] for variant classification, the variant fulfills the following criteria, PS1 – same amino acid change

reported as pathogenic, PM1 – mutation in a hot spot region of a gene, PM2 – absent in population database (gnomAD) in the homozygous state, PP3 – multiple computational tools like MutationTaster, SIFT, and PolyPhen-2 predict the variant to be damaging, PP5 – The variant is reported as Pathogenic in ClinVar ID VCV000025099.6.[12] Hence, the variant in the current case can be classified as likely pathogenic. MutationTaster predicts the variant to be disease causing.[13]

Conclusion

Biotinidase deficiency should be considered even in the second decade of life with unusual bilateral putamen signal changes in the MRI of the brain.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the legal guardian has given his consent for images and other clinical information to be reported in the journal. The guardian understands that names and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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