Congenital biotinidase deficiency - MRI findings in two cases

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Abstract

Congenital biotinidase deficiency is a rare inborn error of metabolism that most commonly presents in infantile age group. Diffusion changes on magnetic resonance imaging (MRI) are sparsely described in the literature. We are presenting diffusion-weighted MRI findings in two confirmed cases of congenital biotinidase deficiency in infantile age group with review of literature.

Key words: Biotinidase deficiency; developmental delay; neurometabolic disorder; seizures

Introduction

Congenital biotinidase deficiency is one of the rare congenital neurometabolic disorders with autosomal recessive inheritance. Early diagnosis is key to prevention of clinical manifestations including mental and physical developmental delay. These cases usually present in infantile age group with signs and symptoms which are common to multiple other inborn errors of metabolism. Therefore, magnetic resonance imaging (MRI) plays an important role in establishing the diagnosis which is confirmed by biochemical assay. Sporadic cases of congenital biotinidase deficiency have been reported in literature with most of reports showing brain atrophy and delayed myelination as imaging findings. Here, we are presenting MRI findings in two proven cases of biotinidase deficiency, including findings other than brain atrophy and delayed myelination.

Case 1

A 5-month-old male child, first born baby of consanguineous marriage, presented with failure to thrive, alopecia, and multiple episodes of generalized tonic–clonic seizures. His milestones were delayed and neck holding was still absent. His routine blood investigations were within normal limit. MRI brain (noncontrast) was done which revealed extensive areas of restricted diffusion seen as hyperintensity on diffusion-weighted images (with increasing brightness on higher b-value) and low signal intensity on apparent diffusion coefficient, in bilateral cerebral white matter – in periventricular location extending along pyramidal tracts in bilateral cerebral peduncles [Figures 1A-C, 2, and 3]. There was involvement of central tegmental tracts, posterior limb of internal capsule, splenium of corpus callosum, and pyramidal tracts in brain stem [Figures 1A-C, 2, and 3]. Periventricular cerebellar white matter and middle cerebellar peduncles were also involved [Figure 2]. Medial temporal lobe, optic radiation, and parahippocampal region were also involved. Delayed myelination was noted with mild cerebral atrophy especially in bilateral frontal lobes. The areas of restricted diffusion revealed T2 and FLAIR hyperintense signal [Figure 1]. Based on these findings, possibility of inborn error of metabolism was raised and...
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Differential diagnosis of maple syrup urine disease (MSUD) and biotinidase deficiency was given, although age of presentation of patient was older for MSUD. His urine examination was negative for MSUD. Biochemical assay of blood revealed congenital biotinidase deficiency.

Case 2
Another 7-month-old female child, first baby of nonconsanguineous marriage, presented with seizure, hypotonia, and neurodevelopmental delay. Her milestones were delayed and neck holding was still incomplete. Her routine blood investigations were within normal limits. Noncontrast MRI brain revealed similar changes in T2 and FLAIR hyperintense signal with restricted diffusion as seen in case 1, but involvement of periventricular cerebral white matter and splenium of corpus callosum was less marked, with noninvolvement of cerebellar white matter [Figures 4 and 5]. Delayed myelination was also noted with more prominent cerebral atrophy especially involving frontal lobes. Biochemical assay of blood was positive for biotinidase deficiency.

Discussion
Biotin is an important vitamin found in some foods. It plays an important role as cofactor for pyruvate, propionyl-CoA, beta-methylcrotonyl-CoA, and two isoenzymes of acetyl-CoA carboxylase in gluconeogenesis, amino acid metabolism, and fatty acid synthesis.[1]

Biotinidase deficiency is a rare and treatable inherited neurometabolic disorder[2] with an estimated incidence of 1:61,067 population. This disorder in its severe form is much rarer with incidence of 1:1,37,401.[3] Clinical findings of this disorder include neurological (seizure, ataxia, hypotonia, neurodevelopmental delay), dermatological (eczematous skin rash, seborrheic dermatitis), immunological, ophthalmological, respiratory...
problems (hyperventilation, apnea and laryngeal stridor), and alopecia.\textsuperscript{[1,4]} Laboratory findings include abnormal organic acids in the urine, metabolic acidosis, and elevated lactate and pyruvate levels in blood. Diagnosis can be confirmed by measuring blood biotinidase activity.\textsuperscript{[5,6]}

Most of the literature have reported MRI findings in biotinidase deficiency as cerebral atrophy, cerebral edema, and bilateral compensatory ventriculomegaly.\textsuperscript{[4]} Apart from it, delayed myelination has also been reported. But these changes are seen late in the course of disease, and there are few reports of imaging studies in biotinidase deficiency in early stage. In late course of disease, MRI shows loss of brain volume, with increased ventricular size and increased subarachnoid spaces. Subdural hygromas or hematomas may also develop.\textsuperscript{[7]} T1- and T2-weighted images show delayed myelination, with reduced diffusion and increased fractional anisotropy in the deep white matter of the cerebral hemispheres.\textsuperscript{[6]} One report suggests that uncommonly, cortical injury may occur.\textsuperscript{[7]} Proton magnetic resonance spectroscopy (MRS) at long and intermediate (135
In Leigh’s syndrome, involvement of grey matter nuclei is more marked when compared with white matter tract involvement. Also, diffusion restriction is less marked in Leigh’s syndrome when compared with biotinidase deficiency and seen predominantly during acute phase.\(^{(13,14)}\)

**Conclusion**

Biotinidase deficiency is a rare neurometabolic disorder that has clinical features common to other inborn errors of metabolism. In addition to findings of delayed myelination and brain atrophy, diffusion-weighted MRI findings as seen in our cases and few other previous case series would be helpful in early diagnosis of disease and thus early institution of treatment leading to prevention of devastating clinical manifestations.

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**Declaration of patient consent**

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

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**Conflicts of interest**

There are no conflicts of interest.
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