Longitudinally Extensive Transverse Myelitis with Optic Neuritis Related to Profound Biotinidase Deficiency: NMOSD Mimic!

Dear Sir,

Biotinidase deficiency is an autosomal recessively inherited neurocutaneous disorder with a wide spectrum of clinical manifestations due to defects in biotin metabolism. It can be classified as profound (<10% of normal) or partial deficiency (10 to 30% of normal).[1] Biotin is essential for energy metabolism in various enzymes including pyruvate carboxylase, acetyl-CoA carboxylase, propionyl-CoA carboxylase, and 3-methylcrotonyl CoA-carboxylase enzymes. Clinical manifestations vary based on the deficiency degree and age of onset. Patients with profound deficiency show developmental delay, seizures, ataxia, and more. Late onset cases have progressive optic atrophy and spastic paraparesis. Associated symptoms include diaper rash, alopecia, and eczema. Respiratory issues can occur in early onset patients.[1] These constellations of symptoms can mimic neuromyelitis optic spectrum disorder (NMOSD), predisposing to misdiagnosis. Herein, we report a rare case of adolescent onset biotinidase deficiency presenting as longitudinally extensive transverse myelitis (LETM) with optic neuritis mimicking NMOSD.

A 9-year-old boy, developmentally age-appropriate, presented with subacute onset bladder symptoms manifesting as urinary frequency and urgency of 2 months duration, followed 15 days later by sequential weakness of both lower limbs (right then left), and subsequent buckling and falls. This was followed 10 days later by bilateral upper limb weakness. Additionally, he had numbness up to the mid-truncal level. Thereafter, he developed subacute onset bilateral painless loss of vision. There was relentless progression of symptoms from onset, with accumulating deficits till the time of presentation, in the form of complete paraparesis, painful urinary retention, and visual perception of light. On examination, he had fluctuating blood pressures. Visual acuity at admission was perception of light, and disc pallor was noted on fundoscopy. Motor system examination

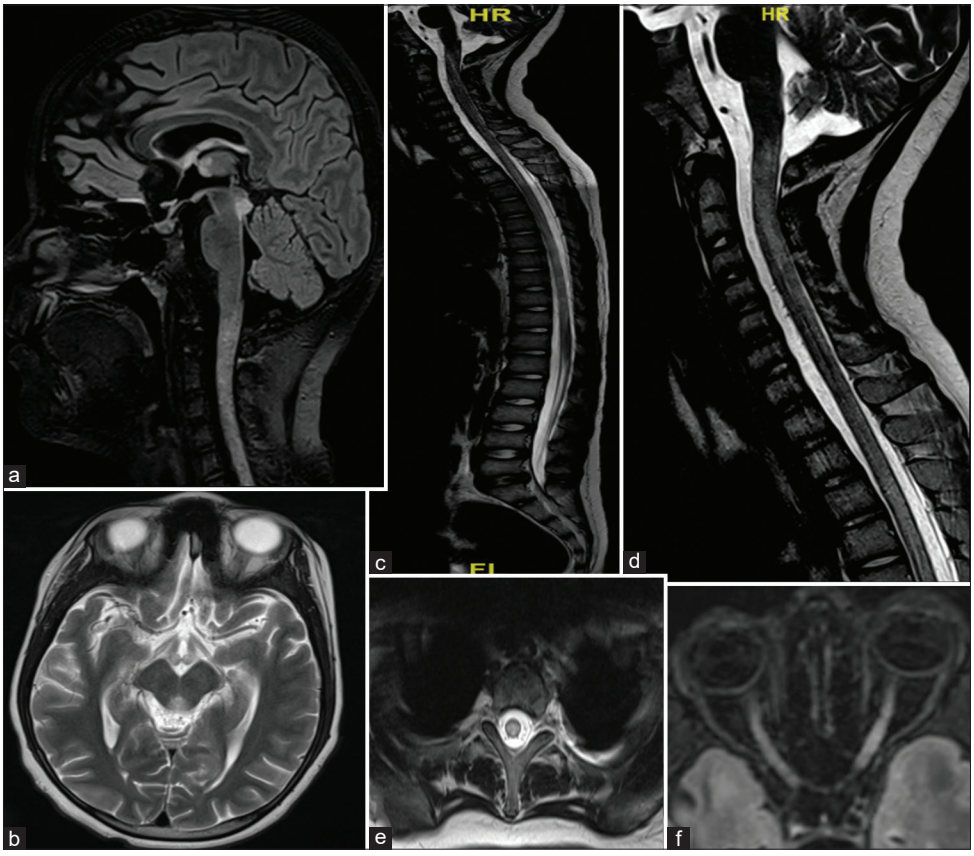

Figure 1: (a) T2 FLAIR sagittal brain image showing hyperintensity involving the body and crus of the fornix and dorsal midbrain. (b) T2 axial brain showing signal changes in the periaqueductal grey matter, mammillary bodies. (c, d) T2 spine sagittal image showing diffuse long segmental hyperintensity in the spinal cord extending from cervico-medullay junction to conus level involving dorsal and lateral columns. (e) T2 axial image showing hyperintensity in the spinal cord involving dorsal and lateral columns. (f) T2 FLAIR axial image of optic nerve cuts showing left optic nerve hyperintensity

Table 1: Review of literature of case reports biotinidase deficiency mimicking neuromyelitis optica

Study	Age/Sex	Clinical presentation	Brain MRI	Spine MRI	Other relevant investigations	Treatment	Variant details	Mutation type/ inheritance	Prognosis
Nasehi *et al.* 2022[2]	6 yr 10 m/F	Recurrent URTI, gradual LoV, subacute flaccid quadriparesis	NA	LETM C2-C5	Serum MOG/NMO negative. CSF- lactate elevation. TMS- profound biotinidase deficiency	Plasma exchange – ten courses : No response T. Biotin 20 mg/day	BTD: c. 838A>C; p.Asn280His	Missense/Hom	At 2 months, patient attained independent ambulation. Visual acuity improved partially in both eyes
Bilge *et al.* 2020[7]	20 yr/F	Numbness and weakness BL UL, LL; inability to walk within 15 days, LoV and SNHL from 1 year of age. Total alopecia at 12 years age	T2-FLAIR showed hyperintensity involving medulla, peri-ependymal regions at the level of 4th ventricle, PAG, AC, and BL mammillary bodies.	NA	Anti-NMO and Serum anti-MOG were negative. Profound biotinidase deficiency	IVMP 1 gm/day T. Biotin 50 mg/day	BTD: c. 1612C>T (p.R538C)	Missense/Hom	Dysautonomia, sepsis, and death after 6 days of admission
Shah *et al.* 2020[8]	26 month/F	Developmental delay, irritability, torticollis, and ataxia	BL symmetric optic neuritis and BL mammillary bodies, dorsal medulla, and area postrema.	LETM dorsal medulla to C7.	Serum Ani-MOG and NMO-negative. Profound biotinidase deficiency on DBS	IVMP 30 mg/kg IVIG 2 gm/kg+oral steroids T. Biotin 10 mg TDS	BTD: c. 1612C>T	Missense/Het	Neurodevelopmental profile was normal after 9 months of treatment
Yilmaz *et al.* 2017[9]	14 yr/M	Rapidly progressive LoV, diplopia, and right Ul weakness for 2 weeks. Horizontal nystagmus, optic atrophy with 3/5 power in right UL	BL symmetric T2 hyperintensity with contrast enhancement of BL optic nerve, optic chiasm, and tectal plate	LETM C1 to C6	Biotinidase enzyme activity was 8%	IVMP T. Biotin 10 mg/day	BTD: c. 98-104delinsTCC; p.V457M	NA	At 3 months of biotin replacement therapy, the control cranial MRI of the case demonstrated a complete regression of the lesions
Girard *et al.* 2016[3]	8 yr/F	ON associated with three episodes of LETM	Hyperintensity involving medulla, optic nerves, and mamillary bodies	LETM from bulb to D10 level	NMO and MOG. Increased CSF lactate levels, C5-OH acylcarnitine elevation	Refractory to corticosteroids, plasmapheresis, and rituximab. T. Biotin 15 mg OD	BTD: c. 643C>T; p.L215F and BTD: c. 1612C>T; p.R538C	Missense/ Compound heterozygous	At 20-month follow-up complete clinical recovery without any relapses
Bottin *et al.* 2015[4]	22 yr/M	Rapidly evolved spasticity pf BL UL and LL, erectile dysfunction and LoV and optic atrophy	T2-FLAIR hyperintensity of fornix, mammillary body, and optic nerve.	LETM cervico-medullary region to D12	CSF- lactate elevated. Negative for NMO and MOG. ^{18}F-FDG PET- increased uptake in spinal cord and optic nerves TMS- multiple carboxylase and biotinidase deficiency	10 days IVMP, seven cycles of plasma exchange T. Biotin 20 mg/day to 300 mg/day	BTD: c. 1316C>A; p.Ala439Asp	Missense/Hom	6 months follow-up: able to walk, but with residual LL spasticity

Contd...

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Santaro *et al.* 2020[10]	13 yr/F	Simultaneous paraparesis and BL Lov	MRI brain – optic nerve hyperintensity.	C3-C7 LETM	Negative for NMO/ MOG with normal CSF lactate Profound biotinidase enzyme activity deficiency	IVMP but patient worsened. T. Biotin 100 mg/ day	BTD: c. 1330G>C (p. A444H)	Missense/Hom	Improvement in the paresis and vision without any relapses
Kasinathan *et al.* 2019[5]	4 yr/M	Rapidly progressive quadriparesis with painless BL LoV, ataxia, and slurred speech	Optic nerve Hyperintensities	Dorsal pons to thoracic level LETM.	Negative for NMO/ MOG. Biotinidase enzyme assay showed severely impaired enzyme activity (0.64 nmol/ml/min)	Pulse steroids, seven cycles of plasmapheresis, and Inj.Rituximab – no response oral biotin supplementation	BTD: c. 98_104 del GCGGCTGinsTCC	Deletion/Hom	Patient's 28-month-old sister had breathing difficulty with ataxia. Showed biotinidase deficiency. Both were improved after oral biotin supplementation

AC=Anterior commissure, BL bilateral, DBS=dried blood spot, Hom=homozygous, LETM=longitudinally extensive transverse myelitis, LL=lower limb, LoV=loss of vision, MOG=myelin oligodendrocyte, NA=Not available, NMO=neuromyelitis optica, ON=optic neuritis, PAG=periaqueductal grey, UL=upper limb, URTI=upper respiratory tract infection, SNHL=Sensorineural hearing loss, IVMP=Intravenous methylprednisolone

showed spastic quadriparesis (medical research council power scores in upper limb: 1/5, elbow: 2/5, wrist: 1/5 and 0/5 across all joints of lower limbs). There was global hyperreflexia, extensor plantar response, and pan-sensory loss up to the level of C3. The modified Rankin score (mRS) was 5 at admission. The clinical possibility of longitudinally extensive holocord syndrome with bilateral optic neuritis and dysautonomia was considered, secondary to a demyelination, infective, nutritional, or metabolic etiology.

On investigations, his complete hemogram, renal and liver function tests, vitamin B12, homocysteine, folate, antinuclear antibody profile (ANA) and antinuclear cytoplasmic antibody (ANCA) panel, thyroid function tests, serum ammonia, and lactate were normal. Primary demyelination work-up for anti-aquaporin-4 (NMO) IgG antibodies and anti-myelin oligodendrocyte glycoprotein (MOG) antibodies were negative. Spine and brain MRI revealed LETM with holocord involvement from cervico-medullary junction till the conus with hyperintensities involving bilateral optic nerve. Signal changes were additionally seen in the bilateral mammillary bodies, periaqueductal grey, dorsal midbrain, fornix, tectal plate, and left optic nerve [Figure 1]. Cerebrospinal fluid (CSF) analysis showed 15 cells/mm^3 (lymphocyte predominant), normal glucose, protein levels (53 mg/dL), and elevated lactate (80 mg/dL). Infective workups for tuberculosis, herpes simplex virus, brucella, neurosyphilis, and fungal etiologies were negative. Oligoclonal bands were detected in CSF. Screening for inborn error of metabolism by Tandem mass spectroscopy showed mild elevation in propionylcarnitine (C3) and methylmalonylcarnitine/3-OH-hexanoylcarnitine (C5-DC/ C6OH) levels. Visual evoked potentials and lower limb somatosensory evoked potentials were absent, whereas brainstem auditory evoked response was normal. Serum biotinidase levels were 0.52 nmol/min/ml (normal range: >5 nmol/min/ml).

Mutation analysis of whole exome sequencing showed compound heterozygous variants in the *BTD* gene. One of the variants had mutation in 3' splice site region at intron 3 (chr3:g. 15635423G>A; Depth: 140x) affecting the invariant AG acceptor splice site of exon 3(c. 51-1 G > A; ENST00000672112.1). The other was a heterozygous 6 base pair deletion in exon 4 of the *BTD* gene (chr3:g. 15635477_15635483delinsTCC; Depth: 187x) resulting in a frameshift and premature truncation of the protein 36 amino acids downstream to codon 35 (p.Cys35PhefsTer36; ENST00000672112.1). This gene was classified as pathogenic based on the guidelines of the American College of Medical Genetics and Genomics (ACMG). Subsequently, the variants were identified as novel based on mutation databases (ClinVar; https://www.ncbi.nlm.nih.gov/ clinvar/?term = BTD) and literature curation.

Patient was treated outside with parenteral course of methylprednisolone at a dose of 1 gm/day for 5 days and

intravenous immunoglobulin (IVIg) at 0.4 mg/kg/day for 5 days. At our institution, prior to the availability of biotinidase test results, he was treated with small volume plasmapheresis for 10 days. Other therapies comprised antihypertensives, hydroxocobalamin injection, folinic acid, and high dose of biotin (200 mg/day). At 6 months and 1 year follow-up, patient was able to walk with support and his mRS improved to 3. Visual assessment showed improvement from the perception of light to 20/200. His blood pressure was normalized in last follow-up, and antihypertensives were stopped.

Discussion

The incidence of biotinidase deficiency ranges from 1:40,000 to 60,000 worldwide.[1] Biotin, formed from biocytin by the action of biotinidase, is a cofactor of multiple carboxylase enzymes (gluconeogenesis pathway), fatty acid synthesis, and organic acid metabolism. Previous studies have highlighted on the challenges to diagnose this entity. All patients had received rescue therapy in the lines of management for demyelination disorders, and some had received higher forms of immunomodulation including rituximab prior to diagnosis.[2-5] Previous studies have highlighted on key pointers including cutaneous manifestations, hearing impairment, elevated CSF lactate levels, acylcarnitine levels, and radiologic features of fornix and mamillary body involvement [Table 1].[2-10] It is important to be aware of the differential, which is particularly relevant in the Indian context where there is no universal national screening program for diagnosing biotinidase deficiency in the neonatal stage. Our case illustrates the importance of having a high index of suspicion for biotinidase deficiency in a pediatric patient presenting with LETM and optic neuritis, with a progressive course, negative serology for demyelinating disorders, high CSF lactate levels, and characteristic MRI findings of hyperintensity involving the fornix, mamillary bodies, and dorsal midbrain. To the best of our knowledge, this is the second case report of biotinidase deficiency mimicking NMOSD from India. Unlike the previous case, our patient had characteristic MRI findings considered to be hallmark for the disease.[5] In addition, the variant identified in our patient has not been previously described in the literature. It is important to be aware regarding this differential in cases with otherwise unexplained optico-myelopathy.

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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References

1. Canda E, Kalkan Uçar S, Çoker M. Biotinidase deficiency: Prevalence, impact and management strategies. Pediatr Health Med Ther 2020;11:127-33.
2. Nasehi M, Karimzadeh P, Tabrizi A, Babaei M. A girl with myelopathy and vision loss, misdiagnosis as NMOSD: The first Iranian case: Report on biotinidase deficiency. Iran J Pediatr 2022;32:e120498.
3. Girard B, Bonnemains C, Schmitt E, Raffo E, Bilbault C. Biotinidase deficiency mimicking neuromyelitis optica beginning at the age of 4: A treatable disease. Mult Scler 2017;23:119-22.
4. Bottin L, Prud'hon S, Guey S, Giannesini C, Wolf B, Pindolia K, *et al*. Biotinidase deficiency mimicking neuromyelitis optica: Initially exhibiting symptoms in adulthood. Mult Scler 2015;21:1604-7.
5. Kasinathan A, Suthar R, Vyas S, Saini AG, Sankhyan N, Attri S. Subacute myelopathy: Think beyond neuromyelitis optica spectrum disorder. Ann Indian Acad Neurol 2019;22:541-2.
6. Wolf B. Biotinidase deficiency should be considered in individuals exhibiting myelopathy with or without and vision loss. Mol Genet Metab 2015;116:113-8.
7. Bilge N, Yevgi R. Biotinidase deficiency in differential diagnosis of neuromyelitis optica spectrum disorder. Mult Scler Relat Disord 2020;44:102280.
8. Shah S, Khan N, Lakshmanan R, Lewis B, Nagarajan L. Biotinidase deficiency presenting as Neuromyelitis Optica Spectrum Disorder. Brain Dev 2020;42:762-6.
9. Yilmaz S, Serin M, Canda E, Eraslan C, Tekin H, Ucar SK, *et al*. A treatable cause of myelopathy and vision loss mimicking neuromyelitis optica spectrum disorder: Late-onset biotinidase deficiency. Metab Brain Dis 2017;32:675-8.
10. Santoro JD, Paulsen KC. Biotinidase deficiency as a mimic of neuromyelitis optica spectrum disorder in childhood. JAMA Neurol 2020;78:118-20.

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