Subacute Myelopathy: Think Beyond Neuromyelitis Optica Spectrum Disorder

Sir,

A 4-year-old boy presented with a 3-week history of rapidly progressive weakness involving the lower limbs followed by upper limbs and bilateral painless visual loss. His symptoms had begun 8 months ago when he had fever followed by acute-onset hearing loss. He was treated with high-dose steroids, resulting in partial recovery. Five months later, he had fever followed by acute ataxia. He was again treated with intravenous steroids, resulting in complete recovery. His current hospitalization was for increasing unsteadiness, clumsiness while walking, slurring of speech, and irritability. He had become bed-bound. The current episode was preceded by a self-limiting febrile illness.

On examination, he was irritable, dysarthric, and had a peculiar abnormal deep sighing respiration. Visual acuity was 20/200, with poor contrast sensitivity. His fundus examination was normal. He had generalized spasticity with bipyramidal signs. He was unable to turnover or sit, but was able to communicate his needs.

A magnetic resonance imaging (MRI) scan of spinal cord revealed contiguous T2 hyperintensity, extending from dorsal pons to thoracic cord [Figure 1a, b]. There was no contrast enhancement. The MRI scan of the brain was unremarkable except for hyperintense signals in bilateral optic nerves. A possibility of neuromyelitis optica spectrum disorder (NMOSD) was considered and he was given a 5-day course of pulse methyl prednisolone. Routine cerebrospinal fluid (CSF) examination was uninformative. Antinuclear, antineutrophilic cytoplasmic, antiaquaporin-4, antimyelin oligodendrocyte antibodies, CSF oligoclonal bands were negative. Pulse steroids were followed by seven cycles of plasmapheresis. Despite transient recovery, child relapsed with fresh-onset episodes of hyperventilation and deepening impaired sensorium on day 30 of hospitalization. A repeat MRI scan of the brain showed progression in the white matter changes [Figure 1c–f]. The child was started on rituximab and megavitamin supplements (including biotin). The metabolic workup (blood acyl carnitine profile/tandem mass spectrometry/urinary organic acids by gas chromatography mass spectrometry) was unremarkable except for elevated CSF lactate (3.7 mg/dl). Thereafter, the child did not have any relapse. At the 2-year follow-up, the child had marked residual spastic paraparesis, he could sit but could not stand, and required regular bladder care. A repeat MRI showed chronic residual changes [Figure 1g, h]. Meanwhile, his 28-month-old sister was admitted with episodes of deep sighing respiration and recently noticed clumsy gait. Her sensorium was intact and examination revealed asymmetric mild spastic paraparesis. Her MRI scan of brain and spine were unremarkable. Her antiaquaporin antibody was not detectable. Biotinidase enzyme assay showed severely impaired enzyme activity (0.64 nmol/ml/min) (normal range 5–9). Her brother (index child) had 10% residual biotinidase enzyme activity 0.3 nmol/ml/min. Molecular genetic analysis of biotinidase deficiency (BTD) gene in the index child revealed a pathogenic homozygous mutation in c.98_104 del GCGGCTGinsTCC in 3p25 coding the biotinidase enzyme. Both the siblings were

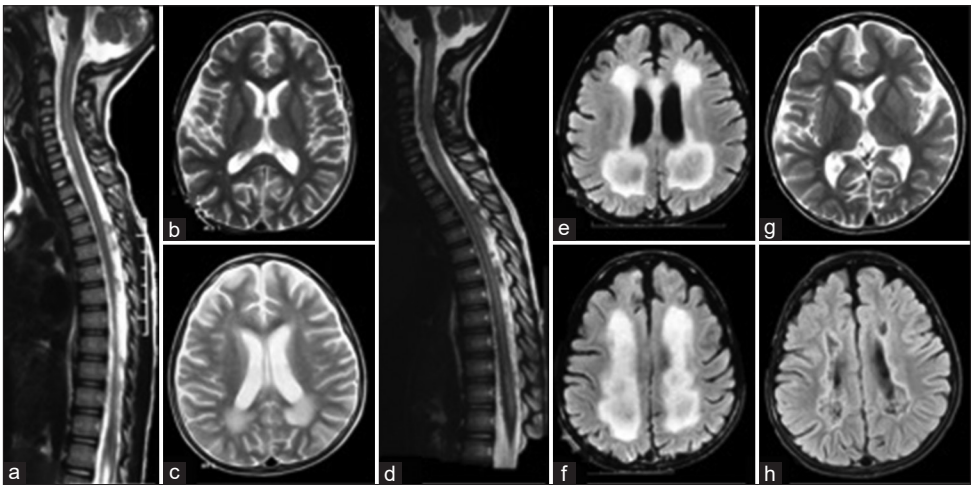

Figure 1: Sagittal T2 image (a) shows longitudinally extensive abnormal hyperintensity extending from pons to thoracic level of spinal cord. The brain parenchyma is unremarkable in axial T2 sections (b). Imaging on day 30 shows longitudinally T2 hyperintense signal involving the entire spinal cord (d) and large symmetrical bilateral white matter hyperintensity predominantly in the periventricular and centrum semi-ovale region with subcortical sparing on axial T2 (c) and FLAIR images (e, f). Follow-up axial T2 (g) and FLAIR (h) images at 2 years show near complete resolution of periventricular white matter changes with residual microcystic areas of rarefaction in the centrum semi-ovale

continued on biotin therapy, and on 3 months follow-up, the younger sibling had resolution of hyperventilation and normalization of gait.

Discussion

The initial presentation in the index child mimicked a demyelinating disorder with special predilection for the spinal cord; however, the refractoriness to immunomodulation, absence of antiaquaporin-4 antibody positivity, and the relentless radiological worsening were sufficient indicators to look for an alternative diagnosis. BTD, with a worldwide prevalence of 1:60,000, is a under-recognized differential of NMOSD.[1] The decreased ATP supply following impaired Kreb cycle is one of the speculated mechanisms of astrocyte swelling in BTD, a finding also seen in NMOSD.[2] BTD is a prototype of a neurocutaneous inborn error of metabolism with developmental delay, seizures, skin eczema, and seborrhea as the key clinical traits.[3] The late-onset form of BTD, with its characteristic limb weakness and vision disturbances, often has a delayed onset of clinical presentation unlike the classical forms.[4,5] Missense mutations are postulated to have residual enzyme activity resulting in delayed presentation despite profoundly low levels. Myelopathy secondary to BTD has been reported by several authors over the last 20 years [Supplementary Table 1].

A review of the literature illustrates the wide variability in the age of onset of BTD from 1 to 22 years. The delayed diagnosis (0–8 years) in most cases highlights the lack of suspicion of this treatable inborn error of metabolism. The recurrence of episodes, cutaneous stigmata, and concomitant visual impairment are cardinal clues to the diagnosis. In addition, several aspects of this case are noteworthy and deserve special mention. Bilateral profound hearing loss, as in our index child, has been reported, by Wolf *et al.* in 76% of children with untreated profound BTD.[6] Hyperventilation episodes, as described in both the siblings, must be recognized as a clue. Hyperventilation episodes with hypocapnia and respiratory alkalosis may be the sole manifestation of BTD.[7] However, this is not specific for BTD and can also be seen in mitochondrial disorders. The persistent elevation of CSF lactate, secondary to impaired biotin-dependent pyruvate carboxylase activity, is another pointer toward BTD in children with myelopathy. Owing to the lack of newborn screening program in resource-limited settings, children with milder forms of enzyme deficiencies will continue to present with a myriad of clinical symptoms at older ages.

To conclude, BTD should be considered as a differential in patients with myelopathy with or without vision loss, and screening by direct assessment of biotinidase enzyme levels is warranted in all such patients and the family members of affected individuals.

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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Supplementary Data

Supplementary Table 1: Profile of 20 patients with late-onset biotinidase deficiency presenting as myelopathy in literature*

Year of publication	Tokatli	Rahman	Wolf *et al.*				Wiznitzer	Kalkanoglu	Yang *et al.*			Aziz	Mcsweeney	Raha	Komur	Bhat	Cabasson	Bottin	Girard	Yilmaz
	1997	1997	1998				2003	2004	2007			2008	2010	2011	2011	2015	2015	2015	2017	2017
Clinical			1	2	3	4														
Age at onset	5	5	-	-	1.5	2	1.5	4.5	7	5	1	3	2	5	3	14	4	22	4	11
Age at diagnosis	15	5.2	-	-	15	-	3	4.6	8	13	3	3.1	2	7	3.1	15	4.2	22	8	14
Myelopathy	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Optic neuritis	N	Y	Y	Y	-	Y	N	N	N	Y	Y	N	N	Y	N	Y	N	Y	Y	Y
Sensorineural Hearing loss	Y	N	N	N	Y	Y	-	N	Y	-	-	Y	N	N	N	-	Y	-	N	N
Respiratory involvement	Y	N					N	Y	N	N	Y	-	Y	Y	Y	N	Y	N	Y	N
Cutaneous stigmata	Y	N	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	-	Y	N	N	N
Preexisting delay	N	N	-	-	-	-	N	N	N	N	N	Y	N	N	N	N	N	N	N	N
Similar past episodes	Y	Y	-	-	-	-	N	N	N	Y	Y	N	N	Y	Y	N	Y	Y	Y	Y
Neuroimaging																				
Spinal cord	-	N	-	-	-	-	Holocord	C, T	C, T	C	C	C, T	C	C, T	C, T	Holo	C	C	C, T	C
Brainstem	-	N	-	-	-	-	M	P, M	N	N	M	MB	P, M	DB	-	-	-	M	M	MB
Optic Nerve	-	N	-	-	-	-	N	N	N	Y	N	N	N	Chiasma	-	-	-	-	Y	Y
Biotinidase assay	0.1	0.07	0.14	0.2	0.1	0	0.09	0	0.1	0.1	0.1	-	0	1	0.13	0.1	0	0.6	0.1	0.58
Genetic testing	-	-	Y	Y	Y	Y	-	-	-	-	-	-	Y	Y	-	-	-	Y	Y	Y

*Y=yes, N=no, C=cervical, T=thoracic, P=pons, M=medulla, MB=midbrain, DB=dorsal brainstem