Reversible Spastic Paraparesis

Sir,

A 6-year-old girl presented with concerns of insidious onset, progressive difficulty in walking for 3 months. She was the second born to nonconsanguineous parents and had an unremarkable perinatal period. Her developmental milestones were attained in an age-appropriate manner. She was a student of the second grade with good scholastic performance. For the past 3 months, she had become progressively clumsy with an increased tendency to fall while walking. Her upper limb fine motor skills were also impaired with difficulty in buttoning clothes and tremulousness on reaching objects. There was no history of bladder or bowel disturbances, loss of sensations, pain, trauma, back deformity, back pain, fever, or weight loss.

On examination, she had a small head (occipitofrontal head circumference, 48.5 cm) and no other significant finding on general physical examination. Her higher mental function and cranial nerves were normal. Bipyramidal signs were elicitable in lower limbs with spasticity, mild weakness (proximal > distal), and exaggerated muscle stretch reflexes. She had an ataxic gait with intention tremors and dysmetria in upper limbs. Her sensory and spine examination was unremarkable. Her psychometric performance was discordant with intelligence quotient of 69 on the Malin's Intelligence Scale for Indian Children (MISC) and 102 on the Vineland Social Maturity Scale. In view of the predominant pyramidal and cerebellar involvement, clinical differentials considered were infantile neuroaxonal dystrophy and craniovertebral junction abnormality.

The magnetic resonance imaging (MRI) of the brain revealed nonspecific periventricular white matter changes in trigones [Figure 1]. The MRI spine was normal. Her complete hemogram revealed borderline high mean corpuscular volume (92fl). Serum homocysteine was grossly elevated (87 mg/dL). Her Vitamin B12 levels were normal (537 pg/dL). Tandem mass spectrometry revealed elevated propionylcarnitine (C3), acetylcarnitine (C2), and low plasma methionine levels, suggestive of methylmalonic acidemia [Table 1]. The urinary methylmalonic acid levels were 1362 mmol/mol of creatine confirming the diagnosis. The child was initiated on daily intramuscular hydroxycobalamin, oral pyridoxine, carnitine, and folinic acid. The spasticity reduced over a period of 4 months, and a repeat MRI of the brain at 1 year showed resolution of the periventricular signal changes. At 2-year follow up, the child is symptom free with normal serum homocysteine and undetectable methylmalonic acid in urine.

Combined methylmalonic aciduria with homocystinuria (CblC) is the most common inherited metabolic disorder of intracellular cobalamin metabolism caused by mutations in MMACHC gene on chromosome 1p34.1.[1] Its cardinal features include psychomotor retardation, failure to thrive, hypotonia, seizures, and acute encephalopathy.[2] The most common phenotype presents during infancy with acute afebrile encephalopathy with high anion gap metabolic acidosis, preceded by vomiting and feeding difficulty. Unlike the classical phenotype, the late-onset forms are exceptionally varied in symptomatology and can present in any decade of life. The neurological spectrum encompasses progressive encephalopathy, thromboembolic phenomena, metabolic stroke, neuropsychiatric features, neuroregression, and subacute combined degeneration of spinal cord. A review of 61 cases of late-onset CblC identified cognitive impairment (43%) and neuropathy/myelopathy (26%) as the most frequent presentations.[3] The most common extraneural features in the review were pulmonary hypertension and hemolytic uremic syndrome. Spastic paraparesis, as the clinical

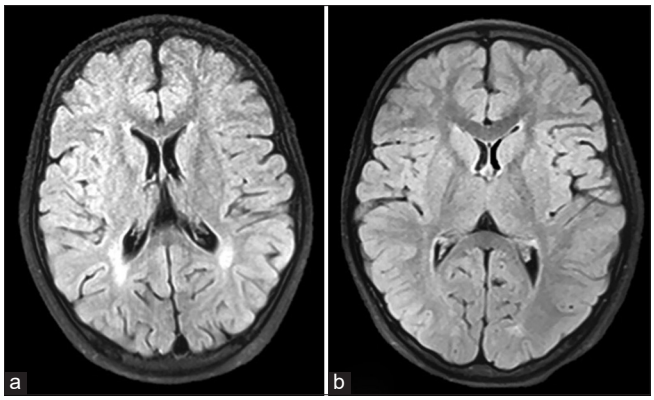

Figure 1: Axial T2-weighted fluid-attenuated inversion recovery magnetic resonance imaging of the brain showing bilateral periventricular white matter hyperintensities (a). Follow-up imaging after 1 year showing complete resolution of the hyperintensities (b)

Table 1: Laboratory profile of the index child

Investigations	Actual value	Reference value
Hemoglobin	10.3 g%	10-12 g%
Mean corpuscular volume	92 fl	80-92 fl
Serum homocysteine	87	5-15 mcmol/L
Vitamin B12	537 pg/dl	200-700 pg/dl
Serum lactate	1.6	2-4 mmol/L
Arterial pH	7.33	7.35-7.45
Nerve conduction study	No evidence of neuropathy	
Tandem mass spectrometry		
C3 propionyl carnitine	3.6	1.78 nmol/ml
C2 acetyl carnitine	7.6	2 nmol/ml
C3:C2	0.48	0.21-0.43
C3:C16	2.9	2.1-4.35
Plasma methionine	9.3	11-35 nmol/ml
Urinary methylmalonic acid	1362	0 mmol/mol

presentation, has been reported anecdotally in four case reports and has been attributed to myelopathy.[4-6]

Our case deserves special mention for multitude of reasons. The unusual combination of spastic paraparesis and cerebellar ataxia without evidence of myelopathy/neuropathy has not been reported in literature and extends the existing spectrum of late-onset CblC disorder. One of the other pointers in our case was macrocytosis without anemia. This, however, is not a consistent finding in late-onset CblC and has been reported in only 18% of the cases.[3] Despite her good scholastic skills, the child had a poor psychometric performance with borderline intelligence on MISC with relative preservation of social and communication skills. This is in consonance with the neurodevelopmental phenotype assessed by Weisfeld-Adams *et al*. in young children with CblC defect detected by the newborn screening program.[7] In addition, the periventricular white matter hyperintensities on neuroimaging that are generally considered as nonspecific changes are one of the distinct patterns seen in CblC defects. Other salient imaging features include diffuse cerebral atrophy, basal ganglia changes, and hydrocephalus.[8] The white matter changes are secondary to edema and abnormal myelination and usually respond to therapy. Daily parenteral hydroxycobalamin therapy (0.3 mg/kg/day) in combination with oral carnitine (50–100 mg/kg/day), folinic acid (5 mg/day), pyridoxine (100–400 mg/day), and betaine (250 mg/kg/day) form the mainstay of management.[1] Given the polysymptomatic nature of the disorder and the high rate of complications, a multiorgan screening for cardiac, ocular, and renovascular involvement is recommended.[8] In the index child, we did not observe any such involvement.

In the absence of a newborn screening program, a heightened awareness of the varied clinical expression of the late-onset cblC needs to be stressed among physicians. Early diagnosis allows specific treatment with parenteral hydroxycobalamin and has a significant impact on the outcome.

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.

Ananthanarayanan Kasinathan, Indar Kumar Sharawat[1], Naveen Sankhyan[1], Sameer Vyas[2], Savita Attri[3]

Department of Pediatrics, Mahatma Gandhi Medical College and Research Institute, Sri Balaji Vidyapeeth University, Puducherry, [1]Department of Pediatrics, Pediatric Neurology Unit, Postgraduate Institute of Medical Education and Research, [2]Department of Radio-Diagnosis and Imaging, Postgraduate Institute of Medical Education and Research, [3]Department of Pediatrics, Division of Pediatric Biochemistry, Postgraduate Institute of Medical Education and Research, Chandigarh, India

Address for correspondence: Dr. Naveen Sankhyan, Additional Professor, Pediatric Neurology Unit, Department of Pediatrics, Postgraduate Institute of Medical Education and Research, Chandigarh - 160 012, India.
E-mail: drnsankhyan@yahoo.co.in

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