

Cobalamin C Disease: Cognitive Dysfunction, Spastic Ataxic Paraparesis, and Cerebral White Matter Hyperintensities in a Genetic but Easily Treatable Cause!

Sir,

A 15-year-old boy presented with complaints of intellectual decline and behavioral change for last 8 months. His scholastic performance dipped and he became less interactive. He was taken to a psychiatrist, deemed to have depression, and started on 20 mg fluoxetine, without improvement. He worsened over the next 3 months and started missing words in sentences, conversing in telegraphic speech, and could not remember the words he wanted to speak. Thereafter, he started forgetting where he placed his belongings and what he had eaten. He became inattentive and was unable to do basic calculations. He developed concomitant stiffness of both lower limbs with transient tremulousness of feet on standing from a recumbent position. Stiffness increased over next 2–3 weeks due to which he required assistance for ambulation. He also developed urinary urgency with occasional incontinence for the past 1 month. He empirically received 4 doses of intramuscular methylcobalamin (1000 µg weekly) outside with some improvement.

Examination revealed impaired frontal and temporal lobe functions, grade 2 spasticity (modified Ashworth scale) in lower limbs, Medical Research Council grade 4/5 power at hip, 4+/5 at knee/ankle, brisk knee jerks, ankle clonus, extensor plantar response, and impaired joint position bilaterally.

His sister had presented in a similar fashion 10 years back (at 11 years of age). Her magnetic resonance

imaging (MRI) of brain had revealed T2-FLAIR bilateral symmetrical hyperintensities in centrum semiovale. MRI spine was normal. She was evaluated and treated at a private hospital as acute disseminated encephalomyelitis with steroids and multi-vitamin injections. Her cognitive symptoms improved, but she was left with residual stiffness and weakness in her legs.

Considering the child's age, presentation with cognitive dysfunction and spastic ataxic paraparesis, a positive family history (autosomal recessive pattern), symmetrical cerebral white matter involvement in the sister, a neuro-metabolic disorder was suspected. This spectrum of clinical presentation

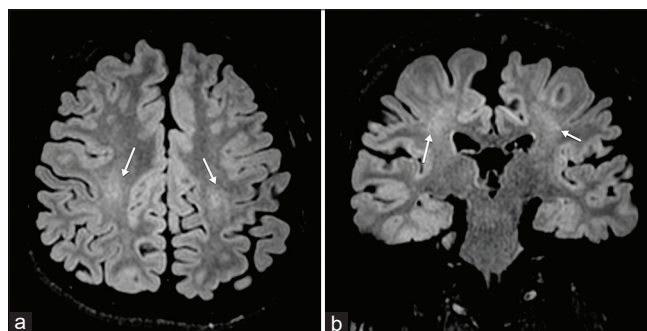


Figure 1: MRI of brain had revealed T2-FLAIR bilateral symmetrical hyperintensities in centrum semiovale on axial (a) and coronal (b) sections

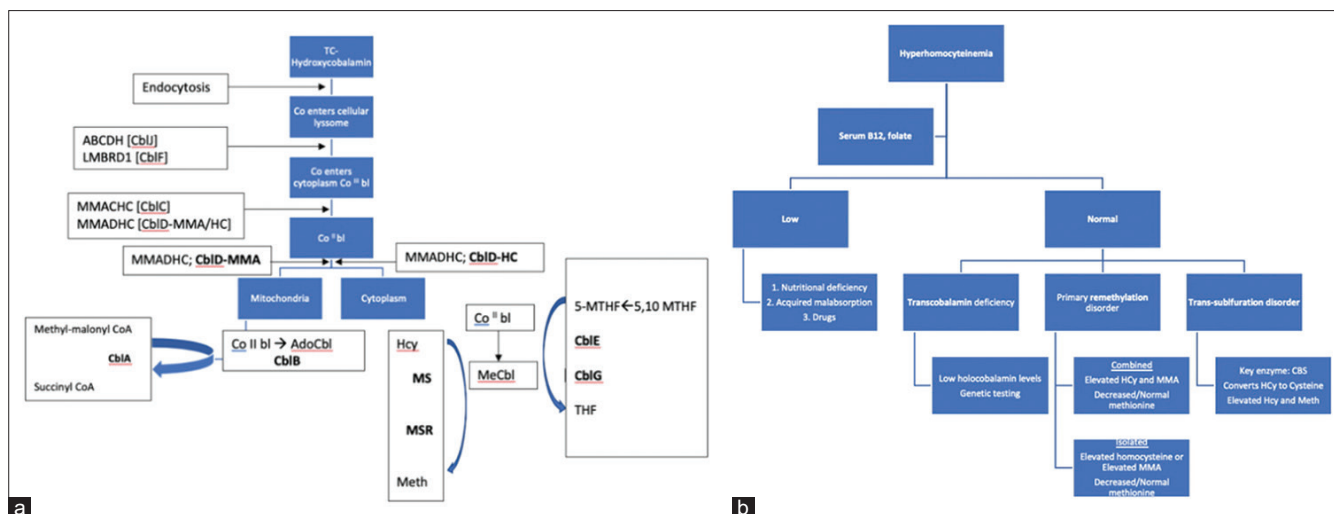


Figure 2: (a) *Cobalamin metabolism and homocysteine remethylation pathway:* Dietary cobalamin (Co) binds to transcobalamin (TC) and enters cells by receptor-mediated endocytosis. Certain proteins help in transport of cobalamin across the lysosomal membrane into the cytosol. Cobalamin is then processed by MMACHC and MMADHC proteins. Cellular cobalamin can then enter into two major pathways, cytosolic or mitochondrial. This sorting is done by MMADHC protein. In the cytosolic pathway, cobalamin is changed to methylcobalamin (MeCbl) after donation of a methyl group by 5-methyl tetrahydrofolate. Methylcobalamin then participates in the conversion of homocysteine (hcy) to methionine (meth). In the mitochondrial pathway, adenosylcobalamin (AdoCbl) is formed and helps in the conversion of methylmalonyl-CoA to succinyl-CoA (cobalamin remethylation defects mentioned in [] or bold headings; genes involved written in block letters). (b) *Differential diagnosis of hyperhomocysteinemia.* Other causes are severe B6 deficiency, renal failure, and hypothyroidism

may be seen in leukodystrophies, complicated hereditary spastic paraparesis (HSP) like SPG11, cerebrotendinous xanthomatosis (CTX), mitochondrial disorders, and homocysteine remethylation defects. Rapid progression (within a year) and history of improvement effectively ruled out CTX, leukodystrophies, and complicated HSP. Mitochondrial diseases were less likely as they tend to involve deep gray matter structures, cerebellum, or present with stroke-like lesions. Periventricular signal abnormalities have been reported in Leber's hereditary optic neuropathy, but only as a minor feature. Lack of disease affecting other organs also made it unlikely. Thus, keeping in mind the overall presentation and a possible improvement after B12 supplementation, work up for homocysteine remethylation defects was planned.

MRI brain of the index case showed similar findings [Figure 1]. His hemogram, serum folate levels, and MRI spine were normal. Serum B12 levels were >2000 pg/mL, homocysteine was >65 $\mu\text{mol/L}$ (range: 5–15 $\mu\text{mol/L}$). Plasma tandem mass spectrometry and urine gas chromatography mass spectrometry were normal. However, in his sister, plasma propionylcarnitine was high (7.86 $\mu\text{mol/L}$, range 0.12–6.65) with methyl-malonic aciduria (1714.3 mmol/mol of creatinine, reference <1216.5).

Combined homocysteinemia and methylmalonic aciduria raised suspicion of combined remethylation disorders affecting cobalamin metabolism. Genetic testing revealed homozygous c. 394C > T pathogenic mutation, in *MMACHC* gene (exon 3), in both siblings, confirming the diagnosis of cblC disease.

Both were given intravenous methylcobalamin (1000 μg) daily for 7 days, followed by weekly intramuscular supplementation,

and folic acid orally (5 mg/day). At 2-month follow-up, there was around 80% subjective improvement in the boy (both cognition and gait) and he successfully cleared his class IX examination in 2nd division. The sister showed less improvement than the brother, probably due to longer duration of her disease.

Dietary folate and cobalamin play an essential role in maintaining blood homocysteine balance. The cobalamin metabolism pathway is summarized in Figure 2a. Any mutation in the common pathway before cobalamin is converted to methyl or adenosylcobalamin leads to combined homocysteinemia and methylmalonic acidemia. Mutations in the individual pathways lead to either methyl malonic acidemia or homocysteinemia. Figure 2b summarizes the differential diagnosis of hyperhomocysteinemia.

The biochemical profile of combined homocysteinemia, methylmalonic acidemia, with normal plasma methionine, B12, and folate levels in our patient raised the possibility of combined remethylation defects which can all present similarly (acute or chronic behavioral or psychiatric abnormalities, cognitive impairment, peripheral neuropathy, subacute degeneration of the spinal cord, and rarely venous thromboembolism) in this age group. Genetic testing revealed a pathogenic mutation in *MMACHC* gene causative for cobalamin C (cblC) disease. CblC disease remains the most common inborn error of cobalamin metabolism.^[1] Clinical presentation varies between early and late-onset types, the former being more severe and the most common presentation of cblC. The affected children present with failure to thrive, regression of milestones, poor feeding, and hematological

malignancies.^[1] Late-onset type (symptom onset after 4 years of age) is rarer with approximately 80 cases described worldwide^[2] and has a less severe presentation, and therefore a better prognosis with early treatment.^[1] However, diagnosis is often delayed/missed due to the rarity of disease and lack of awareness about the same.^[2] The usual presentation includes cognitive decline, neuropsychiatric abnormalities, hematological manifestations, and features suggestive of subacute combined degeneration (SACD) of the spinal cord.^[1] Cerebral or cerebellar atrophy and hyperintensities in the white matter have been described on imaging.^[3]

These patients should ideally be treated with daily parenteral hydroxycobalamin and oral betaine, in doses of 0.3 mg/kg and 250 mg/kg body weight, respectively. These were found to lead to symptomatic improvement and biochemical recovery.^[4,5] However, due to unavailability of hydroxycobalamin and betaine in India, our patient was treated with methylcobalamin and folic acid.

To conclude, late-onset cbIC is a rare neurometabolic disorder which presents with a cognitive-behavioral syndrome and features of SACD in childhood or adolescence. A high index of suspicion is required for diagnosis. Elevated levels of MMA and homocysteine in the urine/plasma should lead to the suspicion of combined remethylation defects, mandating genetic testing for the same.^[1] Normal vitamin B12 levels should not mislead the physician from further investigations. We have reported the first cases of cbIC from India and seek to emphasize the importance of early diagnosis and treatment for a good clinical recovery.

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.

Ayush Agarwal, Vibhor Upadhyay, Anu Gupta, Ajay Garg¹, Venugopalan Y. Vishnu, Roopa Rajan, Mamta Bhushan Singh, Rohit Bhatia, M.V. Padma Srivastava

Departments of Neurology, ¹Neuroradiology, All India Institute of Medical Sciences, New Delhi, India

Address for correspondence: Prof. M.V. Padma Srivastava, Department of Neurology, All India Institute of Medical Sciences, New Delhi, India.

E-mail: vasanthapadma123@gmail.com

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