MTHFR Deficiency: A Potentially Treatable Cause of Adult-Onset Hereditary Spastic Paraparesis

Dear Editor,

A 27-year-old man born out of nonconsanguineous parentage [Figure 1: Pedigree chart] with normal developmental history presented with history of insidious onset, slowly progressive spastic paraparesis for the past 3 years. At the onset, he noticed difficulty in getting up from squatting position, which was associated with stiffness of lower limbs. One year into the illness, he noticed difficulty in walking especially on uneven surfaces with history of slippage of footwear with awareness. There was no associated sensory, upper limb, bowel, bladder, or cranial nerve involvement or cognitive decline. There was no history of similar symptoms in the family. Physical examination revealed grade 1+ spasticity and exaggerated deep tendon reflexes involving both lower limbs.

Magnetic resonance imaging (MRI) brain revealed symmetric T2/FLAIR hyperintensity involving periventricular and deep white matter of bilateral posterior parietal region [Figure 2]. MRI cervicodorsal spine was normal. Possibilities of infective, noninfective inflammatory metabolic myelopathies, genetic and degenerative leukoencephalopathies were considered. Nerve conduction studies and visual evoked potentials were normal. Routine hematological and biochemical blood tests were normal, as were levels of serum cortisol, vitamin B12, and folate. VDRL and HIV were nonreactive. ANA and ENA profile were negative. Fasting plasma homocysteine levels were significantly elevated (136.25 µmol/L; normal 3.3–11.3) with normal methionine levels (5.917 µmol/L; normal 5 to 75). Urine for gas chromatography and blood liquid chromatography and mass spectrometry were normal. Next generation sequencing was ordered with suspicion of Hereditary Spastic Paraparesis (HSP)/Leukodystrophy which showed mutations of MTHFR gene on exome 11 (c.1671_1672dupTG) and exome 3 (c.459C>G), clinching the diagnosis of Homocystinemia due to MTHFR deficiency. Genetic testing in the parents revealed the former mutation in the mother and the latter in the father. The patient was started on oral vitamin B12 1500 mcg/day, folate and pyridoxine supplementation, with some symptomatic improvement.

5,10-Methylenetetrhydrofolate reductase (MTHFR) deficiency is a rare, autosomal recessive, potentially treatable metabolic disorder that usually manifests in the childhood,[1] but can present in adulthood very rarely.[2-9] Hypomethioninemia may decrease global methylation reactions in the central nervous system, hence possibly affecting myelin, as attested by white matter abnormalities often found in cerebral MRIs of these patients.[1] In a case series of 24 patients with adolescent/adult-onset MTHFR deficient patients, the mean age of onset was 22.4 ± 12.1 years.[7] At presentation, gait disturbances (46%) were the most common symptom followed by epilepsy (29%), cognitive decline (21%), psychosis (12%), encephalopathy, and stroke (4% each). The mean homocysteine was 177.3 ± 49.5 micromol/L. Although severe hyperhomocystenemia, often associated with hypomethyoninemia, helps in suspicion of this disease, confirmation of the disease requires genetic analysis. However, there is usually a significant delay from onset to diagnosis (mean 5.75 years).[7] Although radiology might help in early diagnosis, they aren't specific for any particular disease. The most common radiology finding was white matter abnormalities seen in 70% of patients in

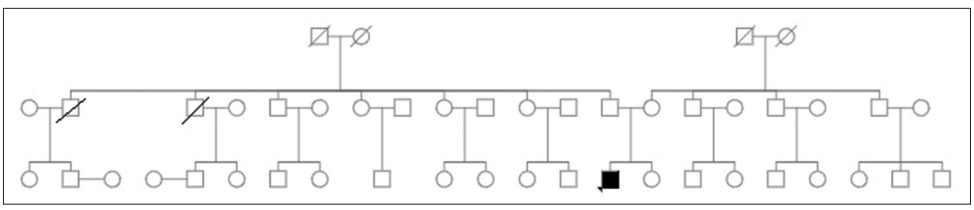

Figure 1: Pedigree Chart

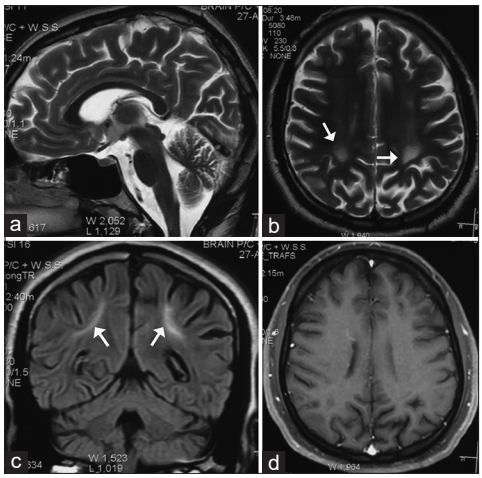

Figure 2: Sagittal T2-WI (a) shows normal thickness and signal intensity of corpus callosum. Axial T2-WI (b) and coronal FLAIR image (c) shows bilateral symmetrical periventricular white matter hyperintensities (arrows). No enhancement is seen in post-gadolinium axial T1-WI (d)

this case series.[7] Usually, early diagnosis and treatment by betaine (9000 mg/day), folinic acid (45 mg/day), vitamins B12 (1000 mg/week), and B6 supplementation (300 mg/day) are truly beneficial as reported in the literature.[1,10]

In a case series, there was a significant improvement in 83% of patients, whereas stabilization was noted in 17% of patients following treatment. However, only a few patients had complete disappearance of their symptoms due to the irreversible neurological damage that accumulates over time. This highlights the need for early diagnosis in MTHFR deficiency.

This case shows the importance of measuring plasma homocysteine levels in patients with presumed HSP because this may lead to the detection of MTHFR mutations and initiation of treatment. Although rare, adolescence/adult-onset MTHFR deficiency is potentially treatable. Hence, homocystenemia should be tested in unexplained spastic paraparesis, epilepsy, or any neuro-psychiatric syndrome, as waiting for a complete clinical picture may render irreversible neurological damage.

Learning points

1. A potentially treatable genetic condition like MTHFR mutation should be considered in cases of spastic paraparesis
2. Serum homocysteine is a useful screening tool for suspected MTHFR mutation in patients with noncompressive spastic paraparesis.

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.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

Pachipala Sudheer, Ayush Agarwal, Ajay Garg[1], M. V. Padma Srivastava, Venugopalan Y. Vishnu

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

Address for correspondence: Dr. Venugopalan Y. Vishnu, Department of Neurology, Room No 704, Cardioneurosciences Centre, Ansari Nagar, AIIMS, New Delhi - 110 029, India.
E-mail: vishnuvy16@yahoo.com

References

1. Saudubray J-M, Baumgartner M, Walter J, editors. Inborn Metabolic Diseases: Diagnosis and Treatment. 6th ed. Berlin Heidelberg: Springer-Verlag; 2016.
2. Pasquier F, Lebert F, Petit H, Zittoun J, Marquet J. Methylenetetrahydrofolate reductase deficiency revealed by a neuropathy in a psychotic adult. J Neurol Neurosurg Psychiatry 1994;57:765-6.
3. Michot JM, Sedel F, Giraudier S, Smiejan JM, Papo T. Psychosis, paraplegia and coma revealing methylenetetrahydrofolate reductase deficiency in a 56-year-old woman. J Neurol Neurosurg Psychiatry 2008;79:963-4.
4. Lossos A, Teltsh O, Milman T, Meiner V, Rozen R, Leclerc D, *et al*. Severe methylenetetrahydrofolate reductase deficiency: Clinical clues to a potentially treatable cause of adult-onset hereditary spastic paraplegia. JAMA Neurol 2014;71:901-4.
5. D'Aco KE, Bearden D, Watkins D, Hyland K, Rosenblatt DS, Ficicioglu C. Severe 5,10-methylenetetrahydrofolate reductase deficiency and two MTHFR variants in an adolescent with progressive myoclonic epilepsy. Pediatr Neurol 2014;51:266-70.
6. Perna A, Masciullo M, Modoni A, Cellini E, Parrini E, Ricci E, *et al*. Severe 5,10-methylenetetrahydrofolate reductase deficiency: A rare, treatable cause of complicated hereditary spastic paraplegia. Eur J Neurol 2018;25:602-5.
7. Gales A, Masingue M, Millecamps S, Giraudier S, Grosliere L, Adam C, *et al*. Adolescence/adult onset MTHFR deficiency may manifest as isolated and treatable distinct neuro-psychiatric syndromes. Orphanet J Rare Dis 2018;13:29.
8. Khan FMA, Dave D, Rohatgi S, Nirhale S, Rao P, Naphade P. MTHFR mutation- A rare potentially treatable cause of adult-onset complicated hereditary spastic paraplegia. J Neurol Sci 2019;405:325.
9. Wiedemann A, Chery C, Coelho D, Flayac J, Gueguen N, Desquiret-Dumas V, *et al*. Mutations in MTHFR and POLG impaired activity of the mitochondrial respiratory chain in 46-year-old twins with spastic paraparesis. J Hum Genet 2020;65:91-8.
10. Burda P, Schäfer A, Suormala T, Rummel T, Bürer C, Heuberger D, *et al*. Insights into severe 5,10-methylenetetrahydrofolate reductase deficiency: Molecular genetic and enzymatic characterization of 76 patients. Hum Mutat 2015;36:611-21.

Submitted: 21-Apr-2021 **Revised:** 26-Jul-2021
Accepted: 06-Aug-2021 **Published:** 12-Jan-2022

DOI: 10.4103/aian.aian_340_21