Case Report

Treatable Neurodegenerative Disorder: Cerebral Folate Transport Deficiency—Two Children from Southern India

Vykuntaraju K. Gowda, Balamurugan Natarajan, Varunvenkat M. Srinivasan, Sanjay K. Shivappa

Departments of Pediatric Neurology and Paediatrics, Indira Gandhi Institute of Child Health, Bengaluru, Karnataka, India

INTRODUCTION

Cerebral folate transport deficiency (CFD) results from impaired folate transport across the blood:choroid plexus:cerebrospinal fluid (CSF) barrier. This leads to low CSF 5-methyltetrahydrofolate (5MTHF), the active folate metabolite, in the presence of normal folate metabolism outside the nervous system.[1] Hardly few case reports are available and there is a paucity of literature regarding this disorder in Indian children. Hence, we decided to report two cases of genetically confirmed Indian children with CFD.

Cerebral folate transport deficiency results from impaired folate transport across the blood:choroid plexus:cerebrospinal fluid (CSF) barrier. This leads to low CSF 5-methyltetrahydrofolate (5MTHF), the active folate metabolite. We are reporting two children with this treatable cerebral folate transport deficiency. Case 1: Seventeen-year-old boy presented with delayed milestones followed by regression, seizures, and intention tremors. On examination child had pyramidal and cerebellar signs. Magnetic resonance imaging (MRI) of brain revealed diffuse cerebral and cerebellar atrophy. Targeted next generation sequencing revealed homozygous missense pathogenic variant in FOLR1 gene in exon 4 c.382C>T p.R128W, confirming the diagnosis of cerebral folate deficiency. Case 2: Six-year-old male child presented with delayed milestones, myoclonic jerks and cognitive regression from 3 years of age. Child had microcephaly with ataxia. Computed tomography (CT) of brain revealed multifocal calcifications. MRI brain revealed cerebellar atrophy with hyperintense T2 signal changes in the subcortical white matter of frontal and temporal lobes. Genetic testing revealed homozygous variant (c.493+2_493+6delTGAGG) in intron 4 of the FOLR1 gene which is a novel pathogenic variant. Both children started on folinic acid and there was a significant improvement in development, behavior, ataxia, and decrease in seizure frequency. In conclusion, cerebral folate transport deficiency should be suspected in every child with global developmental delay, epilepsy, ataxia and neuroimaging showing cerebellar atrophy and calcification. Response to folinic acid supplementation is partial if diagnosed late and treatment initiation is delayed.

KEYWORDS: Cerebral transport defect, folic acid, folinic acid, FOLR1

Case 1

Seventeen-years-old boy presented with delayed milestones since birth, cognitive decline and decreased scholastic performance noticed since early childhood and intention tremors from 3 years of age following a single episode of fever triggered seizures. History of multiple episodes of seizures for the past 2 months. Child had marfanoid habitus, mild facial dysmorphism

Address for correspondence: Dr. Vykuntaraju K. Gowda, Department of Pediatric Neurology, Indira Gandhi Institute of Child Health, Near NIMHANS, Bengaluru 560029, Karnataka, India.
E-mail: drknvraju08@gmail.com

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: wkhpmpedknow_reprints@wolterskluwer.com

How to cite this article: Gowda VK, Natarajan B, Srinivasan VM, Shivappa SK. Treatable neurodegenerative disorder: Cerebral folate transport deficiency—two children from Southern India. J Pediatr Neurosci 2021;16:273-6.
with hypopigmented hair with bilateral pes cavus. Neurologically child had spastic quadriaparesis with exaggerated deep tendon reflexes with positive cerebellar signs. Evaluation for homocystinuria was negative. Magnetic resonance imaging (MRI) of brain revealed diffuse cerebral as well as cerebellar atrophy. Targeted next-generation sequencing revealed homozygous missense pathogenic variant in FOLR1 gene in exon 4 c.382C>T p.R128W, confirming the diagnosis of cerebral folate deficiency. Measurement for CSF metabolites was not performed. Child was started on folinic acid supplementation and oral levetiracetam. Seizures came under control. However, the child continues to have ataxia, cognitive decline, and neurological deficit despite being on oral folinic acid supplementation for more than 18 months.

**Case 2**

Six-year-old male child with normal birth history with delayed milestones since birth, cognitive regression in the last 3 years of age and epileptic spasms in the last 4 years of age. Child had microcephaly and facial dysmorphism. Neurological examination revealed bilateral spastic quadriaparesis with brisk deep tendon reflexes with extensor plantar and ataxia. CT brain revealed intraparenchymal calcification with corresponding gradient MR image showed presence of blooming [Figure 1A–C]. MRI brain revealed cerebellar atrophy with hyperintense T2 signal changes in the subcortical white matter of frontal and temporal lobe [Figure 1D–F]. Electroencephalogram revealed diffuse slowing with multifocal epilepsy. Arterial blood gas, serum lactate, serum ammonia, and tandem mass spectrometry done were normal. Targeted next-generation sequencing revealed homozygous variant (c.493 + 2_493 + 6delTGAGG) in intron 4 of the FOLR1 gene which is a novel pathogenic variant and it is confirmed by multiplex ligation-dependent probe amplification. After starting oral folinic acid, there was a significant decrease in frequency of seizures.

**Discussion**

CFD is a neurological syndrome associated with low CSF 5MTHF, the active folate metabolite, in the presence of normal folate metabolism outside the nervous system.[1] The choroid plexus is the main site of active folate transport to the central nervous system (CNS). The normal folate homeostasis in the CNS depends on intact normal folate transport mechanisms across the choroid plexus and this is mainly mediated by folate receptor protein1 (FR1).[2-5] For passage across the blood–CNS barrier, 5-MTHF, which is the predominant active folate form in plasma is bound by the FR1 which is anchored to choroid plexus epithelial cells and then followed by endocytosis, storage, and subsequent delivery into the CSF compartment where it will be transported into neuronal tissues.[1,6]

Most commonly, CFD results from a defect of the cerebral folate receptor 1-alpha (FR1-α) due to mutations in the folate receptor 1 gene, FOLR1.[7-9] CFD typically manifests in early childhood with psychomotor regression, epilepsy, and delayed myelination.[1,8] CFD is characterized by its onset of symptoms around 4 to 6 months of age to early childhood. They present initially with irritability, deceleration of head growth, neurodevelopmental delay/regression, and later develop spasticity, ataxia, dyskinesia, epilepsy, autistic features, and sometimes visual disturbances and hearing loss.[1]

CFD due to FOLR1 defect is an autosomal recessive condition and there is variability in phenotype. Karin et al.[10] reported marked improvement with folinic acid therapy at 3 mg per kg per day escalated gradually to 5 mg per kg per day. Cairo et al.[11] reported two children, remarkable motor recovery, and with a significant reduction in seizure frequency. Delmelle et al.[12] reported two sisters, where epilepsy was refractory to oral folinic acid supplementation and but controlled with intravenous folinic acid therapy in both the children. However, in both of our cases, epilepsy was controlled with oral folinic acid therapy itself as observed in most of the few published case reports.

Neuroimaging findings can be variable as per literature and it includes normal neuroimaging, hypomyelination/myelination disturbance, cerebellar atrophy, and cerebral atrophy. CT brain can reveal basal ganglia and intraparenchymal calcifications.[1,7-12] Our neuroradiological findings were also consistent with the above case reports. Low CSF 5 MTHF levels were documented in the few published case reports and the gradual increase in its levels in the CSF following folinic acid therapy has been documented.[8-12] However, one of our limitation of our report is that we have not tested for CSF 5 MTHF in both of our cases due to local constraints and the other reason is that there are many neurological disorders like Rett syndrome, Kearns-Sayre syndrome, Aicardi-Goutières syndrome, epileptic encephalopathies, etc., along with other genetic disorders of folate metabolism which have secondary cerebral folate deficiency and these disorders also have low CSF 5 MTHF.[1,12] Hence, we have confirmed the diagnosis using next-generation sequencing in both our cases which has enabled us to provide genetic counseling to both the families.

Ramaekers et al.[11] noted that folinic acid before age of 6 years has a favorable prognosis and sometimes
recover dramatically. This contrasts with children diagnosed at 6 years of age or above who only show partial and delayed recovery. Similar observation was noted in both of our children and they were diagnosed only after 6 years of age. This highlights the importance of early recognition and timely initiation of folinic acid for this treatable neurometabolic disorder.

**Conclusion**

Suspect cerebral folate deficiency in every child with global developmental with epilepsy especially when there is cerebellar atrophy on neuroimaging. Ataxia and intracerebral calcification and can occur. Response to folinic acid supplementation is only partial if diagnosed late and treatment initiation is delayed.

**Financial support and sponsorship**

Nil.

**Conflicts of interest**

There are no conflicts of interest.

**REFERENCES**

1. Ramaekers VT, Blau N. Cerebral folate deficiency. Dev Med Child Neurol 2004;46:843-51.
2. Rosenblatt D. Inherited disorders of folate transport and metabolism. In: Scriver CR, Beaudet AL, Sly WS, Valle D, editors. The metabolic and molecular basis of inherited disease. 6th ed. New York: McGraw-Hill; 1995. p. 3111-28.
3. Suh JR, Herbig AK, Stover PJ. New perspectives on folate catabolism. Annu Rev Nutr 2001;21:255-82.
4. Kamen BA, Smith AK. A review of folate receptor alpha cycling and 5-methyltetrahydrofolate accumulation with an emphasis on cell models in vitro. Adv Drug Deliv Rev 2004;56:1085-97.
5. Sabharanjak S, Mayor S. Folate receptor endocytosis and trafficking. Adv Drug Deliv Rev 2004;56:1099-109.
6. Wang Y, Zhao R, Russell RG, Goldman ID. Localization of the murine reduced folate carrier as assessed by immuno-histochemical analysis. Biochim Biophys Acta 2001;1513:49-54.
7. Ramaekers V, Sequeira JM, Quadros EV. Clinical recognition and aspects of the cerebral folate deficiency syndromes. Clin Chem Lab Med 2013;51:497-511.

8. Steinfeld R, Grapp M, Kraetzner R, Drehu-Kulaczewski S, Helms G, Dechent P, et al. Folate receptor alpha defect causes cerebral folate transport deficiency: a treatable neurodegenerative disorder associated with disturbed myelin metabolism. Am J Hum Genet 2009;85:354-63.

9. Kobayashi Y, Tohyama J, Akiyama T, Magara S, Kawashima H, Akasaka N, et al. Severe leukoencephalopathy with cortical involvement and peripheral neuropathy due to FOLR1 deficiency. Brain Dev 2017;39:266-70.

10. Karin I, Borggraefe I, Catarino CB, Kuhm C, Hoertnagel K, Biskup S, et al. Folinic acid therapy in cerebral folate deficiency: marked improvement in an adult patient. J Neurol 2017;264:578-82.

11. Cario H, Bode H, Debatin KM, Opladen T, Schwarz K. Congenital null mutations of the FOLR1 gene: a progressive neurologic disease and its treatment. Neurology 2009;73:2127-9.

12. Delmelle F, Thöny B, Clapuyt P, Blau N, Nassogne MC. Neurological improvement following intravenous high-dose folinic acid for cerebral folate transporter deficiency caused by FOLR1 mutation. Eur J Paediatr Neurol 2016;20:709-13.