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J Pediatr Neurosci. 2021 Oct-Dec; 16(4): 273–276.
Published online 2021 Jul 12. doi: 10.4103/jpn.JPN_76_20: 10.4103/jpn.JPN_76_20

PMCID: PMC9757528
PMID: 36531775

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

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Received 2020 Apr 14; Accepted 2020 Jul 7.

Abstract

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*

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.

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 with hypopigmented hair with bilateral pes cavus. Neurologically child had spastic quadriparesis 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 quadriparesis 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

CFDis 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).[2,3,4,5] 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*.[7,8,9] 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.[1,7,9,10,11,12] 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.[8,9,10,11,12] 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.*[1] 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.

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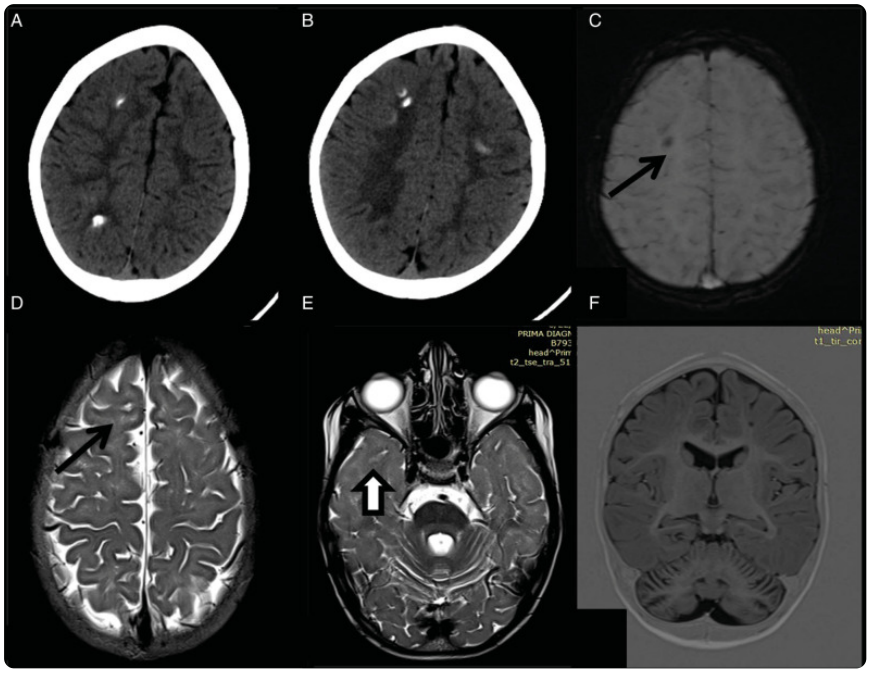
Figures and Tables

Figure 1



CT scan brain (A and B) showing calcification with corresponding gradient MR image (C) showing presence of blooming (black arrow). MRI T2 WI axial (D and E) showing hyperintensity in subcortical white matter of frontal (black arrow) and temporal lobe (white arrow). T1WI IR images (F) show cerebellar atrophy with prominent folia