Case Report
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Cerebral Folate Transport Deficiency in 2 Cases with Intractable Myoclonic Epilepsy

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Cerebral folate transport deficiency due to folate receptor 1 gene (FOLR1) gene mutation results from impaired folate transport across the blood: choroidplexus: cerebrospinal fluid (CSF) barrier. This leads to low CSF 5-methyltetrahydrofolate, the active folate metabolite. We are reporting two children with this treatable cerebral folate transport deficiency. Eight years and 9-month-old female presented with delayed milestones followed by regression, seizures, and intention tremors. On examination child had microcephaly, generalized hypotonia, hyperreflexia, unsteady gait, and incoordination. Magnetic resonance imaging (MRI) of brain revealed dilated ventricular system and cerebellar atrophy. Computed tomography (CT) of brain showed brain calcifications. Whole exome sequencing was finally performed, revealing homozygous nonsense pathogenic variant in FOLR1 gene in exon 3 c.C382T p.R128W, confirming the diagnosis of cerebral folate deficiency. Twelve-year-old female child presented with global developmental delay since birth, myoclonic jerks and cognitive regression. Child had generalized hypotonia and hyperreflexia. Her coordination was markedly affected with intention tremors andunbalanced gait. CT brain showed bilateral basal ganglia and periventricular calcifications with brain atrophic changes. MRI brain showed a prominent cerebellar folia with mild brain atrophic changes. Genetic testing showed a homozygous pathogenic variant was identified in FOLR1 C.327_328 delinsAC, p.Cys109Ter. Both patients were started on intramuscular folinic acid injections with a decrease in seizure frequency. However, their seizures did not stop completely due to late initiation of therapy. In conclusion, cerebral folate transport deficiency should be suspected in every child with global developmental delay, intractable myoclonic epilepsy, ataxia with neuroimaging suggesting cerebellar atrophy and brain calcifications. Response to folinic acid supplementation is partial if diagnosed late and treatment initiation is delayed. **(2024;14:29-36)**

Key words: Intractable epilepsy, Brain calcification, Cerebellar atrophy, Cerebral folate deficiency

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Introduction

Cerebral folate deficiency (CFD) syndrome is a rare treatable neurometabolic disorder with low levels of the active form of folate in cerebrospinal fluid (CSF) arising from different causes such as folate receptor 1 gene (FOLR1) gene mutations or autoantibodies against the folate receptor-alpha (FRα) protein that can block folate transport across the choroid plexus.[1] CFD was defined by Ramaekers and Blau as "any neurological syndrome associated with a low CSF 5-methylene-tetra-hydro-folate in the presence of normal folate metabolism outside the nervous system".[2]

Folate uptake into the brain is mediated by the high affinity FRα (encoded by FOLR1), which is highly expressed in the apical membrane of choroid plexus epithelial cells, lung, thyroid and renal tubular cells. Loss-of-function mutations in the FOLR1 gene (MIM*136430) coding for the FRα predominantly impairs cerebral folate transport.[3]

CFD typically manifests in early childhood with psychomotor regression, intractable myoclonic epilepsy, and delayed myelination. Onset of symptoms ranges between 4 to 6 months of age to early childhood. Patients 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.[4]

The pathophysiological consideration behind the deficiency of cer-

ebral folate on the metabolism of the brain came from the results of magnetic resonance spectroscopy which showed a lack of choline and myoinositol in the brain. The deficit of choline and inositol is consistent with the disturbed myelination found in those patients.[3]

The response to treatment with folinic acid is dramatic with improvement in social interaction, mobility, and seizure control. The earlier the patients receive the folinic acid, the better will be the outcome.[5] The relation between myoclonic epilepsy and CFD is rarely described in the literature. Herein we will describe two unrelated patients who presented with intractable myoclonic epilepsy and frequent drop attacks and were genetically confirmed as CFD.

Case Report

Clinical history was obtained from parentswith special emphasis on development. Complete neurological and physical examination with full ophthalmological evaluation was performed. Routine and long-term video electroencephalography (EEG) monitoring employing standard 10-20 system, and brain magnetic resonance imaging (MRI) using I/V contrast T1-weighted-fluid-attenuated inversion recovery, T2 weighted turbo spin-echo, T2 weighted spectral presaturation with inversion recovery, T2-weighted-fluid-attenuated inversion recovery, and diffusion weighted imaging-1000 regimes in axial, sagittal, and coronal planes with epilepsy protocol were conducted. Trio whole exome sequencing was done for the clinical diagnosis. The informed consent forms were collected from parents for publishing the paper.

Case presentation 1

An 8-year and 9-month-old girl, product of non-consanguineous marriage. Her delivery was via cesarean sectionwith average birth weight and was uneventful. The three other siblings were healthy with no history of similar or other undiagnosed medical condition apart from typical febrile seizures encountered by two of them.

At the age of 7 years, the patient started to experience attacks of

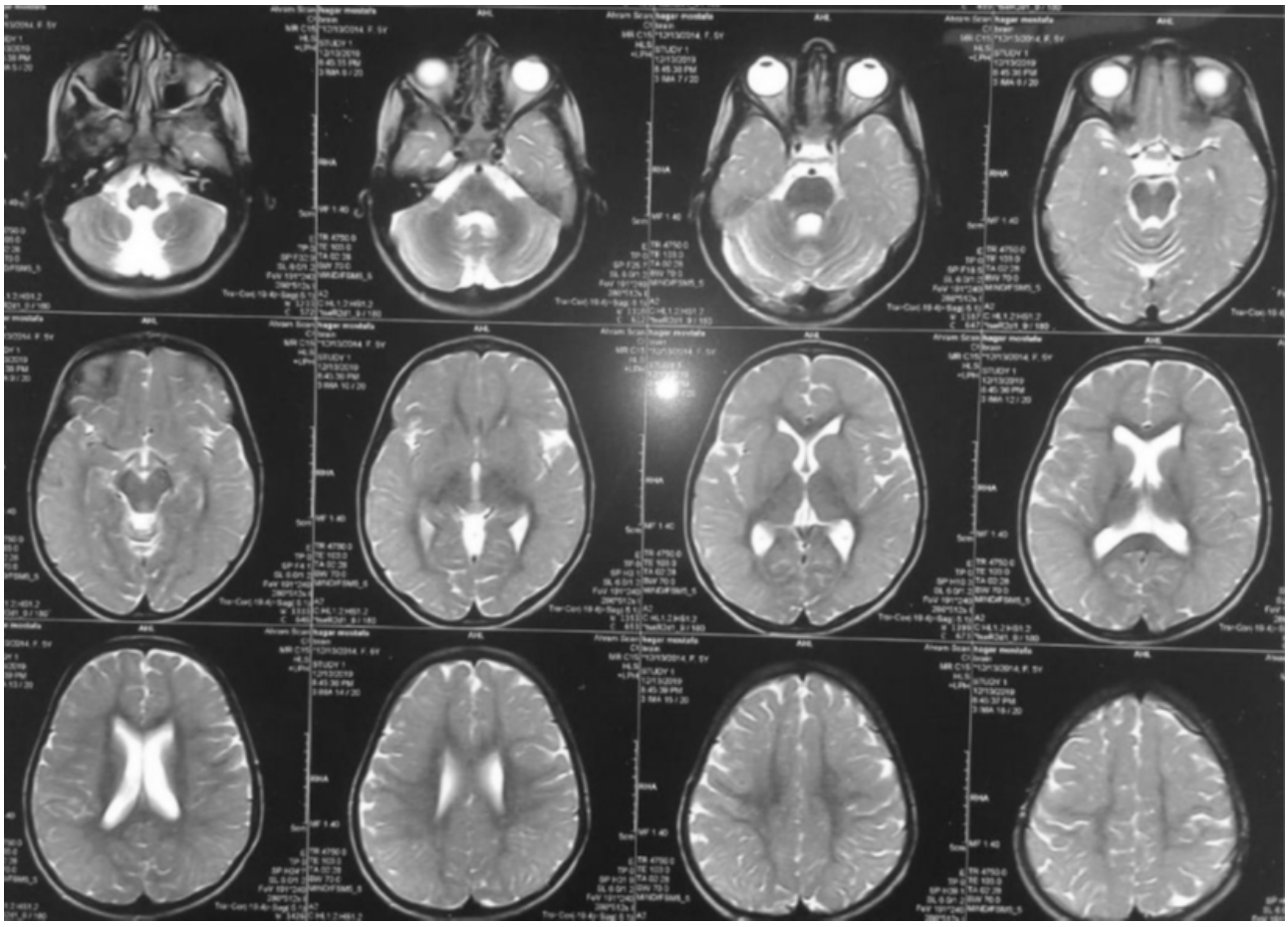

Figure 1. Magnetic resonance imaging (T2) showing a dilated ventricular system and prominent cerebellar folia denoting cerebellar atrophy.

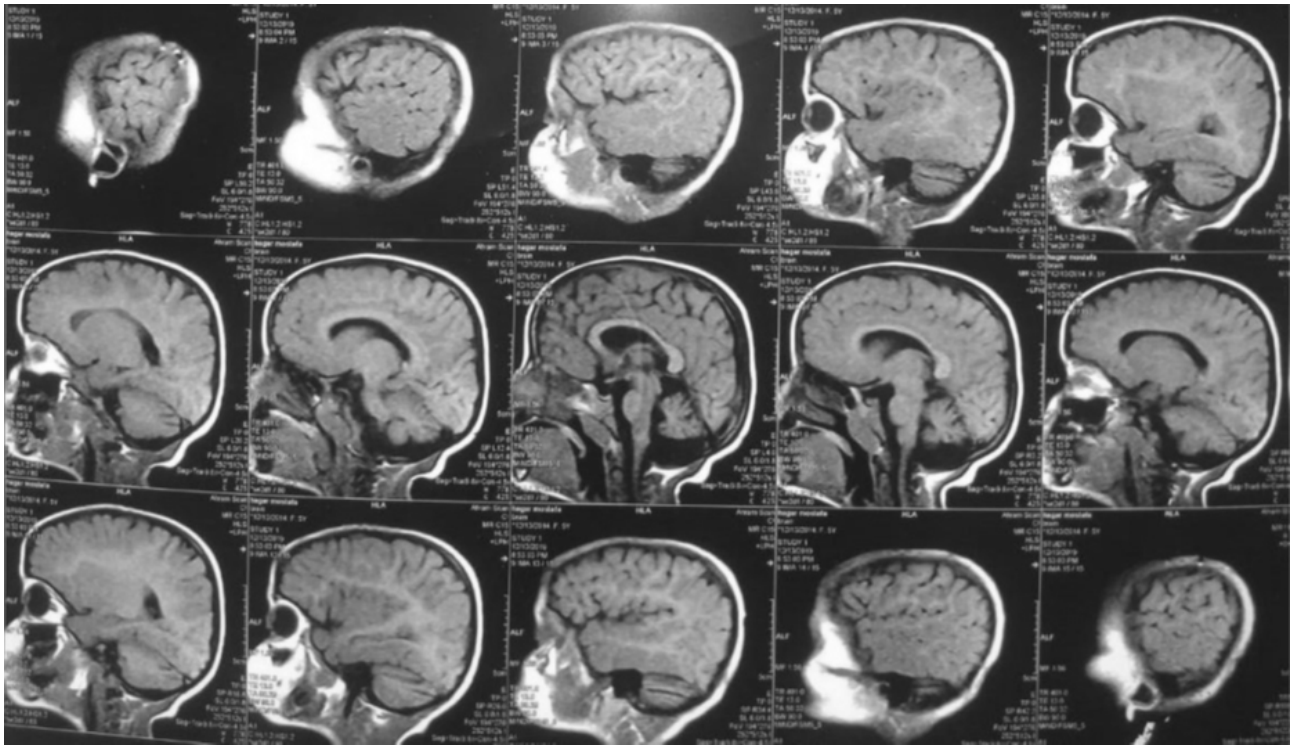

Figure 2. MRI brain (sagittal view) revealing cerebellar vermis atrophy. MRI, magnetic resonance imaging.

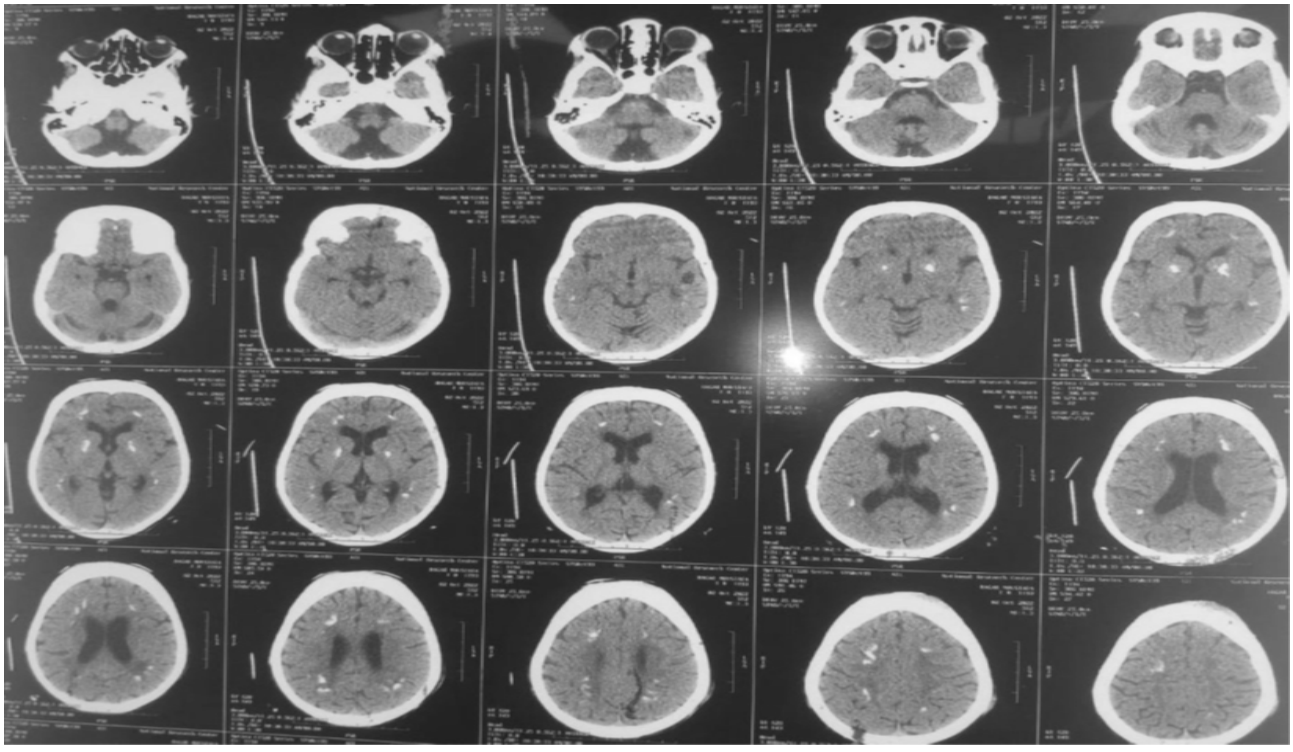

Figure 3. CT brain showing a bilateral small intracerebral calcifications; frontal, parietal lobes, and basal ganglia, together with frontal cephalhematoma. CT, computed tomography.

myoclonic atonic seizures in the form of repeated head drops, followed by abrupt falling. These attacks occurred in a cluster of 15-20 times, recurring repeatedly up to 50 times per day, and were intractable despite receiving adequate doses of appropriate antiepileptic drugs as valproate and levetiracetam. Moreover, topiramate, clonazepam and lamotrigine were tried without any response. The patient had global developmental delay, supported her head at 7 months, sat unsupported at 10 months, crawled at 12 months, walked with support at 1.5 years and walked independently at 2 years. She had delayed speech, can say only single words, but was toilet trained. Her neurological examination revealed generalized hypotonia, hyperreflexia, unsteady gait, incoordination with intention tremors and no neuro-cutaneous stigmata. She had a head circumference of 50 cm (below 3rd percentile) at the time of examination. Systemic examination was unremarkable.

Her brain MRI revealed dilated ventricular system and cerebellar atrophy (Figs. 1, 2). The brain CT scan showed bilateral small intracerebral calcifications; frontal, parietal lobes, and basal ganglia, together with frontal cephalhematoma (Fig. 3). Magnetic resonance spectroscopy was normal. The EEG showed slow spike complexes on top of cerebral dysrhythmia (Fig. 4). Nerve conduction velocity was done and revealed decreased amplitude of examined nerves, suggesting the presence of polyneuropthy. Laboratory investigations as blood ammonia, serum lactate, acyl carnitine profile in blood, and urine organic acid, were done with normal results. CSF glucose, proteins, lactate were normal with normal CSF to blood glucose ratio.

Whole exome sequencing (WES) was finally performed, revealing homozygous nonsense pathogenic variant in FOLR1 gene in exon 3 c.C382T p.R128W, which confirms the diagnosis of cerebral folate deficiency. She started folinic acid, then gradually increased to the present dose of 1 mg/kg/day by intramuscular injection (as we don't have the oral preparation in Egypt). At this dose of folinic acid, seizures became better controlled (less frequent and less duration). Besides, the symptoms including unsteady gait, failure to hold ob-

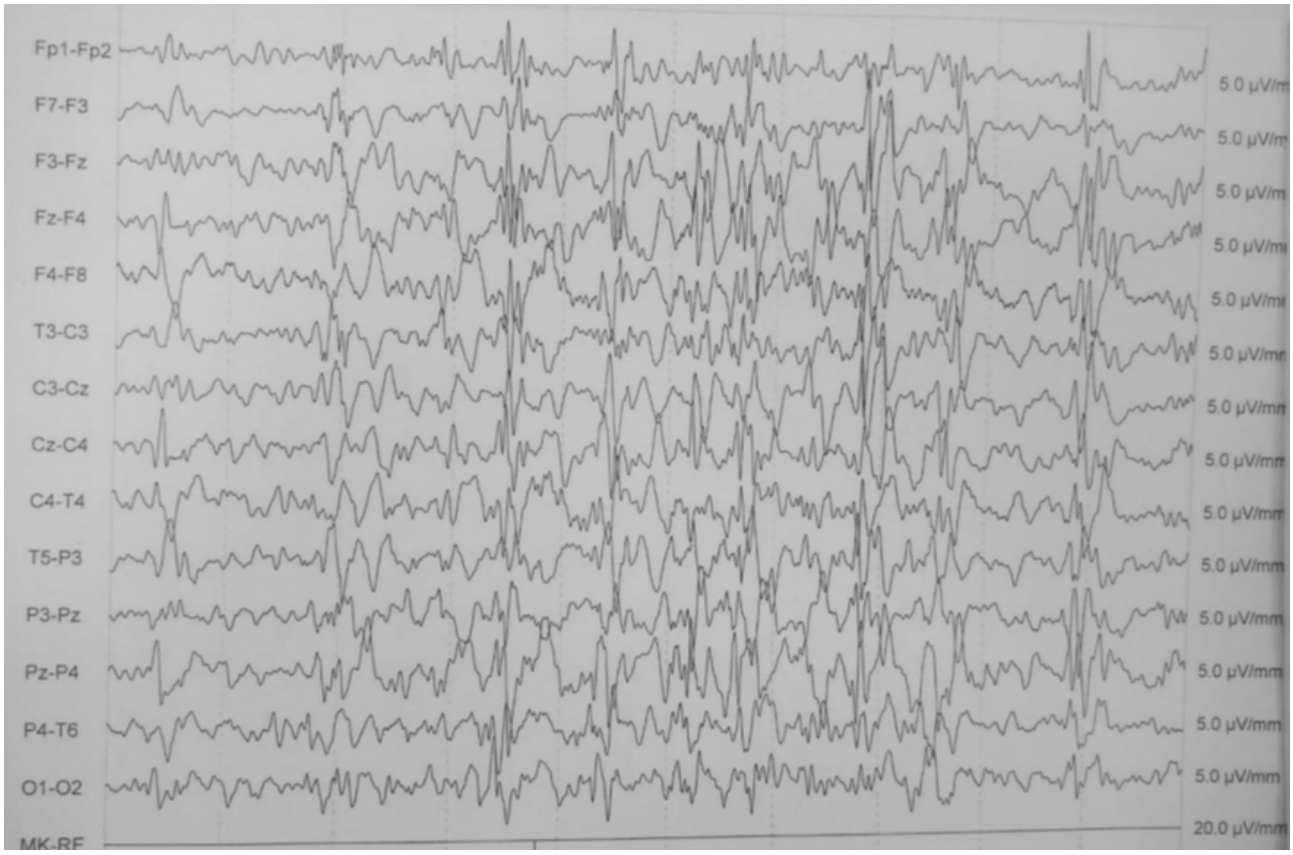

Figure 4. EEG showing paroxysmal discharge of sharp and sharp slow complexes denoting a generalized epileptogenic activity drop attacks from 20 into 7 per day. Fp, frontoparietal; F, frontal; Fz, midline frontal; T, temporal; C, central; Cz, midline central; P, parietal; Pz, midline central; O, occipital; EEG, electroencephalography.

jects readily, were considerably improved, with better social interaction and speech.

Case presentation 2

A female patient 12 years old, the second sibling of consanguineous parents with normal birth history. She had global developmental delay in motor and mental development.

At 6 years of age, the patient started to have attacks of sudden head drops associated with sudden elevation and abduction of her arms which led her to fall instantly. These attacks occurred in clusters of 20 and recurred up to 30 times per day. Sodium valproate, levetiracetam, clonazepam, ethosuximide and even steroids were tried with no response.

Her neurological evaluation revealed a mentally subnormal child who cannot obey orders. There was generalized hypotonia of both upper and lower limbs with grade intravenous muscle power. Her coordination was markedly affected with intention tremors and unbalanced gait. Facial examination revealed bruises due to frequent falls. Systemic examination was unremarkable.

A brain MRI was performed that showed prominent cerebellar folia with mild dilated fourth ventricle, likely cerebellar atrophic changes (Figs. 5, 6). Non contrast multislice CT brain showed bi-

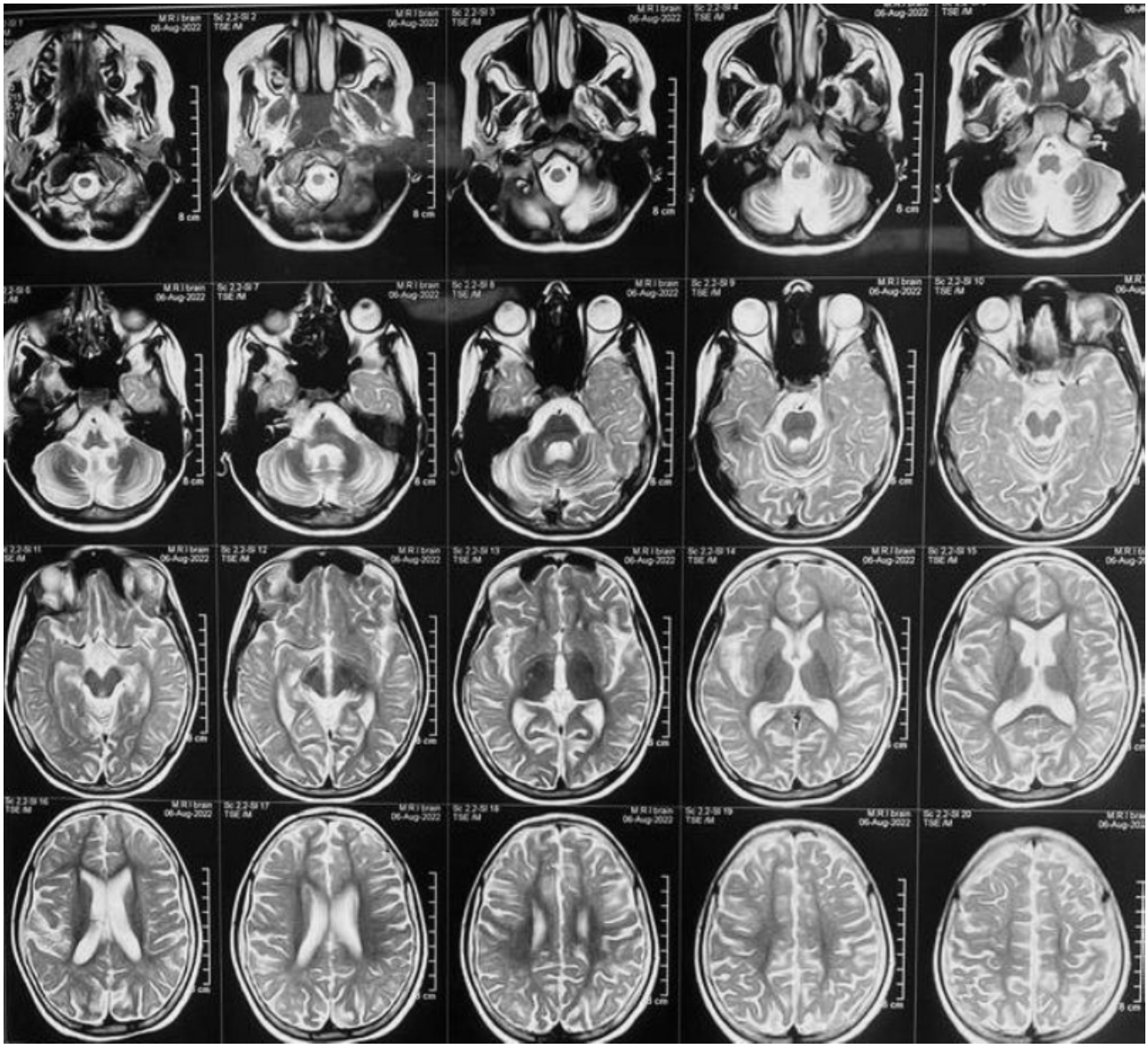

Figure 5. MRI brain (T2) revealed diffuse cerebral and cerebellar atrophy. MRI, magnetic resonance imaging.

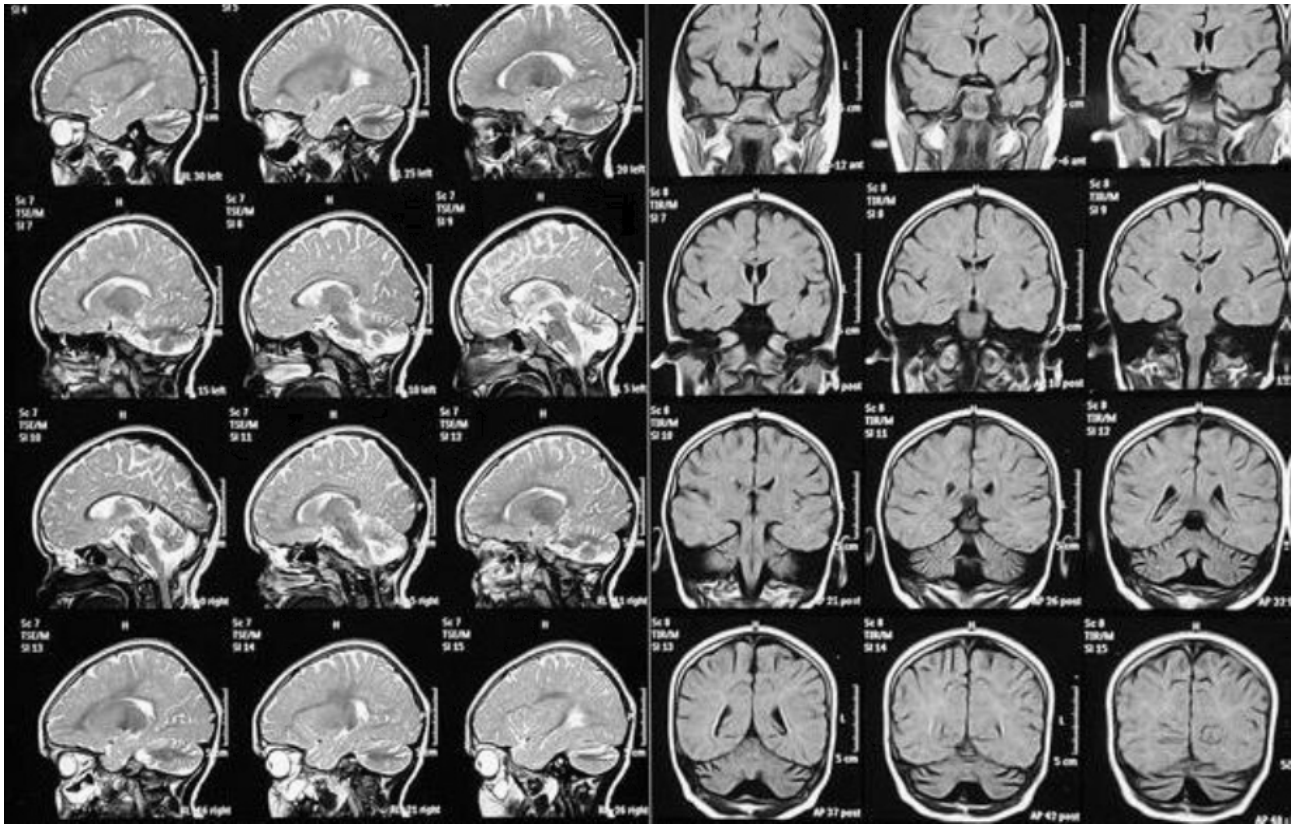

Figure 6. MRI brain (sagittal and coronal views) showed a cerebellar vermis and cerebellar hemisphere atrophy. MRI, magnetic resonance imaging.

lateral basal ganglia, periventricular calcifications, and brain atrophic changes (Fig. 7). EEG showed generalized epileptic discharges and diffuse cerebral slowing. Fundus, electromyography and nerve conduction velocity were done which were normal. Intelligence quotient test was performed with score=36. Extensive metabolic work up was done, and all were normal. WES was performed which showed that a homozygous pathogenic variant was identified in FOLR1 C.327_328 delinsAC, p.Cys109Ter. The patient started on calcium folinate intelligence quotient (IM) at a dose of 2 mg/kg/day with partial reduction in the frequency of seizures.

Discussion

5-methyltetrahydrofolate (5-MTHF) is the biologically active form of folate and is essential for DNA repair and synthesis, as well as homocysteine degradation. 5-MTHF is transported into the CSF, particularly at the choroid plexus, where the FRα is anchored.[6,7]

Cerebral folate transport deficiency (CFD) is an autosomal recessive disorder caused by mutations in the FOLR1 (OMIM #613068).[3] It has a progressive neurological course that may start at the second or third year of life and main characteristics of this disorder are psychomotor regression, ataxia and refractory myoclonic epilepsy. Diagnosis depends mainly on CSF 5-MTHF levels falling 80.0% below the lower limit of reference values.[3] Early recognition is crucial as folinic acid supplementation can ameliorate symptoms and in mild cases it may reverse the clinical picture.[3]

In this report, we documented two unrelated Egyptian patients from two different families who were confirmed genetically to have FOLR1 gene mutation. Our patients presented with global developmental delay, generalized hypotonia, and ataxia before the appearance of intractable myoclonic atonic seizures, which leads them to frequent falling. Onset of seizures ranged from 6 to 7 years with poor response to appropriate anti-seizure medications.

In their review, Pope and his colleagues reported 20 patients affected with FOLR1 worldwide. Their symptoms started between the ages of 6 months to 4.5 years, with a median onset of 2 years. Most cases appeared normal at birth except one Finnish case who had congenital microcephaly. This patient had homozygous deletion in

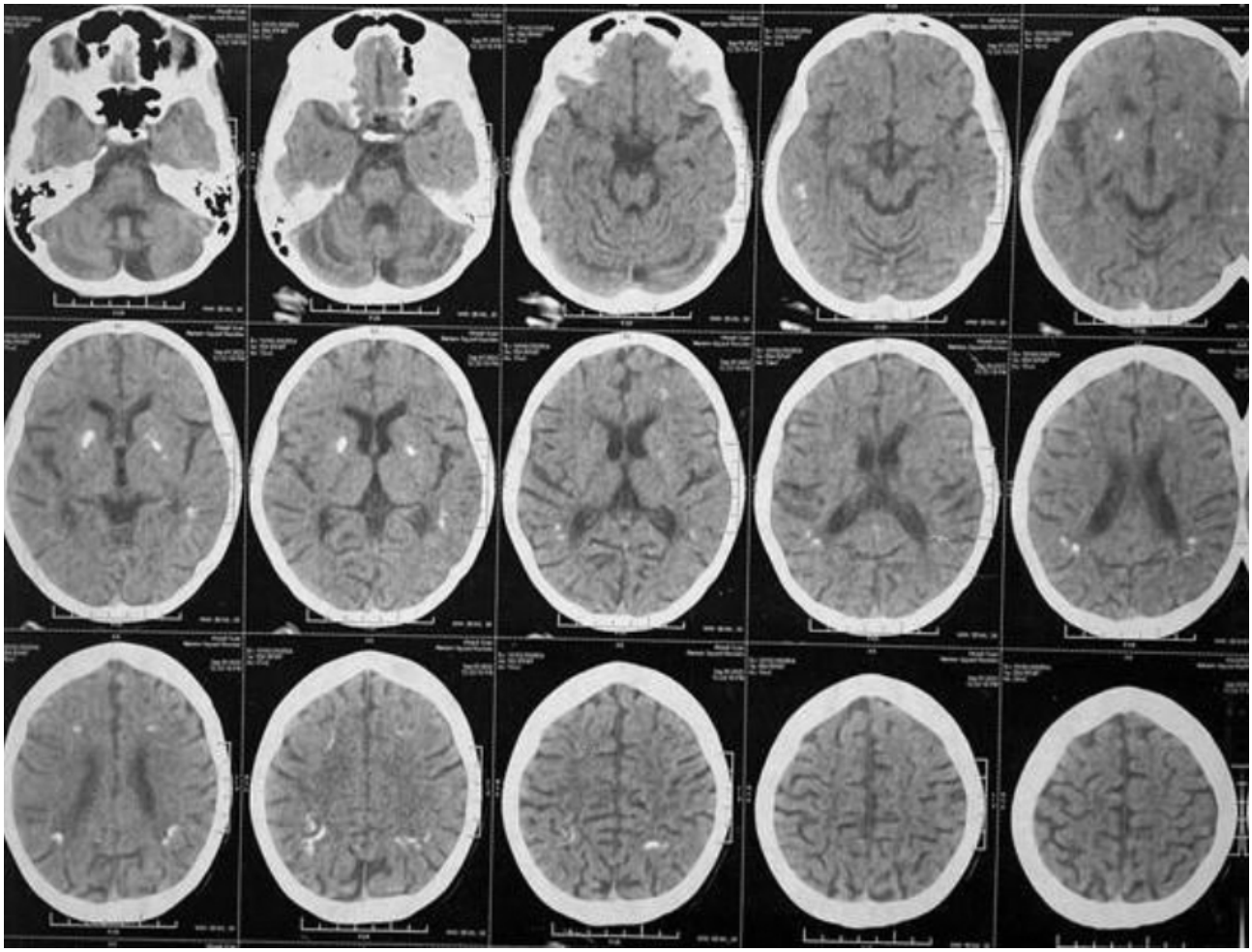

Figure 7. Non contrast multislice CT image showed bilateral basal ganglia and periventricular calcifications together with brain atrophic changes. CT, computed tomography.

FOLR1 gene c.506G>A; (p.Cys 69Tyr).[6,7] Most cases described in literature had a symptom-free interval of variable duration before the onset of their symptoms which suggest that 5-MTHF transport by folate receptor beta may compensate for FRα deficiency in early infancy.[7]

Typical clinical signs described at presentation were tremors, ataxia, hypotonia, developmental delay (mainly motor and speech), developmental regression and intractable seizures. Seizures mostly have a myoclonic feature, but other seizure types including astatic, tonic, tonic-clonic and atypical absences were reported. Recurrent episodes of status epilepticus have been reported in three affected children (two Finnish and one Turkish)[6] and, however, none of our patients encountered status epilepticus at any time of their lives.

Typical seizures in patients with FOLR1 mutation are myoclonic attacks, falls, and spasms.[8] In our two patients, both encountered myoclonic-tonic-drop attacks that were devastating and caused frequent falls and injuries.

Other less commonly clinical features described in patients with CFD were movement disorders such as chorea and athetosis which was described in a Belgian patient by Delmelle et al.[9] On the contrary, none of our two cases had any abnormal movements apart from ataxia. Polyneuropathy was described in one Russian patient and, similarly one of our patients had polyneuropathy as well.[10]

CSF 5-MTHF levels are extremely low in FRα deficiency, typically <5 nmol/L. The highest reported value was 11 nmol/L.[6] Unfortunately, we could not measure the levels of CSF MTHF as the test is not present in our country.

MRI brain was done to our cases and revealed the presence of cerebral and cerebellar atrophy. Cases reported in the literature had MRI findings of early hypomyelination, particularly affecting subcortical

white matter, together with cerebellar and/or cerebral atrophy.[6]

CT brain showed scattered brain calcifications affecting the basal ganglia (BG) bilaterally and the periventricular regions. However, brain calcification was not described in all cases with FOLR1 mutation, Toelle et al.[11] described a Ghanaian boy who diagnosed with FOLR1 mutation with stimulus sensitive myoclonus and had basal ganglia calcification together with cerebellar atrophy. Moreover, two Japanese patients described by Ohba et al.[12] one with basal ganglia and the other with subcortical WM calcifications.

Our two cases started treatment with IM folinate (the available form) after failure of many properly selected antiepileptics, and the dose was gradually increased with significant reduction in the severity and frequency of the attacks, but complete control was not achieved, it might be due to the late diagnosis and hence delayed initiation of the therapy. Treatment with oral folinic acid supplementation (at doses ranging from 0.5 to 7 mg/kg/day) has been reported to result in improvement of seizures, neuro-imaging findings and CSF 5-MTHF levels, but because of the poor response to oral folinic acid in many cases, many recent reports have suggested intermittent intravenous folinic acid therapy, in addition to the daily oral dosing.[13] Interestingly, folic acid is contraindicated in these conditions as it competitively binds to FRα, further reducing 5-MTHF transport into the brain.[6]

In conclusion, in young children presenting with ataxia and seizures that may resemble spasms or myoclonic astatic attacks, in combination with delayed brain myelination, cerebellar atrophy or BG calcification, and CFD should be considered. Early treatment of this treatable condition might save the neurodevelopment of those children and improve their outcome.

Conflicts of Interest

The authors declare no competing interests.

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