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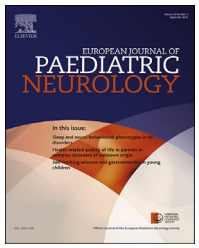

Original Article

Neurological improvement following intravenous high-dose folinic acid for cerebral folate transporter deficiency caused by *FOLR-1* mutation

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ABSTRACT

Background: Cerebral folate transporter deficiency caused by FOLR-1 mutations has been described in 2009. This condition is characterized by a 5MTHF level <5 nmol/l in the CSF, along with regression of acquisition in the second year of life, ataxia, and refractory myoclonic epilepsy. Oral or intravenous folinic acid (5-formyltetrahydrofolate) treatment has been shown to improve clinical status.

Case presentation: We present the cases of two sisters with cerebral folate transport deficiency caused by mutation in the folate receptor 1 (FOLR1) gene (MIM *136430). Following recommendations, we administered oral folinic acid at 5 mg/kg/day, resulting in some initial clinical improvement, yet severe epilepsy persisted. During treatment, cerebrospinal fluid (CSF) analysis revealed normal 5-methyltetrahydrofolate (5MTHF) levels (60.1 nmol/l; normal range: 53–182 nmol/l). Epilepsy proved difficult to control and the younger patient exhibited neurological regression. We then administered high-dose folinic acid intravenously over 3 days (6 mg/kg/day for 24 h, then 12 mg/kg/day for 48 h), which significantly improved clinical status and epilepsy. CSF analysis revealed high 5MTHF levels following intravenous infusion (180 nmol/l). Treatment continued with monthly intravenous administrations of 20–25 mg/kg folinic acid. At 2 years post-treatment, clinical improvement was confirmed.

Conclusions: This report illustrates that cerebral folate transporter deficiency caused by FOLR-1 mutations is a treatable condition and can potentially be cured by folinic acid treatment. As already reported, early effective treatment is known to improve outcomes in affected children. In our study, intravenous high-dose folinic acid infusions appeared to optimize clinical response.

Abbreviations: 5MTHF, 5-methyltetrahydrofolate; CSF, cerebrospinal fluid; FR, folate receptor.

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1. Introduction

Cerebral folate deficiency is a clinically-heterogeneous and etiologically-diverse condition characterized by a slowly progressive neurological disorder. This condition has subsequently been defined as "any neurological syndrome associated with a low cerebrospinal fluid (CSF) concentration of 5-methyltetrahydrofolate (5MTHF) in the presence of normal peripheral folate status". Various factors are known to be involved in intracerebral folate deficiency, including autoantibodies against the folate receptor, yet the underlying cause is often not understood.[1–6] In 2009, Steinfeld described an intracerebral folate deficiency case associated with mutations in the *FOLR1* gene.[7] This condition is characterized by a 5MTHF level <5 nmol/l in the CSF, along with stagnation or regression of acquisition in the second year of life, ataxia, and refractory myoclonic epilepsy.[7–9] Oral folinic acid (5-formyltetrahydrofolate) treatment has been shown to improve clinical status in most of published cases.[7–9] In some patients, intravenous treatment has been administered in the first treatment stage.[10,11] Mutations in the folate receptor 1 (*FOLR1*) gene encoding the folate receptor alpha (FRα) protein have also been confirmed in cases of cerebral folate deficiency.[7–10] This paper describes the cases of two sisters presenting with neurological regression associated with cerebral folate deficiency linked to a mutation in *FOLR1*. Administration of oral folinic acid resulted in only minor improvement, leading to the intravenous administration of higher dosages, which significantly improved development.

2. Patient history

The first girl was referred for developmental delay at the age of 3 years and 2 months. Her family history was unremarkable; she had unrelated Belgian parents and was the second child. The pregnancy, delivery, and neonatal period were uneventful. The girl said her first words at 9 months and made little progress thereafter, never able to form sentences. She acquired sitting position at 9 months and walked at 26 months. The parents noticed persistent gross motor difficulties, with problems running and climbing stairs. The child exhibited challenging behavior and rarely smiled. She was unable to imitate others and demonstrated little interest in other people. Weight, height, and head circumference were all within the normal range. There were no dysmorphic signs. The child was found to be irritable, exhibiting poor eye contact and several stereotypies. She had an ataxic gait, weak deep-tendon reflexes, and no Babinski sign. Mild psychomotor delay was also observed. Brain magnetic resonance imaging (MRI) revealed high signals in the white matter in T1, T2, and FLAIR sequences, indicative of diffuse hypomyelination. There was a depletion of white matter choline on spectroscopy. The CSF cytology, protein, glucose, and lactate levels were normal. Additional metabolic investigations, including peroxisomal, lysosomal, and purine analyses, yielded normal results. Electroencephalography (EEG), nerve conduction velocities, ophthalmological examination, brainstem auditory-evoked responses, and kidney and heart ultrasound were normal. Her clinical evolution consisted of occurrence of myoclonic jerks 3 months later, along with progressive neurological decline, dysmetria, and walking difficulties, and finally severe neurodisability with absence of language, severe axial hypotonia, and choreic movements rendering the child wheelchair-bound. In addition, the patient exhibited severe myoclonic epilepsy, despite treatment with clobazam, sodium valproate, topiramate, and levetiracetam. MRI confirmed previous lesions in the white matter with diffuse hypomyelination. EEG showed major abnormalities with low background rhythm and multifocal epileptiform discharges.

The second case is her younger sister, aged 31 months at the time. Her personal history revealed the same psychomotor evolution, with mild motor delay and minor progress followed by arrested language development. She also had seizures (myoclonic and tonic) and ataxic gait, along with hypomyelination revealed on brain MRI (Fig. 1, A–C) similar to her older sister. Her EEG also revealed disturbances with multifocal epileptiform discharges.

We completed our investigations with analysis of CSF 5MTHF dosage in both girls (aged 5 years and 3 years and 1 month, respectively). These levels were <1 nmol/l, in contrast with normal values of 53–182 nmol/l. Both had normal serum folic acid levels, and hematology indices and molecular investigations confirmed the presence of two mutations, namely c.332G>T (p.Glu108X) and c.373C>T (p.Arg125Cys), in the coding region of *FOLR1* (MIM *136430). The p.Glu108X mutation leads to a C-terminal truncation of the FOLR1 transporter protein, resulting most likely in a non-functional protein. The effect of the c.373C>T mutant allele (p.Arg125Cys) cannot be predicted without functional expression. Both parents were found to be heterozygous carriers and, furthermore, neither of these mutations has been described before, to the best of our knowledge.[4–7,9]

Oral folinic acid was initiated in both girls at 2 mg/kg/day, then increased to 5 mg/kg/day, which raised the CSF 5MTHF level to 60.1 nmol/l. The clinical course revealed a transient improvement in the younger child, though she subsequently deteriorated, presenting with increased seizures, loss of sitting ability, and major regression in language development despite antiepileptic treatment and increased folinic acid doses reaching 7 mg/kg/day. The clinical condition of the older girl remained stable, with severe axial hypotonia, choreic movements, and refractory myoclonic epilepsy.

In response to this evolution under oral treatment for 9 months, we decided to administer high-dose folinic acid intravenously in both girls: 6 mg/kg/day for 24 h in four doses, followed by 12 mg/kg/day in four doses for 48 h. The effect was dramatic, with rapid improvement in terms of eye contact, epilepsy, and muscle tone in the younger girl.

At the time of publishing, both girls were receiving daily oral folinic acid at 7 mg/kg/day and one 20–25 mg/kg injection of intravenous folinic acid (given in four doses over 24 h) every 4 weeks. For practical reasons, this dosage was adapted to the volume of the bottle (500 mg for each girl). The younger