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Case Study

Cerebral Folate Deficiency Syndrome (CFDS) FOLR1 Deficiency Syndrome Neurodegeneration due to Cerebral Folate Transport Deficiency

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Abstract

This report presents the cases of three children diagnosed with cerebral folate transport deficiency (CFD), highlighting the importance of early diagnosis and treatment. Two siblings from a German family exhibited severe neurodegeneration after the age of two. The older brother developed motor impairments, became wheelchair-dependent by age 3 years and 9 months, and suffered from drug-resistant seizures. Folinic acid therapy led to a reduction in seizure severity and allowed him to regain assisted mobility. The younger sister displayed initial motor symptoms at 2 years and 3 months but, due to early folinic acid intervention, achieved complete recovery and has remained asymptomatic. A third case involved a 5-year-old girl from an Italian village, who presented with severe disability, cognitive impairment, and frequent seizures. Diagnosis and folinic acid treatment resulted in gradual clinical improvement. All patients had significantly reduced cerebrospinal fluid (CSF) 5-methyltetrahydrofolate (5-MTHF) levels, which improved with treatment. Brain MRI of the more severely affected patients showed abnormalities in white matter myelination, while MR spectroscopy revealed reduced choline and inositol peaks. These cases underscore the progressive nature of CFD when untreated and emphasize the critical role of early recognition and folinic acid therapy in improving outcomes and preventing long-term neurological damage.

Keywords: *Cerebrospinal Fluid (CSF); 5-Methyltetrahydrofolate (5-MTHF); Cerebral Folate Transport Deficiency (CFD); Cerebral Folate Deficiency Syndrome (CFDS); FOLR1 Deficiency Syndrome; Neurodegeneration*

Case Study

Starting case

We present the case of a four-year-old girl from Jordan who experienced recurrent seizures and multiple strokes over the course of a year, accompanied by cognitive decline of unknown origin. Her condition initially manifested with a sudden weakness on the right side of her body, leading to difficulties in movement. She was admitted to a hospital in Irbid City, where she remained for an extended period without a definitive diagnosis.

A CT brain scan revealed calcifications in the basal ganglia. Laboratory investigations showed decreased levels of serum and cerebrospinal fluid (CSF) folate, low plasma methionine, and increased urinary excretion of formiminoglutamic acid (FIGLU). She was subsequently diagnosed with cerebral folate deficiency syndrome (CFDS), a condition characterized by low CSF folate levels despite normal systemic folate levels.

The clinical presentation of CFDS varies, but in this child's case, the presence of serum folate receptor-alpha (FRα) autoantibodies was identified as the primary cause, impairing folate transport across the choroid plexus into the brain. Less frequently, CFDS may arise from mitochondrial disorders, inborn errors of metabolism, or mutations in the FOLR1 gene.

Recognizing CFDS early is vital, as prompt diagnosis and timely intervention can significantly improve outcomes. This article highlights the role of FRα autoimmunity in CFDS, emphasizing its age-dependent clinical presentations, diagnostic approaches, treatment options, and preventive strategies for at-risk populations.

The infantile form of CFDS typically emerges between 4 to 6 months of age, with early symptoms including agitation, sleep disturbances, and persistent restlessness-often distressing to caregivers. These nonspecific signs can easily be mistaken for common infant conditions such as gastroesophageal reflux, milk allergy, or lactose intolerance. As the disease progresses, neurodevelopmental delays become evident, with slowing head growth, hypotonia, ataxia, and pyramidal signs in the lower limbs. If untreated, this can evolve into spasticity involving all four limbs (tetra-spasticity). Seizures and movement disorders (dyskinesias) develop in approximately one-third of cases. By three years of age, progressive vision loss may occur, and hearing impairment can develop around six years of age.

The underlying mechanisms of CFDS are diverse, with five main pathways proposed:

1. Impaired transport of folates across the blood-brain barrier and into the CSF and brain tissue.
2. Defective folate storage and release from intracellular folyl-polyglutamate reserves.
3. Increased utilization of reduced folates in the nervous system, depleting folate reserves.
4. Accelerated breakdown of reduced folates within the nervous system.
5. Metabolic disturbances affecting folate processing in the CNS.

Folate is critical during pregnancy, and deficiencies have been associated with neural tube defects and developmental disorders, including autism. Systemic folate deficiencies can lead to macrocytic anemia, pancytopenia, immune dysfunction, and neurological issues. CNS-related symptoms include irritability, hypotonia, developmental delays, ataxia, seizures, dyskinesias, and peripheral neuropathy.

In infantile CFDS, FRα autoantibodies are the most common cause. These autoantibodies target the folate receptor on the choroid plexus, impairing the transport of 5-methyltetrahydrofolate (MTHF) into the CSF and brain. Inborn errors of metabolism can also disrupt folate pathways. For instance, 3-phosphoglycerate dehydrogenase deficiency, an autosomal recessive disorder, leads to impaired serine synthesis, affecting one-carbon metabolism vital for folate processing.

If untreated, CFDS can result in autism spectrum disorders and structural brain abnormalities. MRI findings often show delayed myelination, cerebral and cerebellar atrophy, and demyelination in subcortical and periventricular areas. Routine blood work is often normal, making a spinal tap essential to confirm low CSF folate levels. Testing for FRα autoantibodies can confirm the diagnosis, though antibody levels may fluctuate over time. Supplements containing folates should be avoided for at least three days before testing to prevent inaccurate results. When FRα autoantibodies are absent, further investigation into mitochondrial disorders, FOLR1 mutations, and MTHFR variants is warranted. Biomarkers of oxidative stress and essential enzyme cofactors may also be assessed.

The diagnostic approach should be guided by clinical presentation and history, with brain imaging, EEG, and metabolic screening included as needed. A suspected CFDS diagnosis requires comprehensive blood work and a lumbar puncture to measure CSF folate, neurotransmitter metabolites, pterins, amino acids, and lactate. Testing for FRα autoantibodies should be repeated if initial results are negative.

Infantile CFDS can present as an emergency in cases of severe dyskinesia, frequent seizures, or status epilepticus. In such situations, corticosteroids can help reduce FRα autoimmunity while awaiting the effects of folinic acid supplementation and a dairy-free diet. Although intravenous immunoglobulin therapy has been explored, evidence regarding its long-term benefits remains inconclusive.

Early diagnosis and appropriate treatment can significantly alter the disease course, offering affected children an improved quality of life and preventing long-term neurological damage.

Treatment

Early diagnosis and timely initiation of folinic acid treatment, including intramuscular (IM) injections when necessary, can prevent long-term neurological complications in infants with cerebral folate deficiency syndrome (CFDS). It is crucial to maintain a high index of suspicion for infantile CFDS in cases presenting with neurodevelopmental delays and other characteristic symptoms, as prompt intervention is essential to halt disease progression and prevent neurological decline. When treatment begins before the age of two, children have shown remarkable recovery, with some achieving complete resolution of symptoms.

Upon confirming a diagnosis of CFDS caused by folate receptor-alpha (FRα) autoimmunity, treatment should be initiated immediately with high pharmacological doses of folinic acid (5-formyltetrahydrofolate). Recommended dosing includes dl-folinic acid at 0.5 - 1 mg/kg body weight per day, which can be gradually increased to 2 mg/kg per day, not exceeding a maximum daily dose of 50 mg. Alternatively, levo-folinic acid can be administered at 0.25 - 0.50 mg/kg body weight per day, or levo-5-methyltetrahydrofolate may be considered; however, the latter is not approved for medical use in Europe.

Caution is advised when initiating folinic acid therapy. During the first month, the dose should be introduced gradually, starting at half the intended target dose. Rapid increases in folate levels within the brain can lead to an abrupt elevation of tetrahydrobiopterin and neurotransmitters such as dopamine and serotonin, resulting in overstimulation of their respective synapses. This may cause adverse effects, including agitation and aggression. Typically, it takes approximately six weeks for neurotransmitter production and receptor activity to stabilize. If agitation or aggression persists despite gradual dose adjustments, a temporary low dose of risperidone can be considered for symptomatic relief over two to three months.

Long-term follow-up studies of children with infantile CFDS treated with folinic acid have demonstrated that early intervention is associated with significantly better outcomes. When treatment is initiated before the age of two, some children achieve full recovery, underscoring the importance of early recognition and treatment. Therefore, clinicians must remain vigilant and consider CFDS in infants presenting with unexplained neurodevelopmental impairments to ensure timely diagnosis and intervention.

Case 2

We describe a case involving two siblings from a German family who experienced severe neurodegeneration beginning after the age of two. The older child, a boy, developed profound motor impairments and became wheelchair-dependent by the age of 3 years and 9 months. He also suffered from drug-resistant epileptic seizures. Following the initiation of oral folinic acid treatment, his seizures decreased in frequency and severity, and he was eventually able to walk with assistance.

The younger sibling, a girl, exhibited her first motor symptoms at 2 years and 3 months of age. However, due to early recognition and prompt treatment with folinic acid, she achieved complete recovery and has remained symptom-free since.

A third case, reported by Steinfeld., *et al*. involved a girl from a small Italian village who exhibited a similar clinical presentation. By the age of 5, she was severely disabled, cognitively impaired, and experienced frequent epileptic seizures. Upon diagnosis of cerebral folate transport deficiency, she was started on oral folate treatment, which led to a gradual improvement in her condition.

In all three patients, cerebrospinal fluid (CSF) concentrations of 5-methyltetrahydrofolate (MTHF) were significantly reduced but increased following folinic acid therapy. Brain MRI in the two severely affected children revealed pronounced myelination abnormalities, primarily involving the periventricular and subcortical white matter. MR spectroscopy showed decreased choline and inositol peaks in the parieto-occipital white matter. The younger German sister, though showing milder MRI abnormalities, achieved normalization of imaging findings after treatment.

Clinical presentation and disease progression

Children affected by cerebral folate transport deficiency typically develop normally during infancy. However, around the age of two, they begin to experience a decline in previously acquired cognitive and motor abilities, a process known as psychomotor regression. This regression is often accompanied by the onset of intellectual disability, speech difficulties, and recurrent seizures (epilepsy). Movement disorders such as tremors and ataxia (poor coordination) can be severe, leading some affected individuals to require wheelchair assistance.

A characteristic feature of the disorder is leukodystrophy, a condition involving the loss of white matter in the brain. White matter consists of nerve fibers covered by myelin, a fatty substance that facilitates the rapid transmission of nerve impulses. The breakdown of white matter contributes to the worsening neurological symptoms seen in cerebral folate transport deficiency.

Without appropriate treatment, these neurological impairments typically progress over time, leading to increasing disability. However, early diagnosis and intervention with folinic acid can alter this course, potentially enabling recovery and preventing further decline.

These cases underscore the importance of early diagnosis and intervention in cerebral folate deficiency syndrome (CFDS). Early folinic acid supplementation can significantly alter disease progression, preventing severe disability and, in some cases, enabling full recovery.

Early diagnosis and management

Key symptoms prompting evaluation include developmental delays, regression in motor and language abilities, seizures, and movement abnormalities. Diagnosis involves cerebrospinal fluid (CSF) analysis to measure 5-MTHF levels, blood tests to exclude systemic folate deficiency, genetic testing for FOLR1 mutations, and screening for folate receptor autoantibodies. Brain imaging may reveal white matter abnormalities in advanced cases.

Treatment involves folinic acid supplementation (0.5 - 2 mg/kg/day) adjusted based on response. Autoimmune CFDS may require immunomodulatory therapies such as corticosteroids or intravenous immunoglobulin (IVIG). Supportive care includes antiepileptic medications, physical and speech therapies, and nutritional support. Regular follow-up with CSF analysis and clinical evaluations ensures treatment effectiveness and developmental progress.

Early intervention and a multidisciplinary approach can significantly improve outcomes, with some children achieving complete recovery if treated before age two.

Conclusion

Cerebral folate deficiency syndrome (CFDS) is a rare neurological disorder marked by low levels of 5-methyltetrahydrofolate (5-MTHF) in the cerebrospinal fluid despite normal systemic folate levels. It leads to neurodevelopmental delays, movement disorders, seizures, and intellectual disability. Causes include FOLR1 gene mutations, folate receptor autoantibodies, and secondary metabolic or mitochondrial disorders. Early recognition and treatment with folinic acid are critical to improving outcomes, with better recovery prospects when treatment begins before age two. Ongoing research into genetic and immunological mechanisms is essential to refine diagnostic and therapeutic approaches. Multidisciplinary care is key to optimizing the prognosis for affected individuals [1-5].

Supplementary Material

Location	Phenotype	Phenotype MIM number	Inheritance	Phenotype mapping key	Gene/Locus	Gene/Loc MIM number
11q13.4	Neurodegeneration due to cerebral folate transport deficiency	613068	AR	3	FOLR1	136430
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11q13.4	Neurodegeneration due to cerebral folate transport deficiency	613068	AR	3	FOLR1	136430

Table

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