

Brief communication

# Cerebral folate deficiency: life-changing supplementation with folinic acid

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## Abstract

Cerebral folate deficiency is characterized by low cerebrospinal fluid (CSF) concentrations of 5-methyltetrahydrofolate and a broad spectrum of clinical signs and symptoms. A patient with progressive spasticity, gait disturbance, speech difficulties, initially diagnosed as a recessive spastic paraplegia recovered on folinic acid (15–30 mg/day) and her 5-methyltetrahydrofolate in CSF normalized. This report demonstrates the importance of CSF investigation in the diagnosis of cerebral folate deficiency and efficiency of folinic acid (5-formyltetrahydrofolate) supplementation.

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## Introduction

Cerebral folate deficiency (CFD) is defined by low cerebrospinal fluid (CSF) folates [1]. Particularly the active metabolite and C1-donor 5-methyltetrahydrofolate (5MTHF) is significantly reduced in CSF. A number of well characterized inherited neurometabolic disorders may present with CFD, including dihydropteridine reductase deficiency (OMIM 261630; hyperphenylalaninemia due to tetrahydrobiopterin deficiency with progressive mental and physical retardation, hypotonia/hypertonia, swallowing difficulties, hypersalivation, chorea/athetosis, temperature instability, and basal ganglia calcifications) [2], 5,10-methylene-tetrahydrofolate reductase deficiency (OMIM 236250; mental retardation, microcephaly, gait disturbance, psychiatric disturbances, seizures, abnormal EEG, occlusions, and limb weakness) [3], and 3-phosphoglycerate dehydrogenase deficiency (OMIM 601815; microcephaly, megaloblastic

anemia, thrombocytopenia, seizures, spastic tetraplegia, nystagmus, cataract, and hypogonadism) [4]. Disturbed folate transport across the blood-CSF barrier was proposed in 31 patients with CFD characterized by psychomotor retardation, spastic paraplegia, cerebral ataxia, and dyskinesia [5], in eight girls with Rett syndrome [6], and in three patients with a variant of the Aicardi–Goutières syndrome [7]. With the exception of patients with 5,10-methylene-tetrahydrofolate reductase deficiency, they all potentially may benefit from folinic acid substitution. This report documents a girl with CFD who recovered on folinic acid (Isovorin) supplementation, a life-changing treatment.

## Patient and methods

### Case report

Pregnancy, birth, and early development were normal. At the age of 3.5 years the girl presented with spasticity, gait problems, and speech difficulties. She was

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referred to a school for physically handicapped children. Repeated videos from the school reveal disease progression and stagnation of her mental development. At the age of 9.5 years her leg spasticity was so pronounced that i.t. Baclofen was considered. She was drooling. No polyneuropathy was evident. Visual evoked potential suggested prolonged latency. CT, MRS (cerebrum and spinal cord), lysosomal enzymes, long-chain fatty acids, phytanic acid, and other metabolic tests in urine and plasma were all normal. An atypical recessive spastic paraplegia was suspected and a trial with L-Dopa (Sinemet) was initiated, however, without clear improvement of clinical symptoms. Sinemet was stopped at the age of 12 years. At that time ataxia was described for the first time and her bladder spasticity had to be treated with Detrusitol. She was able to walk with a rollator at the age of 12<sup>8/12</sup> years, but with scissoring. There was additional dystonia.

At the age of 12<sup>10/12</sup> years her CSF was investigated for pediatric neurotransmitter disorders and we found reduced neurotransmitter metabolites, 5-hydroxyindoleacetic acid, homovanillic acid, and very low 5MTHF (Table 1). Neopterin and biopterin were normal. Treatment with folinic acid (Isovorin; 5-formyltetrahydrofolate) was initiated at a dosage of 15 mg/day, resulting in an amazing effect after less than one week. She could take a seat without falling, could negotiate stairs, was more alert, brighter and much more interested in school. She soon began walking with elbow sticks and sitting on a normal chair. She had a normal appearance, relaxed, with her legs crossed. There was no more dystonia. Repeated lumbar puncture after 10 weeks on treatment revealed complete normalization of CSF metabolites (Table 1). At the age of 14 years her spasticity increased again and she needed bilateral A-tendon elongation. Her Isovorin dose was doubled to 30 mg/day, again with amazing results. Her gait and stability improved and her speech is now near normal at the age of 14<sup>7/12</sup>.

### CSF folates

Lumbar punctures were performed in the morning, and the first 0.5 ml of CSF was discarded or used for other tests. The next 1 ml of CSF was collected and frozen at  $-80^{\circ}\text{C}$  until analyzed. The procedures used were in accordance with the current revision of the Helsinki

Declaration of 1975. 5MTHF was measured using HPLC with electrochemical detection as described elsewhere [7].

### Results and discussion

The analysis of folate metabolites in CSF is part of the basic investigations for the diagnosis of pediatric neurotransmitter disorders and should be considered in patients presenting with hypo-/hyperkinesia, distal chorea, myoclonic epilepsy, dystonia, oculogyric crises, hypersalivation, temperature instability, aggressive behavior, or mental retardation. We found very low folates (5MTHF) in a girl initially diagnosed with recessive spastic paraplegia. This investigation requires only a small volume of CSF and can exclude a number of other inherited neurometabolic disorders. Immediate substitution with folinic acid (15 mg/day) reversed the clinical symptoms within a few days. Similar benefit from folinic acid supplementation have previously been reported by Ramaekers et al. [5]. They also reported on a similar reduction of the neurotransmitter metabolites 5HIAA and HVA in CSF from some patients with CFD. In our patient levels of both metabolites increased 10 weeks after introduction of folinic acid. Although there are some speculations about the connection between folate and neurotransmitter pathways, there is no rational explanation for the influence of low folates on serotonin and catecholamine homeostasis.

The reason for a reduction of cerebral folate concentrations in patients in whom inherited metabolic disorders (see above) were excluded is still a matter of investigation. The biochemical abnormalities in CSF suggest a transport defect across the blood–brain barrier, although increased folates turnover or reduction by reactive oxygen species cannot be excluded. Folate deficiency in CSF has been shown to be associated with a defect in folate-binding protein (FBP-1) [8]. The FBP-1 is localized at the basolateral surface of the choroid plexus and its inactivation may be responsible for reduced folate transport to the CSF. Another reason for the reduction of CSF folates may be inactivation of folate transport by the presence of autoantibodies against the folate receptor. Such autoantibodies were

Table 1  
5-Methyltetrahydrofolate (5MTHF), neurotransmitter metabolites 5-hydroxyindoleacetic acid (5HIAA) and homovanillic acid (HVA), and neopterin (Neo) and biopterin (Bio) in CSF of a girl with cerebral folate deficiency before and on treatment with folinic acid

Age	5MTHF (nmol/L)	5HIAA (nmol/L)	HVA (nmol/L)	Neo (nmol/L)	Bio (nmol/L)
12 years 11 months (before treatment)	34.4	93	174	14.8	12.1
13 years 2 months (on treatment with folinic acid 15 mg/day)	127.1	154	293	11.6	12.6
Controls (10–16 years) $n = 137$ Median (5.–95. perc.)	67.0	138.0	305.0	13.0	18.0
	42.0–119.6	71.8–231.8	146.3–533.2	8.0–23.0	10.9–32.0

found in women with a pregnancy complicated by a neural-tube defect [9].

Folinic acid supplementation is effective and should be initiated as early as possible. It may offer a life-changing therapy in patients with biochemically confirmed CFD. However, empiric treatment of this potentially very reversible condition in patients without CSF investigations is not recommended.

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