Letters to the Editor

Cerebral Folate Deficiency and Folinic Acid Treatment in Hypomyelination with Atrophy of the Basal Ganglia and Cerebellum (H-ABC) Syndrome

To the Editor

The hypomyelination with atrophy of the basal ganglia and cerebellum (H-ABC) syndrome is a newly recognized entity defined by a unique pattern of MRI changes, and progressive pyramidal/extrapyramidal movement disorder and variable degrees of mental deficit (van der Knaap et al. 2002). Neither biochemical nor genetic markers have been elucidated and causal treatment is not available. So far 8 patients have been described (van der Knaap et al. 2002; Mercimek-Mahmutoglu et al. 2005).

A new patient with progressive atrophy of the nucleus lentiformis, cerebellar atrophy, and hypomyelination of supra- and infra-tentorial white matter has recently been reported in this Journal (Wakusawa et al. 2006). Clinically this male patient had unremarkable motor development during the first 15 months, but he developed progressive hemi-dystonia at age of 2 years. Although cerebrospinal fluid (CSF) levels for dopaminergic neurotransmitters were normal, treatment with levodopa/carbidopa and trihexiphenidyl was started at the age of 35 months. There was no improvement of clinical symptoms upon a low dosage of levodopa/carbidopa, but upon high dosage levodopa/carbidopa (200/20 mg per day) he showed a considerable improvement of his movement disorder.

We described a female patient with H-ABC syndrome and progressive dystonia and spasticity since the age of 3 months (Mercimek-Mahmutoglu et al. 2005). CSF levels of dopaminergic and serotoninergic neurotransmitters and pterines were normal. However this patient had concomitant cerebral folate deficiency: At age of 7 and 20 months, 5-methyltetrahydrofolate (5-MTHF) levels were 75% and 60% of the lowest age-related normal values. Systemic folate deficiency was ruled out by normal plasma and erythrocyte folate levels, and 5-MTHF reductase activity was normal in leucocytes.

Cerebral folate deficiency is a newly recognized condition (Ramaekers et al. 2002), the biochemical and genetic background of which has not been convincingly elucidated so far. Patients present with a variety of neurological deficits including pyramidal and extrapyramidal movement disorder, seizures, psychomotor retardation and cerebral atrophy. Some (mainly young) patients respond favorably to folinic acid substitution. Auto antibodies to folate receptors have been described in 25 out of 28 patients (Ramaekers et al. 2005). We did not determine autoantibodies to folate receptors in our patient.

Our patient is the first with the association of cerebral folate deficiency and H-ABC syndrome. After 5 months of treatment with 1.5 mg/kg/d folinic acid intramuscularly, a clear improvement of opisthotonic, oculogyric and sweating crises was noted. Cerebral 5-MTHF levels were slightly above the lower age related normal value, while dopaminergic and serotoninergic neurotransmitters were again within normal range. With the aim to further improvement residing dystonia, we performed an additional treatment trial with 3 mg/kg/day levodopa/carbidopa (100/25 mg). However, after 11 months of treatment there was no further clinical improvement. In contrast to Wakusawa et al. (2006), we did not try higher dosages of levodopa/carbidopa. One month after discontinuation of levodopa/carbidopa, CSF 5-MTHF levels were 85% of the lower age-related normal range.

Wakusawas’ observation suggests that patients with H-ABC syndrome may respond to high dosage levodopa/carbidopa substitution. Our observation adds that patients may have
concomitant cerebral folate deficiency and may respond to folinic acid substitution. Therefore CSF neurotransmitter and 5-MTHF levels should be determined in patients with H-ABC syndrome and treatment trials with both substances should be performed.

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References