

## **Is folinic acid beneficial for autism?**

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Recent research suggests that folinic acid (a derivative of the B vitamin, folic acid) is beneficial for some people with autism.

Cerebral folate deficiency has been defined as any neuropsychiatric condition associated with abnormally low levels of 5-methyltetrahydrofolate (5-MTHF; the active form of folate) in cerebrospinal fluid (CSF), in association with normal folate status and normal folate metabolism outside the central nervous system. Manifestations of cerebral folate deficiency include marked irritability, slow head growth, psychomotor retardation, cerebellar ataxia, pyramidal tract signs in the legs, dyskinesias, and, in some children, seizures or autism. Cerebral folate deficiency appears to be caused in most cases by the production of autoantibodies that block the receptor involved in transporting folate across the blood-brain barrier. Folinic acid can bypass autoantibody-blocked folate receptors and enter the CSF by a different mechanism,<sup>1</sup> and then be converted to 5-MTHF. In case reports, treatment with folinic acid (or folic acid in a patient who did not have the aforementioned autoantibodies) resulted in improvement in several children with autism associated with cerebral folate deficiency.

Two children (aged 2 and 3 years) with cerebral folate deficiency who were positive for the autoantibodies described above received folinic acid at a dose of 0.5-1.0 mg per kg of body weight per day in 2 divided doses per day. The concentration of 5-MTHF in CSF became normal and the patients showed improvement in autistic behavior and in various neurological abnormalities. Autism did not improve in 2 other patients who were treated at an older age (5 and 12 years). An autistic patient with cerebral folate deficiency but without autoantibodies against the folate receptor recovered completely after receiving 400 µg per day of folic acid.<sup>1</sup>

A follow-up study by the same research group found low CSF levels of 5-MTHF in 23 of 25 children with early-onset low-functioning autism and at least 1 of the major clinical features of infantile-onset cerebral folate deficiency. In these children, supplementation with folinic acid resulted in partial or complete clinical recovery.

Of 25 children (median age, 6.9 years; range, 2.8-12.3 years) with early-onset low-functioning autism and at least 1 of the major clinical features of infantile-onset cerebral folate deficiency, 23 had a subnormal concentration of 5-MTHF in the CSF, despite having a normal serum folate level. In 19 of these 23 children, the low CSF level of 5-MTHF could be explained by the presence of folate receptor autoantibodies. Supplementation with folinic acid normalized CSF levels of 5-MTHF and led to partial or complete clinical recovery after 12 months. The dosage of folinic acid was 1 mg per kg of body weight per day; this was increased to 2-3 mg per kg per day in 2 divided doses per day, if CSF levels of 5-MTHF were still below normal after 3-6 months.<sup>2</sup>

A study of 93 children with autism spectrum disorders found a high prevalence of folate receptor autoantibodies in serum, low-normal CSF concentrations of 5-MTHF, and a positive clinical response to folinic acid in about one-third of patients with folate receptor autoantibodies.

Of 93 children with autism spectrum disorders, 75.3% had folate receptor autoantibodies in serum. Sixteen children with folate receptor autoantibodies had a lumbar puncture; in all cases, the CSF concentration of 5-MTHF was below the normal mean, but above the lower limit of normal. Children with folate receptor autoantibodies were treated with folinic acid (leucovorin calcium) at a dose of 2 mg per kg of body weight per day (maximum, 50 mg per day). Over a mean period of 4 months, compared with a waiting-list control group, the treated patients had significantly greater improvement in verbal communication, receptive and expressive language, attention, and stereotypical behavior. About one-third of children given folinic acid had moderate or much improvement. Four children had to discontinue treatment because of worsening aggression (n = 3) or insomnia and gastroesophageal reflux (n = 1).<sup>3</sup>

These studies suggest that autistic children with low CFS levels of 5-MTHF, and about one-third of those with low-normal levels, can benefit from folinic acid supplementation. In lieu of an invasive lumbar puncture to measure 5-MTHF in CSF, testing serum for folate receptor autoantibodies might help predict who is likely to respond to folinic acid. An Internet search revealed that one commercial laboratory (Iliad Neurosciences, Inc.)<sup>4</sup> is currently offering the serum folate receptor antibody test for \$200.

In many cases, folate receptor autoantibodies may be antibodies to cow's milk proteins which, in susceptible individuals, cross-react with the folate receptor. Among 12 children with cerebral folate deficiency who consumed a milk-free diet for 3-13 months, the mean titer of autoantibodies against the folate receptor decreased by 83%.<sup>5</sup> That finding could explain in part the positive response that some autistic children have to a milk-free diet.

Supplementation with folic acid (and presumably with folinic acid as well) may increase vitamin B<sub>12</sub> requirements. For that reason, some doctors recommend that people taking folic acid or folinic acid also take vitamin B<sub>12</sub> in most cases.

Note: The information provided in this article is for educational purposes only, and should not be construed as personal medical advice or instruction. Consult your healthcare practitioner before taking nutritional supplements.

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<sup>1</sup> Ramaekers VT, Rothenberg SP, Sequeira JM, et al. Autoantibodies to folate receptors in the cerebral folate deficiency syndrome. *N Engl J Med* 2005;352:1985-1991.

<sup>2</sup> Ramaekers VT, Blau N, Sequeira JM, et al. Folate receptor autoimmunity and cerebral folate deficiency in low-functioning autism with neurological deficits. *Neuropediatrics* 2007;38:276-281.

<sup>3</sup> Frye RE, Sequeira JM, Quadros EV, et al. Cerebral folate receptor autoantibodies in autism spectrum disorder. *Mol Psychiatry* 2013;18:369-381.

<sup>4</sup> <http://iliadneuro.com>. Accessed January 20, 2016.

<sup>5</sup> Ramaekers VT, Sequeira JM, Blau N, Quadros EV. A milk-free diet downregulates folate receptor autoimmunity in cerebral folate deficiency syndrome. *Dev Med Child Neurol* 2008;50:346-352.