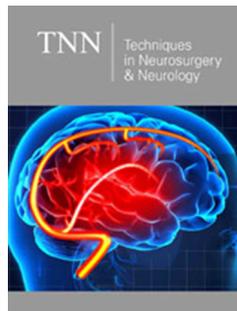


Cerebral Folate Deficiency in Autism Spectrum Disorder

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Abstract

Autism Spectrum Disorder (ASD) is a developmental disability that can create significant behavioral and communication challenges. The prevalence of ASD among children at 8 years of age is approximately 2%, and the prevalence is similar across ethnic groups and countries. Studies have shown that the majority of ASD children make an autoantibody to the high-affinity folate receptor in response to a dietary component. This Folate Receptor Antibody (FRA) blocks transport of folate across the Blood-Brain Barrier (BBB), resulting in a Cerebral Folate Deficiency (CFD). In clinical trials, these ASD children had improvement in their communication when placed on a daily supplement of folate in its reduced form, which can enter the brain via a low-affinity transport. When stressed, this CFD is likely to lead to more severe communication difficulty.

Keywords: ASD; Folate; Nutrition; Stress

Folate in Nervous System Development

Folate (Vitamin B-9) is a key contributor to normal nervous system development [1,2]. This vitamin is present in bio-available form in many foods, including legumes, leafy greens, and fruits. The naturally occurring, bio-available form is methylated, while the synthetic version in most vitamin capsules is the oxidized form, folic acid. Folate is necessary for neural tube formation and closure in the human embryo and plays an essential role throughout fetal brain development [3-5]. Insufficient folate can be implicated in many developmental conditions, including spina bifida in the newborn [6,7]. To reduce such complications, prenatal vitamins contain Vitamin B-9, typically in its stable, oxidized form of folic acid, rather than the reduced form of folate. Most individuals can convert sufficient folic acid to folate. However, about 10% of the population has a limitation in absorbing folate into the brain due to the presence of an autoantibody to the folate receptor [8].

Folate Receptor Antibody and Cerebral Folate Deficiency

This Folate Receptor Antibody (FRA) blocks high affinity folate receptors, preventing folate from crossing the blood brain barrier [8,9]. Clinical studies have shown that blood levels of the FRA can be reduced by changes in diet, particularly elimination of dairy products [10]. If levels of FRA are reduced or eliminated, this could thus allow sufficient folate to enter the brain. While FRA is present in a small minority of the population, clinical tests find that about 70% of ASD children have FRA [11]. Meta-analysis from multiple studies showed that ASD children are 20 times more likely to have FRA [12], pointing to a likely genetic component that restricts brain absorption of Vitamin B-9. While FRA can be reduced with significant change in diet [10], a symptom of ASD is resistance to dietary change. Thus, the dietary factors contributing to FRA are self-perpetuating due to this change resistance, as FRA causes reduction of folate entering the brain. Those with FRA have a reduced amount of folate reaching their brain, creating Cerebral Folate Deficiency (CFD). This CFD can be countered

by supplementation with elevated levels of the natural version of folate, in the form of methyl-folate or folinic acid (but not with folic acid) [8,9,13]. In multiple clinical trials, it has been found that ASD children who have FRA have improvement in their communication when given daily folate supplements (in the form of folinic acid) for three months [14,15]. Further trials are ongoing to evaluate L-folinic acid (levo-Leucovorin) or methyl-folate as the folate sources. But it is now clear that supplementation with reduced folate can help overcome CFD. Once CFD is reduced or eliminated, it could be possible to revise the diet of the ASD children to reduce production of FRA. This may provide an optimal method to reduce ASD symptoms. Key in such a dietary treatment is decreasing agents that can stimulate FRA production and provision of food sources of folate. These two things, elimination of autoantibody-stimulating foods and consumption of the natural form of folate (the reduced form), provide the key conditions for reducing severity of ASD symptoms. Diets that are richer in natural folate include the Mediterranean diet that focuses on olive oil, fresh vegetables and fruits, nuts, legumes and fish.

Folate and Mental Health

The role of folate in depression has been evaluated extensively. Clinical trials have found that in depressed patients with low serum folate, a daily supplement of Vitamin B-9 alleviated the depression [16]. More recently, there has been evidence that individuals with CFD related to the presence of FRA can have improvement from depression with folate supplementation or use of a Mediterranean diet which increases folate absorption [17]. The observation of a higher rate of depression in autism may indeed be related to folate or a common mechanism where folate is involved. This is consistent with observations that ASD individuals have more severe communication difficulties when they experience elevated levels of stress. Whether folate is related to the mechanism by which this is translated is unknown at this time. However, it may be a useful marker to search for in such cases. We note that the link to diet is also telling, given that autistic people often have a repetitive diet. Such a diet is rarely the healthy Mediterranean diet found to be beneficial, and thus when stressed the autistic person would have no nutritional reserve to draw on, exacerbating communication difficulties.

Conclusion

Folate is a key vitamin in neural health. Evidence shows that most autistic people produce the autoantibody FRA, that blocks folate absorption into the brain, resulting in CFD. Stress may exacerbate this deficiency, worsening communication difficulties in ASD. Diets that are rich in natural forms of folate, such as the Mediterranean diet may help alleviate the CFD, and when coupled

with reduction in stress may improve communication in autistic people.

References

1. Alam C, Kondo M, Connor DL, Bendayan R (2020) Clinical implications of folate transport in the central nervous system. *Trends Pharmacol Sci* 41(5): 349-361.
2. Reynolds E (2006) Vitamin B12, folic acid, and the nervous system. *Lancet Neurol* 5(11): 949-960.
3. Pitkin RM (2007) Folate and neural tube defects. *Am J Clin Nutr* 85(1): 285S-288S.
4. Blom HJ, Shaw GM, den Heijer M, Finnell RH (2006) Neural tube defects and folate: case far from closed. *Nat Rev Neurosci* 7(9): 724-731.
5. Bobrowski KN, Ramaekers VT, Sequeira JM, Quadros EV (2021) Folate receptor alpha autoantibodies in autism spectrum disorders: diagnosis, treatment and prevention. *Journal of Personalized Medicine* 11(8): 710.
6. Imbard A, Benoist JF, Blom HJ (2013) Neural tube defects, folic acid and methylation. *Int J Environ Res Public Health* 10(9): 4352-4389.
7. Shapira I, Sequeira JM, Quadros EV (2015) Folate receptor autoantibodies in pregnancy related complications. *Birth defects research. Part A Clinical and molecular teratology* 103(12): 1028-1030.
8. Frye RE, Rossignol DA, Scahill L, McDougle CJ, Huberman H, et al. (2020) Treatment of folate metabolism abnormalities in autism spectrum disorder. *Semin Pediatr Neurol* 35: 100835.
9. Ramaekers VT, Rothenberg SP, Sequeira JM, Thomas O, Nenad BEQ, et al. (2005) Autoantibodies to folate receptors in the cerebral folate deficiency syndrome. *N Engl J Med* 352(19): 1985-1991.
10. Ramaekers VT, Sequeira JM, Blau N, Quadros EV (2008) A milk-free diet downregulates folate receptor autoimmunity in cerebral folate deficiency syndrome. *Dev Med Child Neurol* 50(5): 346-352.
11. Frye RE, Sequeira JM, Quadros EV, James SJ, Rossignol DA (2013) Cerebral folate receptor autoantibodies in autism spectrum disorder. *Mol Psychiatry* 18(3): 369-381.
12. Rossignol DA, Frye RE (2021) Cerebral folate deficiency, folate receptor alpha autoantibodies and leucovorin (folinic acid) treatment in autism spectrum disorders: a systematic review and meta-analysis. *J Pers Med* 11(11): 1141.
13. Ramaekers VT, Blau N (2004) Cerebral folate deficiency. *Dev Med Child Neurol* 46(12): 843-851.
14. Renard E, Leheup B, Guéant Rodriguez RM, Oussalah A, Quadros EV, et al. (2020) Folinic acid improves the score of Autism in the EFFET placebo-controlled randomized trial. *Biochimie* 173: 57-61.
15. Frye RE, Slattery J, Delhey L, Furgerson B, Strickland T, et al. (2018) Folinic acid improves verbal communication in children with autism and language impairment: a randomized double-blind placebo-controlled trial. *Mol Psychiatry* 23(2): 247-256.
16. Bender A, Hagan KE, Kingston N (2017) The association of folate and depression: A meta-analysis. *J Psych Res* 95: 9-18.
17. Lang UE, Beglinger C, Schweinfurth N, Walter M, Borgwardt S (2015) Nutritional aspects of depression. *Cell Physiol Biochem* 37(3): 1029-1043.