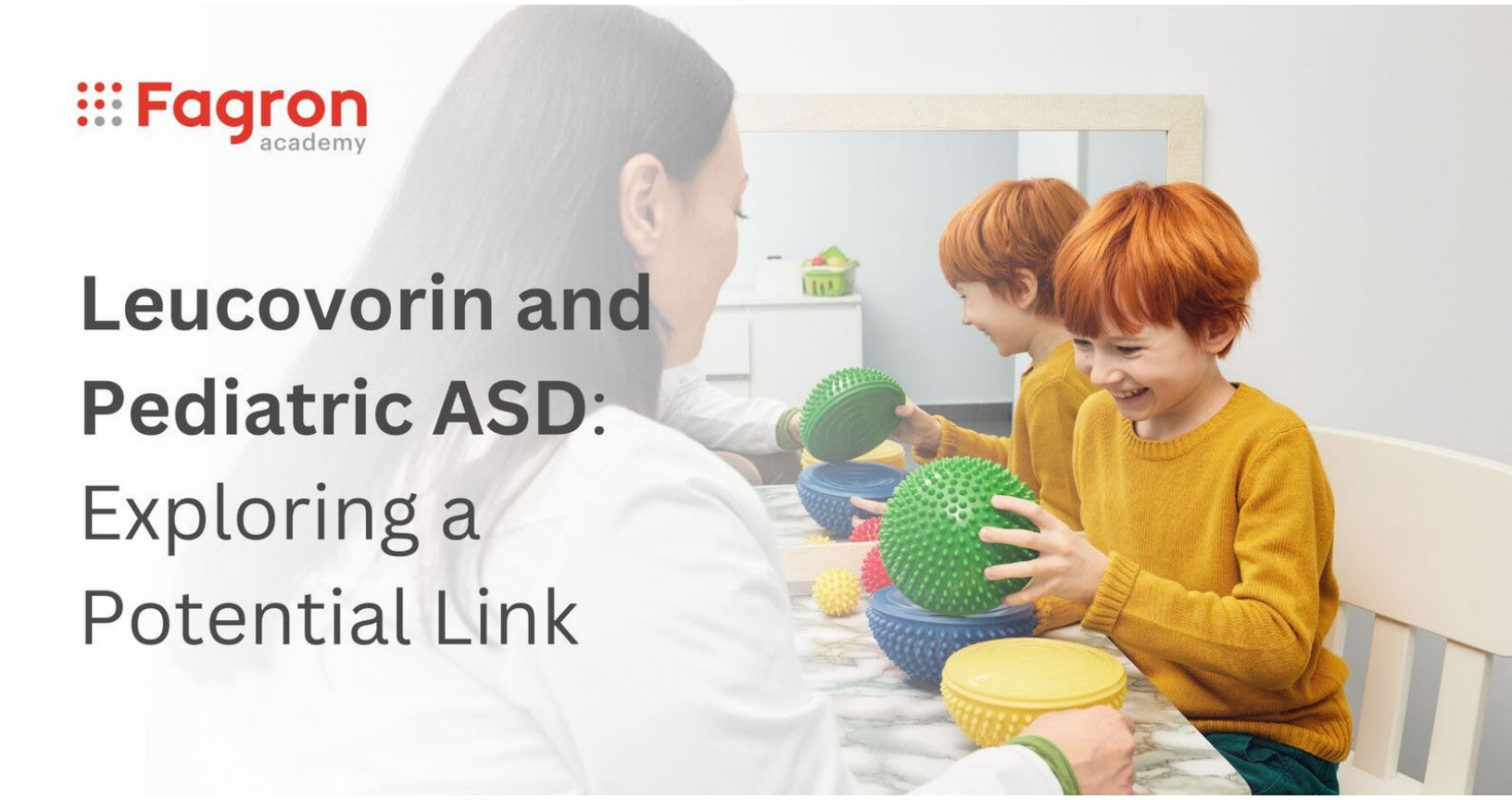

Leucovorin and Pediatric ASD: Exploring a Potential Link

August 6, 2025

Sarah Taylor, PharmD

According to data from the Centers for Disease Control (CDC), approximately 1 in 31 children 8 years of age (3.2%) were identified as having Autism Spectrum Disorder (ASD). Despite the relatively high incidence, there is no FDA approved medical therapy for ASD at this time to address the core symptoms or the pathophysiological processes of this condition. This lack of treatment options may in part be due to the nature of ASD as a highly heterogeneous neurodevelopmental disorder encompassing a wide range of presentations and severities.

Folate Insufficiency and Transport Abnormalities

Despite the challenges for treating ASD, emerging data suggests that folate pathway abnormalities may play a role in the pathogenesis of ASD.[2] Specifically, abnormalities in methylation, including methylation metabolites such as methionine, S-adenosyl-L-methionine (SAM) and S-adenosyl-L-homocysteine (SAH) are present in this population. Deficits in these metabolites, especially SAM are potentially important for DNA and histone methylation in the brain. Folate transport to the brain in patients with ASD may be compromised resulting in subsequent deficiencies in these important metabolites.[2]

In addition to issues with transportation of folate to the brain, ASD is also associated with folate receptor alpha autoantibodies (FRAA). One study evaluating this link found that cerebral folate deficiency was found in 44% of patients with ASD and of those patients with cerebral folate deficiency, FRAAs were noted in 83% of cases. A sibling comparison study found that children with ASD were over 19-fold more likely to test positive for FRAAs than children without ASD.[3]

Leucovorin Calcium Supplementation and ASD

Given this potential link between folate and ASD symptoms, it was hypothesized that folate supplementation may improve symptoms of ASD, especially in those with verbal communication and language impairment.

One study of 48 children (mean age 7 years and 4 months) with ASD and language impairment split patients into two groups, one received 2mg/kg/day (up to 50mg max) leucovorin calcium (folinic acid calcium salt), the other received placebo. The dose was divided into two doses with a taper period in which just half of the target dose was given for the first 2 weeks. Folate receptor alpha autoantibody (FRAA) and glutathione status were evaluated in these patients. Patients were evaluated over a 12-week period and assessed via different ASD related scales. Improvements in the treatment group were noted both behaviorally and in language assessments.[4]

This improvement has been corroborated in other studies both in patients with ASD and other neurological conditions. A study that looked at 0.5-1mg/kg/day leucovorin in patients with cerebral folate deficiency (and related neurological symptoms) found that 90% of those supplemented achieved normal 5-methyltetrahydrofolate cerebral spinal fluid concentrations. Symptomatologic improvement was greater in patients younger than 6 years of age as compared to those who began supplementation at an older age, though, this study was a case series of 20 patients, further randomized controlled trials are needed.[5]

Another study looking at lower doses of folate replacement (5mg twice daily) found improvements in social responsiveness score and autism diagnostic observation schedule score even at this lower dose in a 12 week period as compared to placebo.[6]

Leucovorin Calcium vs Alternative Sources of Folic Acid

Leucovorin Calcium (folinic acid) is the primary folic acid source studied for management of ASD. In the body leucovorin is a biologically active form of folate that exists naturally in food sources, as opposed to folic acid, which is a synthetic form.[7] 5-Methyltetrahydrofolate is the predominant physiological form of folate and performs the function of converting methionine to SAM.[8] Despite methyltetrahydrofolate being the physiologically active form, some studies on patients with methyltetrahydrofolate receptor C677T genotype polymorphisms (a prominent genotype in autism) suggest that folinic acid supplementation may cause higher serum folate levels than similar doses of methyltetrahydrofolate.[9,10]

Ongoing Studies/Future Directions

Future studies aim to investigate the link between folate supplementation and ASD further in larger patient populations. One currently recruiting study plans to evaluate 1mg/kg/day leucovorin calcium divided into two daily doses over a 12-week period as compared to placebo in patients between 2.5 and 5 years of age.[11] Supplementation with leucovorin calcium may represent a relatively well tolerated may to manage some symptoms associated with ASD. Future studies are looking to determine the ideal dosing and establish the benefit of treatment.

References:

1. Autism Spectrum Disorder (ASD). US Centers for Disease Control and Prevention. Data and Statistics on Autism Spectrum Disorder | Autism Spectrum Disorder (ASD) | CDC. Updated April 15th 2025. Accessed April 25th 2025.
2. Frye RE, Rossignol DA, Scahill L, McDougle CJ, Huberman H, Quadros EV. Treatment of Folate Metabolism Abnormalities in Autism Spectrum Disorder. Semin Pediatr Neurol. 2020 Oct;35:100835. doi: 10.1016/j.spen.2020.100835. Epub 2020 Jun 25. PMID: 32892962; PMCID: PMC7477301.
3. Rossignol DA, Frye RE. 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. 2021 Nov 3;11(11):1141. doi: 10.3390/jpm11111141. Erratum in: J Pers Med. 2022 Apr 29;12(5):721. doi: 10.3390/jpm12050721. PMID: 34834493; PMCID: PMC8622150.
4. Frye RE, Slattery J, Delhey L, Furgerson B, Strickland T, Tippett M, Sailey A, Wynne R, Rose S, Melnyk S, Jill James S, Sequeira JM, Quadros EV. Folinic acid improves verbal communication in children with autism and language impairment: a randomized double-blind placebo-controlled trial. Mol Psychiatry. 2018 Feb;23(2):247-256. doi: 10.1038/mp.2016.168. Epub 2016 Oct 18. PMID: 27752075; PMCID: PMC5794882.
5. Ramaekers V, Blau N. Cerebral folate deficiency. Developmental Medicine and Child Neurology. 2004; 46(12): 795-852.
6. Renard E, Leheup B, Guéant-Rodriguez RM, Oussalah A, Quadros EV, Guéant JL. Folinic acid improves the score of Autism in the EFFET placebo-controlled randomized trial. Biochimie. 2020 Jun;173:57-61. doi: 10.1016/j.biochi.2020.04.019. Epub 2020 May 7. PMID: 32387472.
7. Gristan Y, Patel P, Moosavi L. Folinic Acid. StatPearls. Folinic Acid - StatPearls - NCBI Bookshelf. Updated February 28th 2024. Accessed June 18th 2025.
8. Menezo Y, Elder K, Clement A, Clement P. Folic Acid, Folinic Acid, 5 Methyl TetraHydroFolate Supplementation for Mutations That Affect Epigenesis through the Folate and One-Carbon Cycles. Biomolecules. 2022;12(2):197. Published 2022 Jan 24. doi:10.3390/biom12020197
9. Mazokopakis EE, Papadomanolaki MG, Papadakis JA. The effects of folinic acid and l-methylfolate supplementation on serum total homocysteine levels in healthy adults. Clin Nutr ESPEN. 2023 Dec;58:14-20. doi: 10.1016/j.clnesp.2023.09.002. Epub 2023 Sep 7. PMID: 38056998.
10. Sener EF, Oztop DB, Ozkul Y. MTHFR Gene C677T Polymorphism in Autism Spectrum Disorders. Genet Res Int. 2014;2014:698574. doi:10.1155/2014/698574
11. Razi B, Imani D, Makoui M, Rezaei R, Aslani S. Association between MTHFR gene polymorphism and susceptibility to autism spectrum disorders: Systematic review and meta-analysis. Research in Autism Spectrum Disorders. 2020; 70; 101473.
12. Study Details | Early Treatment of Language Impairment in Young Children with Autism Spectrum Disorder with Leucovorin Calcium | ClinicalTrials.gov. Early Treatment of Language Impairment in Young Children with Autism Spectrum Disorder with Leucovorin Calcium. ClinicalTrials.gov ID NCT04060017

For further information or questions, please feel free to reach out to us by heading to www.fagronacademy.us!