Central Folate Abnormalities in Autism Spectrum Disorder and Treatment with Leucovorin Calcium (a.k.a. folinic acid)

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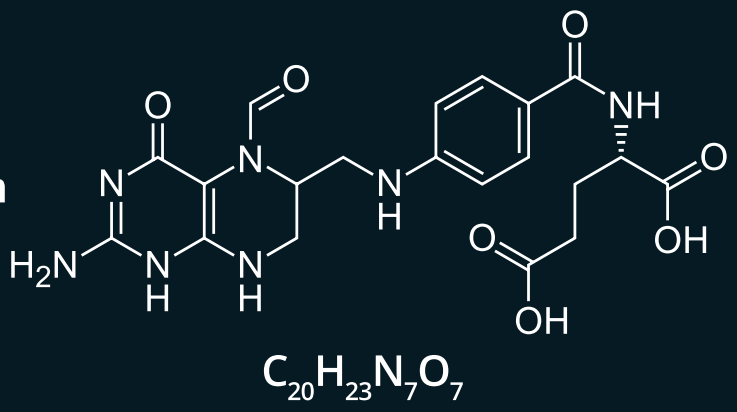


$C_{20}H_{23}N_7O_7$

Autism spectrum disorder (ASD) affects about 1 in 54 children in the United States.[1] Few children with ASD obtain optimal outcomes,[2,3] and many individuals require life-long supportive care.[4]

Promising Treatments for Autism

The only medications approved by the Food and Drug Administration for ASD are anti-psychotic drugs which target an associated symptom of ASD called irritability. However, these medications do not target the core symptoms of social interaction, communication or stereotyped behavior.[5] There are several compounds which do have the potential to address both the underlying biological abnormalities and core symptoms of ASD.[6] One of the most promising treatments has the potential to correct folate metabolism abnormalities in the brain. This treatment, leucovorin calcium (also known as folinic acid), will be discussed in this article.

The Importance of Folate

In order for the body and brain to develop normally, folate (Vitamin B9) is essential. This is because folate is important for several key functions of the cells in our body.[7] Folate is essential for making molecules called purines, which are precursors to making deoxyribonucleic acid (DNA), the building blocks of our genes. Folate is also essential for making an important cofactor in our body called tetrahydrobiopterin, also known as BH_4. BH_4 is an important factor needed for the machinery that makes specific neurotransmitters called monoamine neurotransmitters and for producing nitric oxide. Folate is also essential for producing a compound called S-adenosyl-L-methionine, which is crucial for methylation — the process which turns genes on and off. Folate is connected to the production of the major antioxidant in our body called glutathione through methylation metabolism. It is worth noting that all of these processes associated with folate have been documented to be abnormal in individuals with ASD.[7]

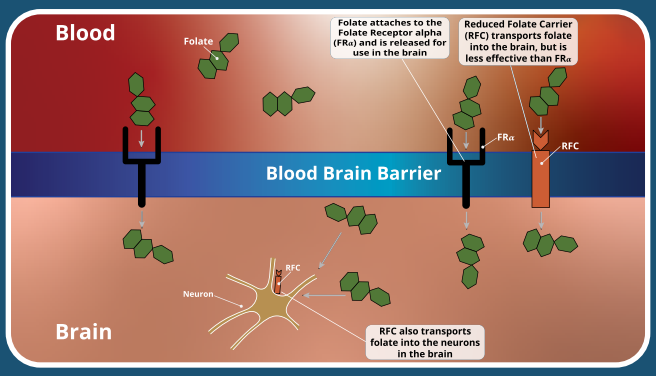
Key Functions of Folate (Vitamin B9)

- Required for DNA Synthesis
- Essential for producing BH_4
- Essential for gene regulation (turning genes on and off)
- Involved in production of glutathione

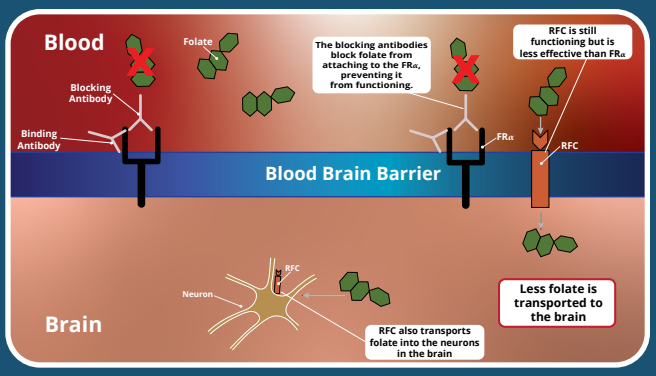
Cerebral Folate Deficiency

Over the past 15 years, we have discovered that ASD is associated with a problem with the transportation of folate into the brain. The brain is a special part of the body, and everything needs to be transported into it across the blood-brain barrier. The folate receptor alpha is the primary transporter for folate across the blood-brain barrier. In a seminal paper published in the **New En-**

Typical Folate Transportation



Abnormal Folate Transportation



Mechanism for folate transport into the brain and the effect of folate receptor autoantibodies. Normally folate is transported into the brain by the folate receptor alpha (FRα). Folate attaches to the FRα on the blood side of the blood-brain barrier and then the FRα transports folate through the cells of the blood-brain barrier into the brain where folate is released for use in the brain. An alternative transporter called the reduced folate carrier (RFC) can also transport folate into the brain but it is less effective. The RFC also transports folate into the neurons in the brain. The FRα can be disrupted by two autoantibodies. The blocking autoantibody blocks folate from attaching to the FRα, preventing it from functioning.

gland Journal of Medicine in 2005, Drs. Ramaekers and Quadros, along with other colleagues, described a new medical disorder known as cerebral folate deficiency.[8] Patients with cerebral folate deficiency were found to have abnormally low levels of folate in the brain but normal levels of folate in the blood. Dr. Quadros discovered that there were antibodies produced by the patient's immune system that interfered with how the folate receptor alpha worked (See figure above).

Some Children with Autism Also Have Abnormalities Getting Folate Into the Brain

As more case reports of cerebral folate deficiency were published, a pattern emerged – many of the cases demonstrated symptoms of ASD. Thus, approximately 10 years ago, Dr. Rossignol and I decided to study children with ASD in our clinics to determine how many of them had autoantibodies that could disrupt the transport of folate into the brain. Of the 93 patients with ASD we tested in our clinics, we found that 75% had at least one of the two antibodies that disrupted folate transportation into the brain.[9] From the previously published case reports we knew that patients with cerebral folate deficiency responded to leucovorin calcium, a special form of folate that can use an alternative transport mechanism to enter the brain. Thus, we offered families with children who had at least one antibody that disrupted folate transportation into the brain treatment with leucovorin calcium. About four months after starting such treatment, we asked caretakers to rate changes in core ASD and related symptoms. In this open-label case-series, we found that treatment with leucovorin calcium resulted in significant improvement in verbal communication, attention and stereotyped behavior.[9]

As open-label studies are susceptible to bias since all involved know that the patient is on the treatment, we launched a double-blind placebo-controlled study. In this type of study, one group of patients is given the active treatment while another group is given an inactive substance called a placebo. In this type of study, neither the caretakers nor the research staff know whether any particular patient is receiving the active drug or placebo. In this study of 48 children with ASD,[10] we found that leucovorin calcium significantly improved verbal communication as well as behaviors associated with ASD including irritability, social withdrawal, stereotyped behavior, hyperactivity, and inappropriate speech. We also found that those children who were positive for the antibodies that disrupted folate transportation into the brain were more likely to respond than those children without such antibodies.

Since our double-blind placebo-controlled study was published, two other studies have been published that support the use of leucovorin calcium. Recently, Dr. Ramaekers published an open-label case-series study of patients with nonsyndromic infantile ASD who choose to be treated with his comprehensive treatment protocol which included treatment with leucovorin calcium. Patients who chose not to be treated were used as controls. Overall, the patients who were treated with the comprehensive protocol demonstrated significant improvements on the Childhood Autism Rating Scale.[11] Additionally, a small single-blind placebo-controlled study from France demonstrated that the treatment with leucovorin calcium improves scores on the Autism Diagnostic Observation Schedule (ADOS).[12]

Treatment for Central Folate Abnormalities in Autism - Ongoing Research

Thus, four controlled studies demonstrate that leucovorin calcium is an efficacious and safe treatment for improving both core (social function, communication, stereotyped behavior) and associated (irritability, hyperactivity) ASD symptoms. Even though leucovorin calcium is a promising treatment, more research is needed. To this end, we are currently conducting three double-blind placebo-controlled clinical trials. One multicenter study involving myself at Phoenix Children's Hospital, Dr. Lawrence Scahill at Emory University and Dr. Christopher McDougle at the Lurie Center at Massachusetts General Hospital, has been launched to verify our previous findings in school-age children with ASD. In two other multicenter clinical trials involving myself at Phoenix Children's Hospital and Dr. Harris Huberman at State University of New York – Downstate, we are researching whether leucovorin will have a beneficial effect in preschool-aged children with ASD.

Conclusion

Given that our previous study suggests that the antibodies that disrupted folate transportation into the brain can predict response to leucovorin calcium, we are further studying whether this antibody, as well as other biomarkers, can predict response to leucovorin calcium treatment in children with ASD. Using a biomarker approach, we hope to develop a personalized precision medicine approach for treating children with ASD.[13] In view of the promising and compelling data, we believe that leucovorin calcium has tremendous promise in improving the lives of children with ASD and their families.

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Richard E. Frye, MD, Ph.D, is a Child Neurologist with expertise in neurodevelopmental and neurometabolic disorders. He received an MD and Ph.D in Physiology and Biophysics from Georgetown University and completed his Child Neurology Residency and Fellowship in Behavioral Neurology and Learning Disabilities at Harvard University/Children's Hospital Boston. Dr. Frye has authored over 200 peer-reviewed publications and book chapters. He has conducted several clinical trials demonstrating the efficacy of safe and novel treatments that target underlying physiological abnormalities in children with ASD. He is the Chief of Neurodevelopmental Disorders at the Barrow Neurological Institute at Phoenix Children's Hospital.