

CEREBRAL FOLATE DEFICIENCY IN AUTISM SPECTRUM DISORDERS

This article is a companion piece to the story of Evan Carkhuff, a child diagnosed with autism who went many years with neither a medical diagnosis nor an explanation for his medical condition. Here we explain the medical science of the underlying neurodevelopmental disorder with which he was eventually diagnosed, called cerebral folate deficiency (CFD). As you will read from the description of his disorder in the accompanying article, Evan had several atypical characteristics that led some physicians down a wrong path. Evan's story is an excellent example of a family who would not give up, and CFD is an excellent example of a disorder that was previously thought to be rare but is now being increasingly recognized to affect some children with autism.

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THE IMPORTANCE OF FOLATE

Folic acid (vitamin B9, also known as folate) is a water-soluble B vitamin that is essential for numerous physiological systems of the body. Folate derives its name from the Latin word *folium*, which means leaf, to signify that the main natural source of this vitamin is from leafy vegetables. However, in the modern western diet, the main source of folate is from folate-fortified foods.

Folic acid is the inactive, oxidized form of the folate compounds. The main active form of folate in the body is 5-methyltetrahydrofolate (5-MTHF). Folic acid is converted to dihydrofolate and then to tetrahydrofolate (THF) by the enzyme dihydrofolate reductase. This reaction, which requires niacin (vitamin B3), can be inhibited by certain medications. 5-MTHF is also converted to THF by the enzyme methylenetetrahydrofolate reductase (MTHFR). 5-MTHF is then converted back to THF through a cobalamin (vitamin B12) dependent enzyme called methionine synthase, a process that recycles methionine from homocysteine.

Folate is important for the *de novo* synthesis of purine and pyrimidine nucleic acids that are the molecules from which DNA and RNA are produced. DNA stores the genetic code and needs to be duplicated when a cell divides and replicates. Thus, folate is extremely important during cell replication, especially

prior to birth during the development of the embryo and fetus. It is also essential during early life when cells are growing quickly.

The folate cycle interacts with the methionine cycle as well as the tetrahydrobiopterin production and salvage pathways. Deficiencies in folates can lead to abnormalities in these pathways. The methionine cycle is essential for the methylation of DNA, a process that is important in controlling gene expression. Tetrahydrobiopterin is essential for the production of nitric oxide, a substance critical for the regulation of blood flow and for the production of the monoamine neurotransmitters, including dopamine, serotonin, and norepinephrine. Production of these neurotransmitters and nitric oxide converts tetrahydrobiopterin to dihydropterin. The conversion of tetrahydrobiopterin back to dihydropterin again requires conversion of 5-MTHF to THF. In addition, tetrahydrobiopterin is produced *de novo* using the precursor purine guanosine triphosphate, a substance that requires THF to be produced.

Several disorders have been linked to folate deficiency. For example, since blood cells need to be constantly replenished, a lack of folate commonly leads to anemia, an insufficiency of red blood cells. Folate deficiency during pregnancy leads to fetal neural tube defects such as spina bifida.

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CEREBRAL FOLATE DEFICIENCY: A RECENTLY DESCRIBED NEURODEVELOPMENTAL DISORDER

One decade ago, Ramaekers and colleagues¹ described a new neurodevelopmental disorder called cerebral folate deficiency (CFD). They described five patients with normal neurodevelopment until four to six months of life. During the second half of the first year of life, these patients demonstrated developmental regression and progressively developed neurological symptoms, including irritability, psychomotor retardation, ataxia, dyskinesias, pyramidal signs, visual loss, and seizures. Patients also demonstrated acquired microcephaly. 5-MTHF was found to be normal in the serum and red blood cells but was low in the cerebrospinal fluid. This new disorder was named CFD to describe the lack of folate specifically in the central nervous system (CNS).

CEREBRAL FOLATE TRANSPORTERS

To understand CFD, it is necessary to understand that the CNS is a protected area of the body. The blood-brain barrier highly regulates the entry of substances into the CNS. For the active form of folate (5-MTHF) to enter the CNS, it must be transported across the blood-brain barrier by one of two specialized carriers. The primary carrier uses a specialized folate receptor known as folate receptor 1 (FR1). Through this system, 5-MTHF binds to FR1, which is located on the apical side (blood vessel side) of epithelial cells of the choroid plexus. FR1 then transports 5-MTHF to the basolateral side of the epithelial cells. On the basolateral side of the cell, 5-MTHF is released into the CNS. This transport process requires energy in the form of an adenosine-5'-triphosphate (ATP) dependent mechanism. FR1 is then recycled back to the apical side of the cell to pick up more 5-MTHF.

A secondary carrier of folate through the blood-brain barrier is the reduced folate carrier (RFC). The RFC has a lower affinity for folic acid and 5-MTHF than the FR1 system but has a higher affinity for 5-formyltetrahydrofolate, also known as folinic acid or leucovorin. The RFC is also responsible for transporting 5-MTHF into neurons once it has entered the CNS.

If blood concentrations of folate are high enough, folate may also diffuse across the blood-brain barrier without a carrier.

CAUSES OF CEREBRAL FOLATE DEFICIENCY

Ramaekers' group¹ examined the gene that encodes FR1 to investigate whether or not genetic mutations accounted for dysfunction in the transport of 5-MTHF into the CNS but could not identify any such mutations. In 2004, Ramaekers and Blau² expanded their case series to 20 patients, none of whom were found to have a mutation in the FR1 gene. However, these researchers did find non-functional FR1 receptors in the patients' cerebrospinal fluid, leading to the hypothesis that some type of molecule, potentially an autoantibody, might be irreversibly binding to the FR1 protein, causing it to become dysfunctional for binding folate. In 2005, Ramaekers and colleagues³ identified high-affinity

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blocking autoantibodies against FR1 in the serum of 25 of 28 children with CFD. These autoantibodies were not found in age-matched control subjects. More recently, Molloy and colleagues⁴ described an additional blocking FR1 autoantibody (termed a "binding" antibody), but this autoantibody has yet to be associated with any pathological disease. Interestingly, although the majority of cases of individuals with these autoantibodies have not been reported to have any obvious inflammatory conditions, FR1 autoantibodies have been associated with juvenile rheumatoid arthritis.⁵

In 2006, CFD was linked to mitochondrial disease in a case report of a child with an incomplete form of Kearns-Sayre syndrome.⁶ Further case reports and case series later expanded the association between CFD and mitochondrial disorders to include complex I deficiency,⁷ Alpers' disease⁸ and complex IV hyperfunction,⁹ as well as a wide variety of mitochondrial disorders in both children and adults.¹⁰ In most of these cases, the autoantibodies to FR1 were not found, suggesting that it was the lack of ATP availability secondary to mitochondrial dysfunction that resulted in the impaired transportation of 5-MTHF into the CNS.

CEREBRAL FOLATE DEFICIENCY AND AUTISM SPECTRUM DISORDERS

Seven of the 20 children portrayed in the second case series describing CFD were reported to have an autism spectrum disorder (ASD),² while five of the 28 patients first described to have the FR1 autoantibody were found to have low-functioning autism with neurological features.³ Further case reports^{9,11} and case series^{12,13,14} have expanded the description of CFD in children with idiopathic autism. Overall, these reports suggest that early-onset low-

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functioning autism with neurological deficits is characteristic of children with both autism and CFD. Interestingly, Rett syndrome, a disorder considered to be a part of the diagnostic group of autism spectrum disorders, has also been reported to have reduced 5-MTHF levels in the cerebrospinal fluid.^{15,16}

It should be noted that only some children with autism who have CFD have been reported to possess FR1 autoantibodies.^{3,13} Because these reports of children with idiopathic autism and Rett syndrome include children with and without the FR1 autoantibody, this suggests that factors other than the FR1 autoantibody might be important for the development of CFD in these children. Although not specifically investigated, it is possible that many children with CFD and idiopathic autism or Rett syndrome who do not have the FR1 autoantibody may have mitochondrial disease. Indeed, as previously noted, mitochondrial disease appears to be associated with CFD,⁶⁻¹⁰ and there appears to be an increased prevalence of mitochondrial disease in children with idiopathic autism as compared to the general population.^{17,18} At least one case series has linked children with mitochondrial disease and regressive-type autism to CFD.⁹ Interestingly, Rett syndrome has also been linked to mitochondrial abnormalities in both an animal model¹⁹ and a case report.²⁰ To a lesser extent, children with idiopathic autism might also manifest dysfunction of the mitochondria without necessarily fulfilling the criteria for strictly defined mitochondrial disease.¹⁸ Thus, it is possible that mitochondrial dysfunction could contribute to the development of CFD in children with idiopathic autism.

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DIAGNOSING CEREBRAL FOLATE DEFICIENCY

Table 1 outlines the signs, symptoms and conditions associated with CFD. It is important to consider CFD in children with Rett syndrome or mitochondrial disease with or without autistic features. A combination of the neurological symptoms outlined in Table 1 that are not explained by a specific neurological condition should also prompt consideration of CFD. Given the accompanying case description, it is clear that CFD can present with atypical features. Thus, it is important to keep a high index of suspicion for this disorder in children with unexplained neurodevelopmental symptoms.

Table 1
When to Suspect Cerebral Folate Deficiency

- Low-functioning autism
- Mitochondrial disease or dysfunction
- Rett syndrome
- Epilepsy or seizures
- Abnormal electroencephalogram: subclinical electrical discharges or slowing
- Ataxia
- Microcephaly
- Dyskinesia: choreoathetosis, ballismus
- Pyramidal tract abnormalities
- Irritability
- Insomnia
- Delayed myelination
- Frontotemporal atrophy

Table 2 outlines the diagnostic workup for CFD. As shown in the table, it is important to begin by ruling out systemic deficiencies in folate or cobalamin that might cause symptoms similar to CFD (Step 1). Next, it is essential to test for FR1 autoantibodies (Step 2). If the FR1 binding autoantibodies are discovered, it is important to investigate the function of other organs that use the FR1 receptor for folate uptake to ensure that the antibodies are not the result of a more general autoimmune process (Step 3). It should be noted that, because the reported relationship between FR1 autoantibodies and cerebrospinal fluid levels of 5-MTHF is nonlinear, some individuals with FR1 autoantibodies have normal levels of cerebrospinal fluid 5-MTHF.¹⁴ If FR1 autoantibodies are negative, it is possible that an underlying mitochondrial disorder might be resulting in secondary CFD. Thus, if CFD is still suspected despite a negative FR1 binding autoantibody, a screening for mitochondrial disorders using established guidelines¹⁸ is recommended (Step 4). If the FR1 autoantibody is detected or a mitochondrial disorder is diagnosed, a lumbar puncture is required to confirm the diagnosis of CFD (Step 5).

A thorough workup should also measure levels of tetrahydrobiopterin because folate is essential in the production of this cofactor. As noted previously, deficits in tetrahydrobiopterin can lead to reduced production of the monoamine neurotransmitters. Interestingly, abnormalities in monoamine neurotransmitter metabolites have been reported in CFD^{2,21} and may improve with folinic acid treatment. Neurotransmitter metabolites in the

cerebrospinal fluid should therefore also be measured during the lumbar puncture. Finally, because inflammatory conditions have been associated with CFD,^{5,8} it is important to measure cerebrospinal fluid neopterin, a measure of inflammation, and an IgG index, a measure of intrathecal antibody production.

Unfortunately, a lumbar puncture is an invasive procedure that requires a specialist with significant experience to perform. For example, at the University of Texas Health Science Center, an experienced neuroradiologist performs non-emergent lumbar punctures under general anesthesia with fluoroscopy guidance. In many cases, parents will not elect for their child to undergo such an invasive procedure, and, in other cases, experienced personnel may not be readily available. Under these circumstances, empirical treatment with folinic acid or 5-MTHF can be a prudent option (see *Treatment of cerebral folate deficiency*). If empirical treatment is pursued, the patient should be closely monitored for behavioral and/or cognitive changes and side effects.

Table 2
Diagnostic Workup for Cerebral Folate Deficiency

- 1 Rule out systemic folate and cobalamin deficiency**
 - a Serum folic acid level
 - b Serum cobalamin level
- 2 Test for FR1 folate receptor autoantibodies**
- 3 If FR1 autoantibodies are positive:**
 - a Test for dysfunction in other organs
 - i Thyroid function tests
 - ii Renal function tests
 - b Test for inflammatory disease
 - i Erythrocyte sedimentation rate
 - ii C-reactive protein
 - iii Antinuclear antibody
- 4 If FR1 autoantibodies are negative or there are symptoms of mitochondrial disorders:¹⁷**
 - a Test for mitochondrial markers¹⁸
 - i Fasting serum lactate, pyruvate, quantitative amino acids, ammonia, metabolic panel, liver function tests, creatine kinase, acylcarnitine panel, carnitine panel, and CoQ10 level
 - ii Fasting urine organic acids
- 5 If FR1 autoantibodies are positive or mitochondrial markers are positive:**
 - a Perform lumbar puncture to confirm cerebral folate deficiency
 - b Test cerebrospinal fluid for
 - i 5-MTHF
 - ii Tetrahydrobiopterin
 - iii Neurotransmitters
 - iv Neopterin
 - v IgG index

The first treatment used for CFD was folinic acid. This therapy, which has an excellent safety profile, has been shown to normalize cerebrospinal fluid levels of 5-MTHF in children with autism and CFD.

TREATMENT OF CEREBRAL FOLATE DEFICIENCY

Treatments for CFD are outlined in Table 3. The first treatment used for CFD was folinic acid. This therapy, which has an excellent safety profile, has been shown to normalize cerebrospinal fluid levels of 5-MTHF in children with autism and CFD.¹³ Reports have suggested that treatment with folinic acid has led to full control of epilepsy and resolution of brainstem, thalamus, basal ganglia, and white matter demyelination in a child with complex I deficiency,⁷ resolution of neurotransmitter abnormalities,² and improvements in seizures, attention, motor skills, neurological abnormalities, verbalizations, perseverative behavior, restricted interests, and social interaction in some children with autism.^{3,11,12,13}

Typical doses of folinic acid range from 0.5-1 mg/kg/day in two divided doses with a maximum of 50 mg/day. However, some case reports have used doses as high as 4 mg/kg/day. Therefore, some children may need higher levels of folinic acid. As described above, folinic acid enters the CNS through an alternative folate carrier known as the reduced folate carrier. Once it enters the CNS, folinic acid can participate in the reactions that use THF. In these processes, folinic acid is converted to 5-MTHF, a step that requires cobalamin to be recycled to THF. Thus, it is essential that adequate levels of cobalamin be available when treating with folinic acid. As folic acid (the inactive, oxidized form of folate) can compete for the binding site on FR1, it is probably wise to discontinue the use of folic acid-containing supplements.

Interestingly, the human folate receptor cross-reacts with folate receptors contained in human, bovine (cow), and goat milk. In 2008, Ramaekers and colleagues¹⁴ demonstrated that a cow's milk-free diet significantly reduced the level of FR1 autoantibodies and that re-exposure to milk significantly increased FR1 autoantibodies. Furthermore, some of the children with autism were found to have marked or partial improvements in attention, communication, and stereotyped movements when placed on a milk-free diet. This provides compelling evidence that supports parental reports of improvements with a casein-free diet in some children with autism and supports previous studies suggesting gastrointestinal tract immune activation in children with autism.

Table 3

Treatments for Cerebral Folate Deficiency

- Discontinue drugs that can interfere with folate metabolism
- Start folinic acid at dose of 0.5 mg/kg/day in two divided doses and increase to 1-4 mg/kg/day in two divided doses (max 50 mg/day)
- Consider cobalamin supplementation (vitamin B12)
- Stop folic acid supplementation
- Start a cow's milk-free diet
- Monitor for changes in cognition and behavior
- Monitor adverse effects

POTENTIAL ASSOCIATION OF THE CEREBRAL FOLATE ANTIBODY WITH BIRTH DEFECTS

Several studies provide interesting and compelling evidence for a relationship between folate receptor autoantibodies and neural tube defects (NTDs). In 2004, for example, Rothenberg and colleagues²² demonstrated that women from the United States with a current or previous baby with NTDs were more likely to have autoantibodies to the human placental folate receptor. In a larger study, Cabrera and colleagues²³ found that mid-gestation levels of both IgM and IgG autoantibodies to the human folate receptor collected from



US women were associated with pregnancies complicated by NTDs. More recently, a study of Norwegian women by Bovies and colleagues²⁴ suggested that mid-gestation autoantibodies were specifically related to NTDs but not to oral facial clefts. Although another rather large study from Ireland (using previously frozen specimens not necessarily collected during pregnancy) did not find any difference between mothers who had a previous pregnancy with NTDs as compared to those without an affected pregnancy,²⁵ the prevalence of autoantibodies to FR1 was very high in this population (approaching 35%), and the findings need duplication in populations where the prevalence is lower. Because these studies reflect important methodological differences (including whether or not autoantibodies were measured during pregnancy) as well as differences in national policies regarding dietary folate supplementation, further research is needed to define whether or not a relationship between folate receptor autoantibodies and NTDs truly exists.

UNANSWERED QUESTIONS: WHAT EVAN CAN TEACH US

It is important to understand that because CFD has only been reported in case reports and case series, there may be a much wider variation in the symptoms associated with CFD. For example, children who do not have neurological symptoms or seizures will rarely undergo a lumbar puncture to look for CFD. This is especially true in autism, where there are diverse opinions regarding the disorder's medical basis. It is possible that many more children with ASD than are currently recognized may suffer from CFD, a treatable condition.

As the accompanying article illustrates, Evan is a good example of the underrecognition of CFD. Whereas one of the symptoms of classic CFD is microcephaly, a study has reported that in children with ASD and CFD, microcephaly was not present.¹² Evan, in fact, had macrocephaly because of congenital ventriculomegaly (a condition in which the fluid-filled structures in the brain are too large). Could this have been a manifestation of his mother having the FR1 autoantibody? Although the ventriculomegaly that Evan possessed is not a neural tube defect (and Evan does not have a neural tube defect), it can be related to NTDs. Evan's growth IGF-1 deficiency raises additional questions, including how it fits into CFD. The fact is, we do not yet know. Evan has taught us that we need to understand our limitations as we continue to search for answers and put together the pieces of a complicated puzzle.

It is possible that many more children with ASD than are currently recognized may suffer from CFD, a treatable condition.

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