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Mini review

Role of Folate in Prenatal and Postnatal Development Of ASD

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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 over 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). Parents of autistic children also have FRA at substantially higher rates than the public. In clinical trials, ASD children with the FRA 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. We reason that supplementing folate earlier in development, including in utero development, may be most effective in reducing the severity of ASD symptoms.

Keywords: ASD, Folate, Autism, Clinical, Prenatal development

Folate in Nervous System Development

Folate (Vitamin B-9) is a key contributor to normal nervous system development [1,2]. Folate is bio-available in its reduced form and is present in many foods, including legumes, leafy greens, and fruits. The naturally occurring 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 in fetal brain development [3-5]. Insufficient folate can is 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, rather the reduced form. Most individuals can convert sufficient folic acid to folate. However, about 10% of the population is limited in absorbing folate into the brain due to the presence of an autoantibody to the folate receptor [8].

The 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 FRA can be reduced by changes in diet, particularly elimination of dairy products [10]. If levels of FRA are reduced or eliminated, this may allow sufficient folate to enter the brain. While FRA is present in a small subsection of the population, clinical tests find that about 70% of ASD children have FRA [11]. Meta-analysis from multiple studies show 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]. These reduced forms of folate cross the blood brain barrier via a low-affinity transport, necessitating larger blood levels to obtain sufficient cerebral levels of folate.

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 folate sources. But it is now clear that supplementation with reduced folate can help overcome CFD. Once CFD is reduced or eliminated, it may be possible to revise the diet of 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), are 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.

An important aspect of FRA contributing to CFD is the finding that this likely starts very early in development. Ramaekers [9,16] documented that when either or both parents have FRA, the chance of their child being ASD is higher. It thus seems that elevated risk of childhood ASD is related to elevated prenatal FRA, particularly when the FRA is present in the mother, but also when it is present in the father. One study found FRA presence in autistic children was 75.6%, with the FRA prevalence 34% in their mothers and 29% in their fathers, as compared to 3% FRA positivity in healthy controls [17]. Another report found FRA prevalence of 76% in autistic children, 75% in unaffected siblings, 69% in fathers and 59% in children, while the prevalence of this FRA in unrelated normal controls was 29% [18].

These findings are consistent with the presence of critical periods in development [19]. The presence of critical periods, first shown for the visual system, is the developmental time when sensory stimulation is necessary for visual perception to become established. If an animal is deprived of sensory input during the critical period, the functional perception of visual images is impaired throughout its life [19,20]. Similarly, depletion of cerebral folate during an infant's fetal development may be similar to a critical period that could lead to increased severity of autism. We postulate that ASD may result from a modified critical period of some type, where CFD impairs neurological development in some manner, increasing the probability of a later diagnosis of ASD.

In pregnancy, the presence of FRA in the mother blocks folate delivery to the developing fetus. These FRAs are common in pregnancies that have births with spina bifida and ASD [6]. Identifying pregnancies where FRA is present and treating the pregnant mother with folinic acid or methyl-folate21 may permit sufficient folate to reach the fetus, in turn lowering the risk of developing ASD and other developmental disorders [21].

There may be an additional advantage to diagnosing FRA in prospective parents. A recent report documented that Vitamins B-9 and B-12 supplementation increase pregnancy and live birth in women who have experienced difficulty in conceiving, [22] indicating an essential role of these vitamins in pregnancy and healthy fetal development.

Clinical studies have shown that when FRA is present, supplementation with folate and B-12 can overcome the FRA to permit sufficient folate for a child's brain development to continue its normal course [11,15].

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 [23]. Diets that are rich in natural forms of folate, such as the Mediterranean diet may help alleviate CFD, and when coupled with reduction in stress may improve communication in autistic people.

We suggest there are modified critical periods in the development of ASD, where the first period is in utero and a later one is in the first five years of life. These periods can predispose a child to be more likely to develop ASD (in utero) and begin to set the conditions for ASD development (ages 2-5). Nutritional supplementation along with psychological counseling was effective for children under five in one study, [24] suggesting therapy and nutrition should be provided in the first years of life to maximize positive outcomes. Additionally, reports indicating that the presence of FRA can predispose a child toward ASD [5,12] leads us to recommend that women presenting with FRA who may become pregnant be advised to take a prenatal supplement that includes a reduced form of folate (such as methyl-folate or folinic acid), and that children born to parents with FRA or children who have FRA would be advised to have nutritional supplementation to ensure sufficient levels of bioavailable Vitamin B-9 for brain development.

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