American Journal of
Biomedical Science & Research

www.biomedgrid.com
ISSN: 2642-1747

Mini Review



# Neurodevelopment with Low Nutritional Folate Increases Childhood Autism

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***To Cite This Article:*** *George Ayoub*. Neurodevelopment with Low Nutritional Folate Increases Childhood Autism. Am J Biomed Sci & Res. 2023 20(6) AJBSR.MS.ID.002784,* DOI: 10.34297/AJBSR.2023.20.002784

**Received:** November 24, 2023; **Published:** December 22, 2023

## Abstract

Folate, also known as Vitamin B-9, is a crucial nutrient required for proper development of the nervous system [1,2]. This vitamin can be found in several foods such as legumes, leafy greens, and citrus fruits. The naturally occurring form of folate is methylated, while the synthetic version found in many vitamin supplements is folic acid, which is oxidized and has a longer shelf life than the reduced form of folate. Folate plays a critical role in neural tube formation and closure during embryo development and is essential for the development of the fetal brain [3-5]. Inadequate levels of cerebral folate are associated with various developmental disorders, including spina bifida in newborns [6,7]. To mitigate these risks, prenatal vitamins typically contain Vitamin B-9 in the stable, oxidized form. Although most people can efficiently convert folic acid to folate, approximately 5-10% of the population may experience limited absorption of folate due to the presence of an autoantibody for the folate receptor [8].

**Keywords:** Autism, ASD, Folate, Nutrition, Folate deficiency

## Folate in Nervous System Development

### Folate Role in Development

Folate Receptor Antibody (FRA) impedes the high affinity folate receptor, hindering the transfer of folate across the blood-brain barrier [8,9]. Clinical studies suggest that dietary modifications, particularly the elimination of dairy, can decrease FRA levels in the bloodstream [10]. This reduction in FRA levels may potentially restore the brain's uptake of folate. Although FRA is found in a small portion of the population, studies reveal that 70% of ASD (autism spectrum disorder) children exhibit FRA [11]. A meta-analysis of multiple studies has demonstrated that ASD children are 20 times more likely to have FRA, implying a genetic aspect that inhibits the absorption of Vitamin B-9 by the brain [12]. While FRA levels can be reduced with significant dietary changes [10], ASD children often show resistance to dietary modifications. This resistance to change perpetuates the dietary factors that contribute to FRA, leading to Cerebral Folate Deficiency (CFD) due to the reduced folate levels in the brain. This deficiency can be treated with elevated levels of the natural forms of folate, such as methyl-folate or folinic acid (but not folic acid) [8,9,13]. Since the natural forms of folate can also cross the blood-brain barrier via a low-affinity transport, higher blood levels are necessary to achieve adequate levels of cerebral folate, but it can be accomplished even in the presence of FRA.

### Folate Receptor Antibody

Antibodies are proteins produced by the adaptive immune system typically in response to foreign agents. Antibodies bind to target antigens and neutralize them. Autoantibodies are generated against host tissue in instances where misdirected attacks occur. While autoantibodies generally do not harm the adult brain due to the blood-brain barrier preventing their entry, those from the mother can cross the placenta during fetal development and react against fetal brain proteins, resulting in Maternal Autoantibody-Related (MAR)-ASD, a clinical finding linked to ASD diagnosis [14].

### Immunological Impacts in Development

Studies have identified autoantibody targets common in mothers whose children were subsequently diagnosed with ASD, and the presence of these circulating maternal autoantibodies was associated with a higher incidence of stereotypical behaviours in

ASD children. Maternal stress, such as infection or exposure to environmental toxins, has been shown to trigger the immune response resulting in the production of autoantibodies that can react with fetal brain proteins [15,16]. This has been implicated in the pathogenesis of neuropsychiatric disorders such as ASD [17]. Both human and animal studies have observed a link between maternal stress and the development of ASD, with maternal immune activation induced by viral or bacterial infection during pregnancy, as well as exposure to environmental toxins, being associated with an increased risk of ASD in offspring [14]. Overall, maternal stress appears to play a critical role in triggering the immune response that may result in neurodevelopmental changes leading to neuropsychiatric disorders such as ASD [16,18,19].

### Clinical Trial Evidence

Studies have shown that ASD children who have FRA may experience improvement in their communication abilities when given daily folate supplements (in the form of reduced folate such as folinic acid) for three months [8,20,21]. It is 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, which may thus provide a means to reduce ASD symptoms by reducing production of FRA. The key elements of such a dietary treatment are to remove or reduce foods that can stimulate FRA production and to provide food sources of natural folate. A diet that is rich in natural folate, such as the Mediterranean diet that includes olive oil, fresh vegetables and fruits, nuts, legumes and fish, may be beneficial.

However, a challenging fact is that FRA contributing to CFD likely starts early in development. Studies have shown that when either or both parents have FRA, their child has a higher risk of ASD. It appears 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 in 75.6% of autistic children, while the prevalence of FRA positivity was 34% in their mothers and 29% in their fathers, compared to only 3% in healthy controls. Another study found FRA prevalence of 76% in autistic children, 75% in unaffected siblings, 69% in fathers and 59% in mothers, while the prevalence of FRA in unrelated normal controls was 29% [22-24].

### Critical Periods in Neurological Development

Critical periods in development may play a role in the link between Cerebral Folate Deficiency (CFD) and Autism Spectrum Disorder (ASD). The presence of critical periods was first documented for the visual system, where sensory input is necessary for visual perception to develop [25,26]. Similarly, during fetal development, a depletion of cerebral folate could impact a critical period leading to increased severity of autism. We hypothesize that ASD may result from a modified critical period, where CFD impairs neurological development and increases the likelihood of an ASD diagnosis later.

In pregnancies where the mother has Folate Receptor Autoantibodies (FRA), folate delivery to the developing fetus is severely diminished. This is a common occurrence in pregnancies that result in spina bifida and ASD. By identifying pregnancies where FRA is present and treating the mother with folinic acid or methyl-folate, sufficient folate can reach the fetus, potentially lowering the risk of developing ASD and other developmental disorders.

Additionally, diagnosing FRA in prospective parents may have other advantages. A recent study indicates that supplementation of Vitamins B-9 (as folinic acid but not as folic acid [27]) and B-12 increases pregnancy and live birth rates in women experiencing difficulties in conceiving, highlighting the essential role of these vitamins in healthy fetal development [28].

Clinical trials have shown that when FRA is present, supplementing with folate and B-12 can help overcome FRA and provide sufficient folate for normal brain development in children [8,14,20,21]. Folate plays a vital role in neural health, and the autoantibody FRA, which is present in most autistic people, blocks folate absorption into the brain leading to CFD. Stress can exacerbate this deficiency, leading to communication difficulties in ASD individuals. Diets rich in natural folate, such as the Mediterranean diet, may help alleviate CFD, and reducing stress can improve communication in autistic people [29]. We propose that critical periods in the development of ASD occur in utero and in the first five years of life, making children predisposed to develop ASD during these periods. Nutritional supplementation, combined with psychological counseling, was found to be effective in children under five in one study, highlighting the need for therapy and nutrition in the first years of life to maximize positive outcomes [30]. Additionally, prenatal supplementation with reduced folate (such as methyl-folate or folinic acid) should be recommended to women presenting with FRA who may become pregnant. Children born to parents with FRA or those who have FRA should receive nutritional supplementation to ensure adequate levels of bioavailable Vitamin B-9 for brain development.

## Diagnosis and Nutritional Intervention

### Early Diagnosis

To achieve optimal treatment outcomes, it is crucial to make an early diagnosis of neurodevelopmental disorders such as ASD, including a prognostic diagnosis in early pregnancy. One potential predictor for ASD development in childhood is the presence of FRA in either biological parent, which requires a blood sample for confirmation [23]. However, a non-invasive screening test for widespread use would be preferable. Several screening tests for ASD are under development, including retinal imaging, computer algorithms based on behavioral phenotypes, and machine learning methods [31-33]. We propose using a rapid screening method based on the presence of ASD, depression, or spina bifida in any immediate family member of the birth parents, followed by a FRA test. Such screening systems can be implemented effectively today, and quickly identify potential ASD cases. We hypothesize that testing for the FRA biomarker in newborns and in parents at the start of pregnancy is the optimal time to assess the likelihood of elevated potential for neurodevelopmental disorders such as ASD.

### Treatment with Folate

For optimal management of neurodevelopmental disorders like spina bifida and ASD, early testing for FRA in both maternal and paternal biological parents is recommended. If FRA is present, the mother should be supplied with prenatal vitamins that include reduced folate such as methyl-folate or L-folinic acid. The treatment should be continued post-partum, with the mother continuing to take the folate-containing prenatal vitamin while nursing, and the infant receiving liquid folate (L-folinic acid in a measured dosing bottle) post-weaning. Regular testing for FRA can be used to determine the continuation of folate treatment during infancy and toddlerhood. A diet rich in plant sources of folate such as leafy greens and legumes, and reduced exposure to bovine milk products, may also aid in folate absorption.

### Therapy

In early childhood, a combination of Cognitive-Behavioural Therapy (CBT) and physical therapy may be beneficial for children with neurodevelopmental disorders such as ASD. Complementary non-pharmacological interventions, such as PISTA, which combines physical exercise, cognitive training, and behavioural therapy, have shown potential in improving attention and reducing impulsivity in children with ADHD, and may also improve social interaction, motor coordination, and adaptive behaviour in autistic children [30,34,35].

## Summary

As learned from recent clinical trials, it is likely that autism originates during critical periods in utero when the fetus is predisposed for development of neurotypical pathways. Early identification and intervention are crucial in mitigating the severity of ASD in children. One promising intervention is nutritional supplementation aimed at restoring folate levels in the developing brain and promoting normal development during these critical periods. Further, new therapies are emerging that offer the potential to improve the quality of life for families with autistic children.

## Acknowledgement

None.

## Conflict of Interest

None.

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