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Factors Predisposing for Autism

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Abstract
Autism Spectrum Disorder (ASD) prevalence has tripled this century, such that over 2% of children in the US are autistic. While there seem to be many variants of the condition, there are some common variables that may increase the likelihood of an ASD diagnosis. These factors represent a complex interplay between genetic, environmental and lifestyle factors. Some factors that contribute to ASD risk include oxidative stress exposure and cerebral folate deficiency (CFD). Nutritional interventions to mitigate the effects of oxidative stress and CFD include supplementation of folate in its reduced form, consumption of fruits and vegetables naturally high in the reduced form of folate, and elimination of cow's milk from the diet to reduce or eliminate production of folate receptor antibodies.

Keywords
Autism, Folate, Stress, Nutrition

INTRODUCTION

Oxidative Stress in the Brain

Certain environmental and lifestyle factors increase oxidative stress during fetal development and early childhood. These include maternal infection (Lautarescu et al., 2020; Usui et al., 2023), emotional stress (Van Den Bergh et al., 2020), dietary pattern (Fitzgerald et al., 2020; Lopez-Yañez Blanco et al., 2022), and certain pharmaceutical drugs (Zengeler et al., 2023). Under conditions of oxidative stress, the brain mobilizes its immune system. The brain's immune system includes microglia, which are cells located in the brain that prevent damage. Some of these oxidative stress inducing factors, especially if present for an extended period, result in a depletion of nutrients that support the microglia, which reduces their action. Reduction of brain levels of cysteine and taurine are markers of this diminished immunity (Jong et al., 2021; Samad et al., 2023).

When microglia are less active, then a specific developmental stage termed synaptic pruning is less effective. Synaptic pruning occurs in neurodevelopment to reduce synapses to just the ones needed. Prior to synaptic pruning, there is extensive neurogenesis and migration of neurons, accompanied by formation of excessive synapses. As these synapses become active, the ones with most activity are retained and the inactive excess are removed (pruned). This process occurs in neurotypical development and is believed to be related to why individuals are able to focus on a task at hand and bring multiple features from memory and the senses to accomplish the task.

If synaptic pruning is diminished, then a person would have more synapses retained, which may partially explain two features seen in autism. One is that autistic individuals tend to recall a lot of what they have encountered or learned, and the other is that these same individuals often are less able to keep focus on one task or recognize which features are relevant as they experience a cacophony of signals reverberating continually. Thus, if such an individual is working on a task and hears a sound or feels something or sees something, these other signals become as dominant as the first and progress on task is lost.

Stress thus has long term impacts on childhood development. We know from the work on adverse childhood events (ACEs), that children experiencing four or more ACEs have higher levels of oxidative stress (Horn et al., 2019; Janšáková et al., 2021) and greater risk of developing heart disease, cancer, or other chronic diseases (Lin et al., 2021). So, it is not surprising that this would be true for a neurological disorder as well.

Cerebral Folate Deficiency

A nutrition factor that appears to be associated with ASD risk is cerebral folate deficiency (CFD). About 5-15% of the population produce an antibody to the primary folate receptor (Berrocal-Zaragoza et al., 2009; Frye et al., 2013, 2020; Molloy et al., 2009). This folate receptor is responsible for transporting folate from the blood to the brain. The brain is a protected environment, surrounded by the blood brain barrier that prevents substances from entering. This barrier has specific transporters that move needed compounds, such as vitamins and nutrients, into the brain and keep everything else out. Folate, or vitamin B9, is a necessary compound that is important in regulating DNA synthesis and repair. This means folate functions as a switch to produce the necessary proteins for brain development.

When the body's immune system makes an antibody to the primary folate receptor, this antibody locks onto the folate transfer site and prevents folate from entering the brain, resulting in a lower level of folate in the brain, or CFD (V. Ramaekers et al., 2013; V. T. Ramaekers et al., 2005). The blocked folate receptors are no longer active, so the brain relies on a second category of folate carrier to get a minimal level of folate. Essentially, the primary brain folate transfer site is able to pump in folate to levels much higher than in the blood, but the secondary site can only carry over the same level as is present in the blood. The brain needs the higher level of folate to develop and function effectively. So with CFD, there is reduced DNA regulation, resulting in a concomitant reduction of neurogenesis, among other things. With CFD, the result may be slower neurodevelopment of specific brain pathways, which may present in a child as the reduction in social connection and recognition of emotion, common features seen in ASD.

NUTRITIVE REMEDIES

The reduced form of folate is methyl folate or folinic acid, while the oxidized form is folic acid. The human body can only utilize reduced folate, although it has a limited capacity to convert a small amount of oxidized folate into the reduced form. Studies have shown that among autistic children, 70% have the folate receptor antibody (Frye et al., 2013; Hyland et al., 2010). The antibody appears to be made in response to some component of cow's milk, such that when a child consumes no milk products then their body stops making the antibody (V. T. Ramaekers et al., 2008). Trials further show that in children producing the folate receptor antibody, supplementing with a reduced form of folate for three months resulted in improvement in communication and social connection. By providing the reduced form of folate directly, the secondary folate transfer system is able to bring in this folate and allow brain function to be more typical (Bobrowski-Khoury et al., 2021, 2023; Frye et al., 2020; V. T. Ramaekers et al., 2016).

Cow's milk and its byproducts are ubiquitous in a Western dietary pattern. Unfortunately, food selectivity is a common trait seen in children with ASD. These two actualities may create a self-propagating cycle of CFD. Children with ASD may have a narrow palate of foods consumed, often containing significant amounts of cow's milk, which continues the production of folate receptor antibodies. Further, food selectively often results in refusing fruits and vegetables which naturally contain high amounts of reduced folate. By placing children with ASD on supplemented reduced folate, it may be possible to improve communication and reduce food selectivity to the point that a family can modify dietary patterns and eliminate dairy to no longer produce the folate receptor antibody. Since reduced folate is in most leafy greens, beans, and other plant foods, this should make for a long-term solution to address CFD.

Addressing the decreased microglia activity would entail reducing the oxidative stress stimuli. This may be more difficult, as the environment that produces the stress may be less amenable to modification. However, supplementing to replenish the reduced cysteine and taurine may be beneficial. In this case, foods that are richer in these compounds could be consumed to mitigate some of the damage from the stress. Further, general modification of the dietary pattern to include less dairy, animal products, and ultra-processed foods and more whole plant foods such as fruits, vegetables, whole grains, beans, and nuts and seeds has been shown to both decrease the overall oxidative stress load of the dietary pattern as well as increase total body antioxidant capacity to handle oxidative stress (Aleksandrova et al., 2021; Clemente-Suárez et al., 2023; Kim et al., 2012; Peña-Jorquera et al., 2023; Tan et al., 2018; Zirilli et al., 2023).

CONCLUSION

ASD has a complex array of environmental and lifestyle factors that contribute to the development of the condition. Recent literature has highlighted the contribution of oxidative stress, brain inflammation and immune dysfunction, folate receptor antibodies and reduced folate dietary deficiencies as key contributors to ASD risk. Supplementing high ASD risk pregnancies and infants with reduced folate, maintaining a cow's milk free diet and increasing whole plant foods are nutritional interventions that could help decrease ASD risk or mitigate symptomatology. Early clinical trials have supported the benefit of these nutritional interventions and larger scale trials are needed.

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DECLARATION OF CONFLICT

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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