Gluten Intolerance and Neurodevelopmental Disorders: Is Nitric Oxide the Common Biomarker Linking These Conditions?

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Abstract
Cruchet et al. attempt to tease out the myths and facts surrounding the growing popularity of certain dietary approaches in the management of neurodevelopmental disorders, like attention-deficit hyperactivity disorder (ADHD) and autism spectrum disorders (ASDs). The authors identify a particular exclusionary-type approach that seeks to eliminate dietary gluten. Although the relationship between celiac disease (CD) and ADHD/ASD is not well established, a repeated clinical feature noted in CD is the elevated levels of nitric oxide in serum and urine. Elevated oxidative stress has also been observed in neurodevelopmental conditions, and the author of this correspondence has been the first to propose that chronic, environmental exposure to the air pollutant, nitrous oxide may contribute to these oxidative stress profiles through neural cholinergic perturbation. Therefore, the purpose of this correspondence is to highlight this biochemical connection between these conditions so as to identify the clinical populations who may realize the greatest benefit of these dietary approaches, while minimizing any potential risk of nutrient deficiencies.

Cruchet et al. [1] tease out the myths and facts surrounding the growing popularity of certain dietary approaches in the management of neurodevelopmental disorders. The authors identify a particular exclusionary-type approach that seeks to eliminate dietary gluten. Indicating moderate success with the amelioration of hyperactive symptoms, the authors conclude that elimination diets may work for a subgroup of attention-deficit hyperactivity disorder (ADHD) subjects. Some benefits have been recorded in certain populations having autism spectrum disorders (ASDs), but the methodological quality of these studies has been poor.

As preliminary as the evidence may be in support of exclusionary diets as a dietary adaptation in the management of ADHD and ASD, the authors offer limited clinical insight regarding their findings in order to help understand for whom the specific benefit of such dietary adaptations may exist. Nitric oxide (NO) is one biomarker that has been noted to be elevated in ADHD, ASD and celiac disease (CD). The purpose of this correspondence is to highlight this biochemical connection between these conditions so as to identify the clinical populations who may realize the greatest benefit of these dietary approaches, while minimizing any potential risk of nutrient deficiencies.

Although the relationship between CD and ADHD/ASD is not well established [2–4], a repeated clinical feature noted in CD is the elevated levels of NO in serum and urine [5–8]. A recent meta-analysis reporting on oxidative stress in ADHD found elevated NO in the blood of ADHD subjects [9], and similar findings have been made on levels of plasma NO in ASD [10]. These studies point to a biochemical marker that could be useful in delineating the ADHD/ASD subjects who may find the most therapeutic benefit from a gluten-free diet (GFD).

Heightened NO metabolism may help to explain the preliminary evidence sug-
suggesting a tepid connection between ADHD, ASD and CD. The author of this correspondence has been the first to suggest that chronic exposure to the pervasive air pollutant, nitrous oxide (N₂O), may be the dominating etiological factor in the development of conditions like ADHD and ASD [11–14]. Through neural cholinergic inhibition, N₂O exposure could adversely impact central NO metabolism; rapid, peripheral induction of NO could serve as a compensatory exercise to restore central NO status [14]. Given the clinical and in vitro findings, which indicate elevated NO production amid a gluten challenge [8, 15], consumption of wheat gluten in ADHD/ASD may augment N₂O-induced oxidative burden, contributing to the symptoms of gluten intolerance. Not only is this notion consistent with the role of NO as a regulator of intestinal inflammation [16, 17] but also represents a qualification to the proposed involvement of air pollution as a potential modulator of gut microbiome health [18, 19].

Therefore, Cruchet et al. [1] should recognize the utility of exclusionary diets, like GFD, that may exist for a certain subgroup of ADHD/ASD subjects; in particular, cessation of gluten intake in a subset of ADHD/ASD subjects with elevated oxidative stress may be a clinical recommendation that is worthy to more fully explore.

References


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