Minireview Article

A MINI REVIEW OF GASTROINTESTINAL PATHOLOGY AND NUTRITION IN AUTISM SPECTRUM DISORDER

ABSTRACT

Autism spectrum disorder (ASD) is a complex, heterogenous group of neurodevelopmental disorders that result due to interaction of genes and environmental factors. ASD is associated with behavioural alterations and deficits in social communication. Current research on pathophysiology has proposed a link between severity of symptoms of ASD and gastrointestinal disturbances. Intestinal inflammation, dysregulation of gut microbiome may affect intestinal permeability, mucosal immune function and subsequently cause GI symptoms. Studies have also proposed the role of metabolic activity of the gut microbiome and dietary components (food allergens/toxins) to be associated with behavioral alterations in neurodevelopmental conditions including ASD. The present review aims to highlight the potential role of nutrients and dietary changes on gastrointestinal pathology and symptoms of ASD.

Key Words: Autism Spectrum Disorder, Gastrointestinal, Diet, Nutrients

INTRODUCTION

Autism spectrum disorder (ASD) is a neurodevelopmental condition presenting with restricted, repetitive patterns of behaviors, interests, and activities, or persistent deficits in social communication and interaction. The Diagnostic and Statistical Manual of Mental Disorders (DSM), 2013 now classifies all individuals previously diagnosed with Autism, Asperger's Syndrome, Pervasive Developmental Disorder not otherwise specified under the umbrella of Autism Spectrum Disorder.

Autism Spectrum Disorder has strong genetic basis with several genes, Gamma-aminobutyric acid (GABA) A receptor, Beta 3 (GABRB3), Oxytocin receptor (OXTR), N-methyl-D-aspartate receptor (NMDA; GRIN2B) to name a few, being consistently implicated in pathogenesis of the condition. Recent studies, however, have described a number of environmental, non genetic factors and associated disturbances in gastrointestinal and immune systems in the pathophysiology of ASD. These factors may have a direct link in the pathogenesis or may act as 'gene modifiers' thereby aggravating the primary causative mechanism [1]. Several research groups have studied the link between intestinal mucosal permeability, abnormal gut development, gastroesophageal reflux and intestinal infections in ASD with inconclusive results regarding cause or effect relationship of the mentioned factors [2, 3, 4]. Research is also being conducted to analyze the role of diet and nutrition in ASD, with attention being focused on food allergens, toxicity, and sensitivity. The present review aims to highlight the potential role of nutrients and dietary changes on gastrointestinal pathology and symptoms of ASD.

Role of maternal factors and breastfeeding in ASD

Prenatal maternal factors such as lifestyle, nutritional status especially during critical periods of fetal neurodevelopment have been shown to be associated with higher risk of ASD [5]. Post-natally, breastfeeding has been described as a chief environmental factor affecting the chance of occurrence of ASD [6]. Protective effects of breastfeeding on the developing GI tract have been described with, shorter duration of breastfeeding (less than 6 months) being associated with increased chance of infants developing ASD. Data from parent interview-based studies revealed early occurrence of GI symptoms (within 2-3 years of age) in children diagnosed with ASD, especially in those who were fed with infant formula and bovine milk [7, 8, 9].

Protein content of breast milk is low compared to bovine milk and infant formula products. Of the two protein components in milk-casein and whey, casein has a tendency to curdle thereby becoming more difficult to digest subsequently leading to GI symptoms in the infant such as constipation or diarrhea and abdominal pain. Breast milk is low in casein, which protects the infant from GI disturbances. Additionally, bioactive agents present in breast milk aid in development of the brain and immune system [10].

Dietary considerations:

Exclusive breastfeeding for the first 6 months of life will aid in optimal growth and development of the infant, while preventing occurrence of GI symptoms thereby reducing exacerbation of neurological symptoms of autism. The WHO recommends continuation of breastfeeding for up to 2 years of age along with introduction of solid food items. Substituting bovine milk with coconut or soya milk may aid in reducing severity of symptoms in children with ASD.

Gut-Brain Axis

Dysregulation in the gut microbiome and subsequent metabolic activity have been suspected to alter behavior and cognition in several neurodegenerative diseases, such as Alzheimers disease, Parkinson's disease etc. Thus, it may be hypothesized that gastrointestinal factors may play a role in neuroinflammation and subsequent brain dysfunction in ASD [11]. There exists a bi-directional communication between the gut and the brain which involves afferent and efferent pathways. The afferent pathway includes cytokines, intestinal hormones and microbiota while the efferent pathway includes neuro-endocrine and autonomic regulation [12]. The gut-brain axis plays a role in modulation of body metabolism through regulation of appetite and energy homeostasis as well as behavioral factors such as response to stress and pain, emotions and attitude etc.

The homology between the gut-blood barrier and blood-brain barrier has been suggested to play an important role in communication between the gut and brain [11]. Disruption of integrity of either barrier due to activity of inflammatory mediators may be associated with systemic dissemination of toxins. In context of ASD, neurotropic viruses or bacterial toxins from the intestine may reach the CNS through enteroendocrine cells or directly via vagus nerve, thereby causing aggravation of symptoms of the condition [13, 14].

Diarrhea, constipation, abdominal pain, gaseousness are commonly reported gastrointestinal symptoms in patients with ASD. Presence of IgG-class antibodies directed against food antigens has been considered as indirect evidence of increased intestinal permeability. A study done by Lau et al. (2013) reported that children with autism have significantly higher levels of IgG Antigliadin Antibodies (but not IgA) compared with healthy controls, particularly those with gastrointestinal symptoms [15]. Recent studies confirmed these findings and also reported an

increase in antibodies directed to several other food allergens, including casein and whole milk [16].

Role of intestinal microorganisms

Studies have reported overgrowth of obligate anaerobic organisms such as Clostridium spp. as well as Vibrio spp. in children with autism [14, 17]. These organisms do not breakdown fermentation end products such as short chain fatty acids-propionate, butyrate and acetate. Propionic acid especially has been detected in high levels in stool and urine samples of patients with ASD. Short chain fatty acids are capable of crossing the gut-blood and blood-brain barriers, thereby may be associated with symptoms of developmental delay, seizures along with GI manifestations in ASD [18].

Dietary considerations

Dietary modifications based on identification of GI factors/symptoms, may aid treatment planning and in alleviating pain, constipation/diarrhea and other symptoms as well as improve non verbal behaviors (agitation, anxiety, aggression, self-injury, sleep deprivation) as seen in ASD. In addition, a low carbohydrate diet that would reduce the production of short chain fatty acids may be advised in ASD. Studies have suggested a link between intestinal microbiota and metabolism in children with ASD and hyperoxalemia/hyperoxaluria [19]. Impaired oxalate metabolism may be associated with increased GI permeability and decreased intestinal microflora, which as described earlier may result in aggravation of neurological symptoms of ASD. It would therefore be advisable to avoid foods high in oxalates such as berries, grapes, apples; millets, oats; and nuts.

Gluten sensitivity in ASD

In order to prevent/ameliorate GI and neurological manifestations, it is imperative to identify trigger food items and follow a restriction/elimination diet. Gluten, a protein complex, found in cereals such as wheat, barley, rye etc. has been implicated in the pathogenesis of several intestinal disorders [20]. Several research groups have studied the effect of gluten in ASD with conflicting results [21, 22, 23]. One aspect to be considered in the pathogenesis of ASD is the opioid phenotype of autism that is linked to 'exorphins'- food related oligopeptides. Exorphins are derived from incompletely digested gluten and/or casein due to reduced activity of dipeptidyl peptidase-4 (DPP-4) enzyme [24]. These exogenous opioid peptides may influence GI functions and may also elicit behavioral changes through their effects on dopaminergic, serotoninergic and GABAergic systems in the brain [25]. It may thus be hypothesized that a gluten-free, casein-free (GFCF) diet may reduce production of exorphins and prevent development or worsening of symptoms of ASD.

De Magistris et al. (2010) reported a high percentage of abnormal intestinal permeability test values [as established by the lactulose/mannitol (L/M) ratio] among patients with autism [26]. The study observed that patients with autism on a reported GFCF diet had significantly lower intestinal permeability test values compared with those who were on an unrestricted diet and controls. However, despite the increasing popularity, efficacy of the GFCF diet in improving autistic behavior remains to be proven. A Cochrane review (2008) reported that only two small randomized controlled trials investigated the effect of the GFCF diet in children with ASD (n = 35) [27]. The review concluded, based on the outcomes evaluated (overall autistic traits, social

isolation, and overall ability to communicate and interact), that the evidence for efficacy of such an exclusion diet is poor, and large-scale good-quality randomized controlled trials are needed to validate the results [27]. Similar conclusions were reported by a recently published systematic review on treatment of autistic children with the GFCF diet [10]. However, in a two-stage randomized controlled study of the GFCF diet in children with ASD, Whiteley et al. (2010) reported significant group improvements in core autistic and related behaviors after 8 and 12 months [28].

Several potential factors appear to influence response to dietary intervention in terms of symptom presentation. Age was found to be the strongest predictor of response, and participants between 7 and 9 years of age seemed to derive most benefit from the GFCF dietary intervention [29]. The above data suggest that removing gluten from the diet may positively affect the clinical outcome in some children diagnosed with ASD. Based on the findings, it may also be suggested that autism may be part of the Non-celaic gluten sensitivity spectrum, at least in some cases.

Nutritional deficiencies in ASD

Pathogenesis of ASD may begin during fetal developmental stages. As previously explained, maternal nutrition plays an important role in brain development and deficiencies have been reported to be associated with adverse neurodevelopmental outcomes [30]. Nutritional deficiencies may be caused due to increased fetal metabolic demands or pre-existing maternal health conditions which directly influence structural and functional brain development, thus increasing the risk of ASD [31]. Maternal vitamin A, D, folate, Vitamin B12, magnesium, omega-3 fatty acid and iron supplementation has been shown to protect the developing brain from inflammatory changes, neurotoxins and enhance neuronal development [5].

Studies have reported feeding problems, food selectivity, unusual eating patterns in patients with ASD [32]. Additionally, significant associations have been found between oral-motor, gastrointestinal and sensory problems in children with ASD. Dietary supplementation of essential nutrients is therefore widely employed in children with ASD to aid in growth and development, as well as prevent worsening of ASD status.

Dietary considerations:

Vitamin B12 and Folinic acid

Studies have reported low methionine, homocysteine, cysteine in children with ASD. Additionally, reduced antioxidant capacity and abnormal trans-sulfuration metabolism have also been reported. Supplementation of vitamin B12 was found to elevate methylation capacity and improve 'redox status', thus improving clinical behavioral outcomes in children with ASD [33]. Vitamin B12 is naturally found in animal products such as, fish, meat, poultry, milk and milk products but generally absent in plant foods. Moreover, an inherent drawback of dietary vitamin B12 supplementation is that, oral absorption is less effective and does not guarantee adequate concentrations. Therefore, further studies are required to identify the most appropriate route of supplementation of vitamin B12 in patients with ASD.

Similarly, folinic acid, which is a reduced form of folate, plays a role in the metabolism of homocysteine and glutathione, similar to Vitamin B12. Folinic acid is naturally found in foods such as, chickpeas, beef liver, asparagus etc. A recent RCT reported improvement in verbal communication after supplementation of folinic acid in patient with ASD [34].

Vitamin D

Vitamin D is a fat soluble agent that plays the role of a 'neuroactive steroid' during brain development. The vitamin aids in cell proliferation and differentiation, calcium signaling and exerts neurotrophic and neuroprotective effects. Vitamin D also plays an essential role in myelination, thus may have effects on synaptic plasticity and neurotransmission [35]. In context of ASD, the plausible mechanism of action of vitamin D are: anti-inflammatory effects on the brain, and regulation of serotonin. In an RCT done by Saad et al. (2018), improvement in behavioral measures (Autism Evaluation Checklist, CARS, SRS) was observed 4 months after supplementation of vitamin D in children with ASD [36]. Sunlight is the best source of vitamin D, however, cheese, egg yolk, fatty fish such as tuna, salmon also provide the vitamin. Studies have reported improvement in core symptoms of autism, thus dietary supplementation must be considered, especially in autistic children with deficiency of vitamin D.

Omega-3 fatty acids

The two omega-3 fatty acids: Eicosapentanoic acid (EPA) and Docosahexanoic acid (DHA), play an important role in normal growth and development of the body, including neurodevelopment. Low concentrations of EPA and DHA have been observed in patients with ASD as well as other neurodevelopmental anomalies, considering that these orthomolecules have functional sites exclusively on cell membranes, including nerve cells [37]. Although, data from clinical trials have not directly reported benefits of omega-3 fatty acids in core symptoms of ASD, supplementation was safe and well tolerated and was found to benefit general neurodevelopment in children [38, 39].

Probiotics

Probiotics are live microorganisms (bacteria and yeast) that provide health benefits by restoring or improving normal gut microbiota. Probiotic therapy has been proposed as a relatively risk-free, adjuvant modality to ameliorate gastrointestinal symptoms in patients with ASD [40]. Supplementation has been demonstrated to increase counts of Lactobacilli and Bifidobacterium *spp.*, which improve both GI and core behavioral symptoms of ASD [41]. However, most studies are associated with the limitation of small sample size; therefore, future research should be conducted on a larger scale in order to accurately elucidate the effect of probiotics in patients with ASD.

CONCLUSION

Identification of trigger foods and dietary modification in ASD is a gradual process and may differ between affected individuals. The present review highlights some of the common food allergens and nutrients/nutritional deficiencies responsible for exacerbation of symptoms of ASD. Further research is required to establish the effects of these agents as well as identify other probable food toxins and allergens affecting the pathology of autism spectrum disorder.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is

absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

REFERENCES

1. Samsam M, Ahangari R, Saleh AN. Pathophysiology of autism spectrum disorders: Revisiting gastrointestinal involvement and immune imbalance. World J Gastroenterol 2014 August 7; 20(29): 9942-9951.
2. Buie T, Campbell DB, Fuchs GJ III, Furuta GT, Levy J, Vandewater J, et al. Evaluation, diagnosis, and treatment of gastrointestinal disorders in individuals with ASDs: a consensus report. Pediatrics. 2010;125(suppl 1):S1–S18.
3. Samsam M. Functionally Oriented Regional Anatomy. 2nd ed. Plymouth, MI: Hayden McNeil publishing, 2013: 209-302.
4. Williams BL, Hornig M, Buie T, Bauman ML, Cho Paik M, Wick I, et al. Impaired carbohydrate digestion and transport and mucosal dysbiosis in the intestines of children with autism and gastrointestinal disturbances. PLoS ONE. 2011;6(9): e24585.
5. Lyall K, Schmidt RJ, Hertz-Picciotto I. Maternal lifestyle and environmental risk factors for autism spectrum disorders. International Journal of Epidemiology, 2014, 443–464.
6. Schultz ST, Klonoff-Cohen HS, Wingard DL, Akshoomoff NA, Macera CA, Ji M, et al. Breastfeeding, infant formula supplementation, and Autistic Disorder: the results of a parent survey. Int Breastfeed J. 2006; 1:16.
7. Horvath K, Perman JA. Autism and gastrointestinal symptoms. Curr Gastroenterol Rep. 2002; 4(3):251–258.
8. Dominick KC, Davis NO, Lainhart J, Tager-Flusberg H, Folstein. Atypical behaviors in children with autism and children with a history of language impairment. Res Dev Disabil. 2007; 28(2):145–162.
9. Penn AH, Carver LJ, Herbert, Lai TS, McIntire MJ, Howard JT et al. Breast Milk Protects Against Gastrointestinal Symptoms in Infants at High Risk for Autism During Early Development. J Pediatr Gastroenterol Nutr. 2016 February; 62(2): 317–327.
10. Schultz ST, Klonoff-Cohen HS, Wingard DL, Akshoomoff NA, Macera CA, Ji M, et al. Breastfeeding, infant formula supplementation, and Autistic Disorder: the results of a parent survey. Int Breastfeed J. 2006; 1:16.
11. Wasilewska J, Klukowski M. Gastrointestinal symptoms and autism spectrum disorder: links and risks – a possible new overlap syndrome. Pediatric Health, Medicine and Therapeutics 2015:6 153–166
12. Mayer EA, Tillisch K, Gupta A. Gut/brain axis and the microbiota. J Clin Invest. 2015;125(3):926–938.
13. Theoharides TC, Zhang B. Neuro-inflammation, blood-brain barrier, seizures and autism. J Neuroinflammation. 2011;8:168.
14. Bolte ER. Autism and Clostridium tetani. Med Hypotheses. 1998; 51(2):133–144.

15. Lau NM, Green PH, Taylor AK, Hellberg D, Ajamain M, Tan CZ, et al. Markers of celiac disease and gluten sensitivity in children with autism. PLoS ONE. 2013;8(6).
16. De Magistris L, Picardi A, Siniscalco D, Riccio MP, Sapone A, Cariello R. Antibodies against food antigens in patients with autistic spectrum disorders. Biomed Res Int 2013;2013:729349.
17. Tomova A, Husarova V, Lakatosova S, Bakos J, Vlkova B, Babinska K, et al. Gastrointestinal microbiota in children with autism in Slovakia. Physiol Behav. 2015;138:179–187.
18. Al-Owain M, Kaya N, Al-Shamrani H, Al-Bakheet A, Qari A, Al-Muaigl S, et al. Autism spectrum disorder in a child with propionic acidemia. JIMD Rep. 2013;7:63–66.
19. Konstantynowicz J, Porowski T, Zoch-Zwierz W, Wasilewska J, Kadziela-Olech H, Kulak W, et al. A potential pathogenic role of oxalate in autism. Eur J Paediatr Neurol. 2012;16(5):485–491.
20. Catassi C. Gluten Sensitivity. Ann Nutr Metab 2015;67(suppl 2):16–26.
21. Navarro F, Pearson DA, Fatheree N, Mansour R, Hashmi SS, Rhoads JM. Are 'leaky gut' and behavior associated with gluten and dairy containing diet in children with autism spectrum disorders? Nutr Neurosci. 2015;18(4):177–185.
22. Whiteley P, Shattock P, Knivsberg AM, Seim A, Reichelt KL, Todd L, et al. Gluten- and casein-free dietary intervention for autism spectrum conditions. Front Hum Neurosci. 2012;6:344.
23. Elder JH, Shankar M, Shuster J, Theriaque D, Burns S, Sherrill L. The gluten-free, casein-free diet in autism: results of a preliminary double blind clinical trial. J Autism Dev Disord. 2006;36(3):413–420.
24. Johnson B, Ulberg S, Shivale S, Donaldson J, Milczarski B, Faraone SV.Fibromyalgia, autism, and opioid addiction as natural and induced disorders of the endogenous opioid hormonal system. Discov Med. 2014;18(99):209–220.
25. Cieslinska A, Sienkiewicz-Szlapka E, Wasilewska J, Feidorowicz E, Chawla B, Moszynska-Dumara M, et al. Influence of candidate polymorphisms on the dipeptidyl peptidase IV and mu-opioid receptor genes expression in aspect of the beta-casomorphin-7 modulation functions in autism. Peptides. 2015;65C:6–11.
26. De Magistris L, Familiari V, Pascotto A, Sapone A, Frolli A, Iardino P, et al. Alterations of the intestinal barrier in patients with autism spectrum disorders and in their first-degree relatives. J Pediatr Gastroenterol Nutr 2010;51:418-424.
27. Millward C, Ferriter M, Calver S, Connell-Jones G. Gluten- and casein-free diets for autistic spectrum disorder. Cochrane Database Syst Rev 2008;2:CD003498.
28. Whiteley P, Haracopos D, Knivsberg AM, Reichelt KL, Parlar S, Jacobsen J, et al. The ScanBrit randomised, controlled, single-blind study of a gluten- and casein-free dietary intervention for children with autism spectrum disorders. Nutr Neurosci 2010;13:87-100.
29. Pedersen L, Parlar S, Kvist K, Whiteley P, Shattock P. Data mining the ScanBrit study of a gluten- and casein-free dietary intervention for children with autism spectrum disorders: behavioural and psychometric measures of dietary response. Nutr Neurosci 2014;17:207-213.
30. Black MM. Micronutrient deficiencies and cognitive functioning. J Nutr 2003;133(11 Suppl 2):3927S–31S.
31. Institute of Medicine. Nutrition During Pregnancy 1990. Washington, DC: National Academy Press, 1990.

32. Nadon G, Feldman D and Gisel E. Feeding Issues Associated with the Autism Spectrum Disorders. Recent Advances in Autism Spectrum Disorders - Volume I
33. Han Y, Xi QQ, Dai W, Yang SH, Gao L, Su YY, et al. Abnormal transsulfu-ration metabolism and reduced antioxidant capacity in Chinese children with autism spectrum disorders. Int J Dev Neurosci (2015) 46:27–32.
34. Frye R, Slattery J, Delhey L, Furgerson B, Strickland T, Tippett M, et al. Folinic acid improves verbal communication in children with autism and language impairment: a randomized double-blind placebo-controlled trial. *Mol Psychiatry* (2016).
35. Cannell JJ. Vitamin D and autism, what's new? Rev Endocr Metab Disord (2017) 18(2):183–93.
36. Saad K, Abdel-Rahman AA, Elserogy YM, Al-Atram AA, El-Houfey AA, Othman HA, et al. Randomized controlled trial of vitamin D supplementation in children with autism spectrum disorder. J Child Psychol Psychiatry (2016).
37. Yehuda S, Rabinovitz S, Mostofsky D. Essential fatty acids and the brain: from infancy to aging. Neurobiol Aging (2005) 26(1):98–102.
38. Mazahery H, Stonehouse W, Delshad M, Kruger MC, Conlon CA, Beck KL, et al. Relationship between long chain n-3 polyunsaturated fatty acids and autism spectrum disorder: systematic review and meta-analysis of case- control and randomised controlled trials. Nutrients (2017) 9(2):155.
39. Yui K, Koshiba M, Nakamura S, Kobayashi Y. Effects of large doses of ara-chidonic acid added to docosahexaenoic acid on social impairment in indi-viduals with autism spectrum disorders: a double-blind, placebo-controlled, randomized trial. J Clin Psychopharmacol (2012) 32(2):200–6.
40. Shaaban SY, El Gendy YG, Mehanna NS, El-Senousy WM, El-Feki HSA, Saad K, et al. The role of probiotics in children with autism spectrum disorder: A prospective, open-label study. Nutr Neurosci. 2017 Jul 7:1-6.
41. Patusco R, Ziegler J. Role of Probiotics in Managing Gastrointestinal Dysfunction in Children with Autism Spectrum Disorder: An Update for Practitioners. Advances in Nutrition, Volume 9, Issue 5, 1 September 2018, Pages 637–650.