

Autistic Spectrum Disorders and Diet: the Present and the Future

Irene Mateos Rodriguez

Abstract

The frequent presence of gastrointestinal problems in Autistic Spectrum Disorder (ASD) has led to attempts to understand how gastrointestinal disturbances relate to behaviour, and how modifying diets may help to modify behaviour. This review paper aims to summarise the rationale for managing symptoms of ASD through diet, the current status of research on diet and ASD, and the future of employing this approach to manage ASD.

School of Clinical Medicine, Cambridge University

*Corresponding author: im409@cam.ac.uk

1. Introduction

“Let food be thy medicine and medicine be thy food.” – Hippocrates

Autistic Spectrum Disorder (ASD) is defined as a triad of impairments including social functioning, communication difficulties, and lack of flexibility of thought and behaviour [1]. Prevalence studies have estimated that 1% of school children between five to nine years old in the UK have a diagnosis of ASD [2].

In the UK, ASD is diagnosed through thorough assessments conducted by an ‘autism team’ as recommended by NICE guidelines (National Institute for Health and Care Excellence). After the diagnosis is made, interventions are mainly supportive – to parents, in educational settings, and through community groups [3]. ASD is a lifelong neurodevelopmental condition, where impairments persist into adulthood and have important implications for learning and social integration.

The pathophysiology of ASD has proven to be complex and multifaceted [4, 5]. One aspect of ASD research that has received important yet insufficient attention is the impact of the gut and its microbiota on the behaviours associated with autism.

Food and behaviour

Feeding difficulties are common problem in up to 89% of children with ASD, significantly greater than what has been found in typically developing children [6, 7]. This includes picky eating, often restricting the variety of foods; fussy eating, with difficulties around texture or colour sensitivity;

and food neophobia, with a reluctance to try new foods [6, 7]. These feeding difficulties have raised concerns regarding the short and long term impact on the physical development of the child, and also on how the particular foods may interact via a range of mechanisms with the behaviours associated with the condition.

The link between food allergies, hypersensitivity to foods or particular ingredients and behavioural problems dates back to the 1920s [4]. In the 1970s Feingold discussed a potential link between food colourings and symptoms of hyperkineticism (now known as ADHD – attention deficit hyperactivity disorder) [9]. A recent meta-analysis seems to show some potential for a food-colouring-exclusion diet in improving behavioural symptoms in children with ADHD [8]. These findings have shaped European Union (EU) regulation, where warning labels are now mandatory in foods containing food colourings that have been associated with ADHD [8]. Exclusion diets, or diets aimed at changing the gut microbiota have also gained traction in the management of other neurological conditions such as depression [10, 11].

Current guidelines on diet for ASD

In the context of ASD, current guidelines, including the NICE guidelines in the UK, make no mention of any potential benefits of dietary changes in the management of ASD. The National Centre for Complementary and Integrative Health in the US claims that there is insufficient evidence for the use of supplements (e.g. melatonin, omega-3 fatty acid, probiotics, secretin, vitamin B6) or exclusion diets (e.g. casein-free-gluten-free diet or ketogenic diet) for the

management of ASD, and warn against the potential nutritional harms of using supplements or restricting diets in the development of the child [12].

Linking ASD and diet

Despite current guidelines not recommending changes in diet, there is consistent and robust data showing that children with ASD have persistent gastrointestinal problems [13]. How these may then influence behaviour is still far from fully understood, but there is strong evidence to support a relationship.

One theory suggests that there is an increased intestinal permeability in children with ASD, so called ‘leaky-gut’, and thus certain foods may be able to cross the gut barrier and interact with receptors on certain tissues like the brain [5, 13, 14]. Specifically, exposure to casein and gluten in the diet has been associated with ASD symptomatology [5]. Casein (protein derived from cow milk) and gluten (from wheat, barley and rye) both produce peptides that interact with opioid receptors. Given the permeability of the gastrointestinal tract in children with ASD, these peptides can therefore cross the gut barrier and interact with opioid receptors, enhancing their effect, and potentially influencing the central nervous system. There is some evidence that the administration of opioid blockers, like naltrexone, may help improve symptoms in patients with ASD [16]. There is also some mixed evidence that administering a synthetic form of secretin, a hormone produced normally by the pancreas, can act to breakdown these peptides, thereby reducing opioid excess, thus improving function in children with ASD [17]. Individual case studies report significant improvements in ASD traits following the use of secretin, but larger studies suggest it has no greater effect than placebo [17]. Secretin is currently being used as a homeopathic remedy for the management of ASD. As an aside, it is possible that using secretin on a subgroup of children with ASD and a ‘leaky-gut’ may help tease apart who may benefit from this ‘treatment’, if any. It has also been repeatedly found that children with ASD have higher levels of these peptides in the cerebrospinal fluid and in the urine compared to matched controls [13, 14]. Whether these findings contribute to the pathogenesis of ASD or result from its development is unclear, but determining the significance of these findings is crucial to understanding any potential for diet in either the management or prevention of ASD.

Another theory suggests that children with ASD show an increased immune response to casein and gluten, compared to matched controls [5, 18]. As an example, there is evidence suggesting that children with ASD show elevated levels of serum antibodies specific for milk derived allergens (e.g. IgA, IgG, IgM), serum IgE and pro-inflammatory cytokines, all relative to matched controls [5, 18].

Gluten-free-casein-free diets (GFCF)

Given the potential link between ASD and casein and gluten, the effects of GFCF diets on ASD were assessed by a Cochrane Review in 2008 [15]. This review revealed that there has been extensive research examining the potential link between GFCF and improvement in ASD symptoms. However, only two studies out of over 30 identified papers met the criteria of randomised controlled trials (RCTs) [15]. The review went on to critically appraise these two studies. They report that in a sample of 35 children with ASD, a GFCF diet had a positive effect overall on ASD behaviours [15]. They found that ‘social isolation’ and ‘bizarre behaviours’ were reduced in the diet group. With regards to social isolation they reported a lower resistance and greater ability to communicate and interact. With regards to ‘bizarre behaviours’ they reported, amongst many, lower patterns of compulsive/stereotypic communication and less inappropriate emotional reactions when in highly arousing states. They also report no evidence in the short-term of any harmful effects of such diet. These findings, though encouraging, are based on very small samples, where parents completing the outcome measures had not been blinded to the treatment group, thus leaving room for a placebo effect [15]. There was also the suspicion that the diets had been breached by the children with ASD, who had eaten food offered by siblings. A further limitation to both these studies is the lack of washout period, which, given the residual capacity of both gluten and casein, leaves them open to the argument that those in the treatment group had not been totally deprived of gluten and casein.

More recently, Hyman and colleagues (2016) [19] published an RCT which showed no effects of the GFCF diet on ASD symptoms. There were 14 participants. These were randomly allocated to one of four conditions: casein, gluten, casein and gluten, or placebo. They were all put on a GFCF diet for 4–6 weeks, and then whilst continuing with the diet, were given one of the four equipped ‘snacks’. It was not clear whether during this period they were still on a GFCF diet, despite having received their allocated-group-snack. Still, no effect was found on ASD symptoms, behavioural problems, or psychological functioning. This study is again based on a very small sample, and hence the validity and reliability of their findings and the strength of any effects would be compromised by a reduced power.

Future studies should also address the long term impact of a GFCF diet on the physical growth of the child with ASD. There is already preliminary evidence suggesting that children with ASD have a lower bone mineral density relative to their peers [20] and that children on gluten free or gluten and dairy free diets are smaller when compared to their peers on national averages [21]. The former study was based on a small sample of eight children with ASD, where four of these were on the GFCF diet, one was on a gluten-free diet, and one other on a lactose-free diet; the remaining four were not on any special diet [20]. These were

compared to eight matched controls on different measures of bone mineral density. In both groups seven out of the eight children were taking vitamin D supplements. There was a significant difference in bone mineral density, where children with ASD scored significantly lower than the control group despite controlling for diet type or supplements use. These findings may suggest that children with ASD are already at a disadvantage in absorbing and utilising vitamin D and calcium, although this conclusion is based on a very small sample of children with ASD. However, this raises an important point regarding the further risk of a diet that excludes dairy products, like the GFCF diet. It is important to acknowledge that the absorption of vitamin D and bone mineralisation is also dependent on exercise and spending time outdoors, which children with ASD tend to do less [20].

Despite the mixed picture described by research to date, there is room for future studies employing larger samples to investigate the potential for dietary changes in the management of perhaps a subgroup of children with ASD, and other studies have highlighted the importance of following the physical as well as the behavioural development of these children.

Ketogenic Diet

The ketogenic diet has also received some attention in the field of ASD; this is a high-fat low carbohydrate diet. This diet has been found to help reduce seizures in children with epilepsy [22]. Seizures have often been associated with ASD, and therefore there are some small scale studies that have assessed the role of the ketogenic diet on managing seizures in this group of children [23, 24]. One study showed that indeed the incidence of seizures was reduced in the group of children with ASD on the ketogenic diet [23], and they also found that there was an improvement in their behaviour. This included an improvement in their ability to learn and socialise with others [23]. However, a review of the current literature found no significant associations between the ketogenic diet or the GFCF diet and seizures or behaviours in ASD [24]. The review highlighted the need for larger and more powerful studies to fully assess the nature of this potential relationship, and the need to understand further by what mechanism exclusion diets may be influencing behaviour.

Microbiome and ASD

The microbiome refers to the microbes that live in our gastrointestinal system [25]. Certain bacteria within the microbiome have been receiving a lot of attention for their role in the treatment of a range of neurological conditions, including depression [10, 11]. The mechanism by which this occurs is far from being understood; nonetheless, there are hypotheses, which lie beyond the scope of this paper,

that suggest that the microbiome may be somehow interacting with the brain, the immune system, and the endocrine system, and through this affecting behaviour [10, 11].

There is preliminary evidence suggesting that in children with ASD the microbiome is of a different composition, and that it behaves in a different way to that observed in healthy matched controls [26, 27]. Animal models of ASD have been found to have a dysregulated microbiome, and find that microbiome-specific probiotics seem to reduce ASD-like behaviours [27, 28, 29]. There is evidence from mouse models of ASD that mice being fed *Bacteroides fragilis*, one of the commensal bacteria found in normal intestinal microbiome, show significant improvement in the ASD-like behaviours and in their gastrointestinal functioning [28]. These results need to be translated into studies investigating the role of the microbiome in children with ASD to fully understand its potential. Interactions between the microbiome and the vagus nerve have been reported to modulate depression-like symptoms in mice, these not being present if mice undergo a vagotomy [30], thus suggesting that one mechanism the gut microbiota may be influencing the brain is via the vagus nerve. Lastly, interactions between microbiome, specifically *Bacteroides fragilis* and the immune system, has led to microbe-based therapies to treat symptoms of multiple sclerosis and depression in mouse models [30, 31], suggesting another mechanism by which the gut microbiome may be influencing the brain. This suggests a potentially important interaction between the microbiome in the gut, the immune system, and neurological functioning [27, 28, 29, 30, 31]. Alterations in the diet could therefore potentially interact in a favourable way to decrease the pro-inflammatory state observed in some children with ASD, which seems to be related to the behavioural and cognitive difficulties observed in these children.

Future Research

Whilst the evidence regarding the relationship between diet and ASD is inconclusive at this stage, preliminary findings suggest that this is an avenue worth exploring. Larger randomised controlled studies are needed to assess the full potential of GFCF and ketogenic diets on ASD behaviour. With this in mind, it is important to accept that ASD captures a very broad spectrum of symptoms, and thus it may be that an exclusion diet may be likely to benefit a subgroup of children with ASD. Interestingly, screening for specific casein and gluten serum antibody markers, or directly targeting groups of children with ASD who also suffer from seizures, may help identify those subgroups that are likely to benefit from such exclusion diets. The relationship between gut microbiota and ASD behaviour may also be worth exploring, as addressing this has shown to be a simple yet effective intervention in a range of neurological-related conditions. As with any special diet, especially those aimed at children, it is important

to have a solid evidence base for their implementation, to ensure these do not harm the child's both physical and mental development.

References

- [1] American Psychiatric Association. Diagnostic and Statistical Manual (DSM) of Mental Disorders. 5th ed. Washington DA, Editor. 2013.
- [2] Baron-Cohen S, Scott FJ, Allison C, Williams J, Bolton P, Matthews FE, et al. Prevalence of autism-spectrum conditions: UK school-based population study. *Br J Psychiatry*. 2009;194:500—9.
- [3] National Institute for Health and Care Excellence. Autism spectrum disorder in under 19s: recognition, referral and diagnosis [Internet]. NICE guidelines CG128. 2011 [cited 2016 Jul 14]. Available from: <https://www.nice.org.uk/Guidance/CG128>
- [4] Mandy W, Lai M. Annual Research Review: The role of the environment in the developmental psychopathology of autism spectrum condition. *J Child Psychol Psychiatry*. 2016;57(3):271–92.
- [5] Ly V, Bottelier M, Hoekstra PJ, Arias Vasquez A, Buitelaar JK, Rommelse NN. Elimination diets' efficacy and mechanisms in attention deficit hyperactivity disorder and autism spectrum disorder. *Eur Child Adolesc Psychiatry*. Springer Berlin Heidelberg; 2017;(Feb 11):1–13.
- [6] Ledford JR, Gast DL. Feeding Problems in Children With Autism Spectrum Disorders: A Review. *Focus Autism Other Dev Disabl*. 2006;21(3):153—66.
- [7] Marshall J, Hill R, Ziviani J, Dodrill P. Features of feeding difficulty in children with Autism Spectrum Disorder. *Int J Speech Lang Pathol*. 2014;16:151–8.
- [8] Nigg JT, Lewis K, Edinger T, Falk M. Meta-Analysis of Attention-Deficit/Hyperactivity Disorder or Attention-Deficit/Hyperactivity Disorder Symptoms, Restriction Diet, and Synthetic Food Color Additives. *J Am Acad Child Adolesc Psychiatry*. 2012;51(1):86–97.
- [9] Feingold B. Hyperkinesis and learning disabilities linked to artificial food flavors and colors. *Am J Nurs*. 1975;75(5):797–803.
- [10] Foster JA, Neufeld KM. Gut — brain axis: how the microbiome influences anxiety and depression. *Trends Neurosci*. Elsevier Ltd; 2013;36(5):305—12.
- [11] Dash S, Clarke G. The gut microbiome and diet in psychiatry: focus on depression. *Curr Opin Psychiatry*. 2015;28(1):1–6.
- [12] NCCIH. Autism Spectrum Disorder and Complementary Health Approaches: What the Science Says. NCCIH Clin Dig Heal Prof [Internet]. 2016; Available from: <https://nccih.nih.gov/health/providers/digest/autism-spectrum-disorder-sciences>
- [13] Horvath K, Perman J. Autistic disorder and gastrointestinal disease. *Curr Opin Pediatr*. 2002;14(5):583–7.
- [14] 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(4):418–24.
- [15] Millward C, Ferriter M, Calver, S J, Connel-Jones, G G. Gluten-and casein-free diets for autistic spectrum disorder. *Cochrane Libr*. 2008;(April):1–29.
- [16] Roy A, Roy M, Deb S, Unwin G, Roy A. Are opioid antagonists effective in attenuating the core symptoms of autism spectrum conditions in children: A systematic review. *J Intellect Disabil Res*. 2015;59(4):293–306.
- [17] Williams K, Wray JA, Wheeler DM. Intravenous secretin for autism spectrum disorders (ASD). *Cochrane Libr*. 2012;(January).
- [18] Jyonouchi H, Geng L, Ruby A, Reddy C, Zimmerman-Bier B. Evaluation of an association between gastrointestinal symptoms and cytokine production against common dietary proteins in children with autism spectrum disorders. *J Pediatr*. 2005;146(5):605—10.
- [19] Hyman SL, Stewart PA, Foley J, Cain U, Peck R, Morris DD, et al. The Gluten-Free/Casein-Free Diet: A Double-Blind Challenge Trial in Children with Autism. *J Autism Dev Disord*. Springer US; 2016;46(1):205–20.
- [20] Neumeyer AM, Gates A, Ferrone C, Lee H, Misra M. Bone density in peripubertal boys with autism spectrum disorders. *J Autism Dev Disord*. 2015;43(7):1623–9.
- [21] Berry MJ, Adams J, Voutilainen H, Feustel PJ, Celestin J. Impact of elimination diets on growth and nutritional status in children with multiple food allergies. *Paediatr Allergy Immunol*. 2015;26(18):133–8.
- [22] Martin K, Jackson CF, Levy RG, Cooper PN. Ketogenic diet and other dietary treatments for epilepsy. *Cochrane Libr*. 2016;(January).
- [23] Napoli E, Dueñas N, Giulivi C. Potential therapeutic use of the ketogenic diet in autism spectrum disorders. *Front Pediatr*. 2014;2:1—9.
- [24] Frye RE, Rossignol D, Casanova MF, Brown GL, Martin V, Edelson S, et al. A review of traditional and novel treatments for seizures in autism spectrum disorder: findings from a systematic review and expert panel. *Front Public Heal*. 2013;1:1–26.
- [25] Ursell, L; Metcalf, J; Wegener Parfrey, L; Knight R. Defining the Human Microbiome. *Nutr Rev*. 2012;70(Suppl 1):S38–44.

- [26] Parracho HMRT, Bingham MO, Gibson GR, McCartney AL. Differences between the gut microflora of children with autistic spectrum disorders and that of healthy children. *J Med Microbiol.* 2005;54(10):987–91.
- [27] Sandhu K V., Sherwin E, Schellekens H, Stanton C, Dinan TG, Cryan JF. Feeding the Microbiota-Gut-Brain Axis: Diet, Microbiome and Neuropsychiatry. *Transl Res.* 2017;179(1):223–44.
- [28] Hsiao EY, McBride SW, Hsien S, Sharon G, Hyde ER, McCue T, et al. Microbiota Modulate Behavioral and Physiological Abnormalities Associated with Neurodevelopmental Disorders. *Cell.* Elsevier Inc.; 2013;155(7):1451–63.
- [29] Buffington SA, Viana G, Prisco D, Auchtung TA, Ajami NJ, Petrosino JF, et al. Microbial Reconstitution Reverses Maternal Diet- Induced Social and Synaptic Deficits in Offspring Article Microbial Reconstitution Reverses Maternal Diet-Induced Social and Synaptic Deficits in Offspring. *Cell.* Elsevier Inc.; 2016;165(7):1762–75.
- [30] Bravo JA, Forsythe P, Chew M V, Escaravage E, Savignac HM. Ingestion of *Lactobacillus* strain regulates emotional behavior and central GABA receptor expression in a mouse via the vagus nerve. *Proc Natl Acad Sci U S A.* 2011;108:16050–5.
- [31] Ochoa-Repáraz J, Mielcarz DW, Lauren E, Burroughs AR, Begum-Haque S, Dasgupta S, et al. Central Nervous System Demyelinating Disease Protection by the Human Commensal *Bacteroides fragilis* Depends on Polysaccharide A Expression. *J Immunol.* 2010;185:4101–8.