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Nutritional management of (some) autism: a case for gluten- and casein-free diets?

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Autism spectrum disorders represent a diverse and heterogeneous array of conditions unified by the variable presence of specific behaviours impacting social and communicative functions (social affect) alongside other presentation. Common overt characteristics may come about as a consequence of several different genetic and biological processes differentially manifesting across different people or groups. The concept of plural 'autisms' is evolving, strengthened by an increasingly important evidence base detailing different developmental trajectories across the autism spectrum and the appearance of comorbidity variably interacting with core symptoms and onwards influencing quality of life. Reports that dietary intervention, specifically the removal of foods containing gluten and/or casein from the diet, may impact on the presentation of autism for some, complement this plural view of autism. Evidence suggestive of differing responses to the use of a gluten- and casein-free diet, defined as best- and non-response, has combined with some progress on determining the underlying genetic and biological correlates potentially related to such dietary elements. The preliminary suggestion of a possible diet-related autism phenotype is the result. This review will highlight several pertinent aspects onwards to an effect of food in some cases of autism including research on the pharmacological activity of food metabolites, immune response, issues with gut barrier function and some contribution from the gut microbiota. These represent promising areas in need of far greater research inspection in order to potentially define such a diet-related subgroup on the autism spectrum.

Autism spectrum disorder: Diet: Gluten: Casein: Intervention

Currently defined solely on the basis of presented behavioural symptoms and analysis of developmental history, the autism spectrum disorders (ASD) remain a mysterious spectrum of conditions. The manifestations of ASD variably affect important aspects in areas of social and communicative functions (social affect) alongside the appearance of other features related to stereotyped and/or repetitive actions. More than 70 years after the first formal description of autism[1] significant financial and research resources have been allocated to finding the common genetic and biological pathways linked to the onset of the condition. Currently however, universal findings outside of the clinical description of the condition are few and far between.

Despite this, the consensus is that autism, a term often used interchangeably with ASD, probably comes about as a result of a complex interplay between genetic and environmental factors. Whereas previous research efforts were dedicated towards finding an 'autism gene', contemporary approaches have come to focus on the idea that a multitude of genes may be implicated in the onset and pathology of autism, with particular attention being paid to the impact of genomic point mutations[2]. The rise of the science of epigenetics, where analyses focus on factors affecting gene expression rather than just structural changes to the genome, is also beginning to impact on autism research[3]. The associated concept of gene–environment interactions involved in autism onset is

Abbreviations: ASD, autism spectrum disorders; CD, coeliac disease; GFCF, gluten- and casein-free; GI, gastrointestinal.
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also influencing our understanding of autism as, for example, noted with investigations on environmental pollutants[4] and emerging data on a role for maternal infection impacting on offspring autism risk[5]. That being said, further investigations are required to substantiate these still preliminary findings.

The continued state of not-knowing when it comes to the reasons why autism comes about and the precise nature of the underlying genetic and biological functions which are implicated has led to a shift in how autism is conceptualised. It is becoming clear that the wide variation in presented behaviours associated with autism make it less and less likely that autism reflects just a single condition. Several strands of evidence point to a more plural concept of autism, the autisms, as perhaps being a more accurate representation of manifestations on the spectrum[6].

Although data are still sparse on how autism progresses as a person ages, there is emerging evidence suggesting that autism is a relatively dynamic entity and symptom presentation may be more fluid than was previously thought. Several studies have reported different patterns of developmental trajectory to present across the autism spectrum[7] including developmental pathways illustrative of some people moving out of the diagnostic classification of autism[8,9]. Debates continue as to whether these 'bloomers' showing 'optimal outcome' reflect previous misdiagnosis or truly reflect a loss of symptoms considered for an autism diagnosis. What is becoming clear from this collected research however is that autism may not be as stable a concept as was previously thought for at least some people on the spectrum.

Further evidence for the notion of a plural autism comes from examination of various comorbidities known to be present alongside a diagnosis of autism. It has long been known that in some 40 % of cases of autism, a degree of intellectual disability is present[10]. That also conditions such as epilepsy or related seizure-type disorders can present with autism is not new to autism research[11]. There is also a growing interest in the comorbid presentation of conditions such as attention-deficit hyperactivity disorder alongside autism[12]. These factors, and their often important yet variable impact on the presentation of autism, also provide important evidence that autism is probably not just one condition. More recent discoveries on specific genetic issues presenting as an inborn error of metabolism manifesting autistic behaviours and epilepsy[13] add to the increasing knowledge in this area.

Various other comorbidities have also contributed to the concept of the autisms, specifically focused on somatic issues. Sleeping problems represent one of the more widely researched issues[14] and how such disruptions can often have a profound effect on presented behaviours. Gastrointestinal (GI) issues, whether functional GI problems[15] or more pathological conditions/states[16] have also been reported as occurring alongside cases of autism.

To some degree stigmatised as a result of various heated discussions on the possible factors leading to a diagnosis of autism, the presence of GI issues co-occurring alongside autism has been reported on numerous occasions[17]. Although relatively little is still known about how and why such issues come about, discussions are starting to move towards implicating a more direct association between GI issues and the presence of certain facets of autism. This work builds on a long history of research implicating a possible gut–brain interface[18] as being potentially important to some cases of autism and analysis of some of the variables involved in this process. It also implicates diet as potentially playing some role as a consequence of the regular contact food has with the GI tract.

Dietary intervention for autism

Dietary intervention as an ameliorative tool to impact on facets of the ASD and/or their comorbidities has a long and sometimes inconclusive research history. Foods containing the protein gluten (found in various cereal products) and casein (a protein found in mammalian milk and dairy sources) have garnered the greatest research attention in this area. With a specific focus on the use of a gluten- and/or casein-free (GFCF) diet, several reviews and meta-analyses have covered the peer-reviewed evidence presented so far[19–21] looking at the efficacy of such dietary intervention. In the most part, such reviews have found the research base in this area to be limited and not yet indicative of any population-wide effect to be had from such dietary changes. Calls for further, more methodologically sound evidence to be produced on any dietary effect in cases of autism are a regular feature of such analyses.

Discussions on the effectiveness and types of effects reported following experimental testing of the GFCF diet in cases of autism have been reported elsewhere[22]. Various different behavioural and psychometric changes have been documented connected to dietary use with some people with autism covering core areas of communication and social interaction, and peripheral areas such as attention, concentration and aspects of self-injury and aggression. Debate continues as to how changes to symptom presentation potentially brought about by dietary intervention may impact each other. Importantly, the issue of whether dietary use targeting non-core areas such as attention and hyperactivity may be the more important effect when it comes to dietary effectiveness mirrors other research on diet and conditions such as attention-deficit hyperactivity disorder [23].

Pertinent to the theme of a more plural definition for autism are the beginnings of experimental study attempting to look at possible response differences to dietary intervention across the autism spectrum. Pedersen *et al.*[24] reported initial results based on a re-examination of collected data derived from a controlled trial of the GFCF diet[25]. Outside of the suggestion of chronological age being linked to dietary effect or not and some suggestion of attention-deficit hyperactivity disorder-related behaviours being impacted by diet, no other behavioural variables were found to be predictive of diet response in that cohort. There was however some indication that a

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urinary marker, *trans*-indolyl-3-acryloylglycine[26] may merit some closer inspection in relation to response categorisation.

The gut–brain link and autism

That the gut and brain may be linked and potentially implicated in some cases of autism still has the ability to invoke significant discussion and argument. The idea however has a long history when it comes to autism[27] and other conditions such as schizophrenia[28] based on various sources of data. Hans Asperger, the father of Asperger syndrome, a condition currently represented in at least one of the diagnostic schedules covering ASD, talked about a possible link between cases of Asperger syndrome and the autoimmune gluten-related condition coeliac disease (CD)[29]. CD represents the archetypal gluten-related condition based on a defined set of serological and gastroenterological diagnostic markers and is managed primarily through the adoption of a gluten-free diet. Although subsequent research has hinted that CD may be related to some cases of autism [30], the current view is that the frequency of CD is probably not any greater than that seen in other populations[31]. Nonetheless, case reports continue to emerge on the co-occurrence of autism and CD, and indeed, the potential benefits of using a gluten-free diet both on CD markers and other extra-intestinal presentation.

When talking about the gut–brain axis and autism, several themes have emerged over the years based on several converging areas: (i) issues with the metabolism of certain foodstuffs, (ii) a role for the intestinal barrier, (iii) involvement of the GI immune system and (iv) issues with the gut microbiota.

Autism and the metabolism of food

The discovery that the proteins gluten, derived from various cereal produce, and casein, found in mammalian milk produce, are metabolised into opioid peptide species[32,33], the exorphins, has historically prompted some interesting discussions in autism research circles. The opioid activity of these compounds mimicking other more well-known analgesics led in part to the suggestion of an opioid-excess[34] potentially present in some cases of autism. Based on the early work highlighting increased endorphin activity linked to cases[35] and the presentation of certain behaviours, the suggestion that foods containing gluten and casein may be a source of external morphine-like compounds took hold accompanied by initial evidence on a positive effect from removal of gluten- and casein-containing foods from the diets of people with autism[36]. Similar studies of opioid-blocking pharmaceutics such as naltrexone-affecting behaviours present in autism[37] added to the research interest.

That being said, the route to detecting these peptides as a way of substantiating the opioid-excess model has been a difficult one. Some teams have reported positive results on the detection of food-derived peptides in urine in cases of autism[38], while other groups have not been so successful[39].

Outside of any direct pharmacological effect from the proposed dietary-derived peptides, other areas of research have also emerged discussing a role of abnormal food metabolism in relation to cases of autism. Some studies have pointed to the possible issues with carbohydrate metabolism as being present in cases of autism[40]. Distinct from the notion of protein/peptide chemistry being problematic in relation to gluten and casein, evidence has emerged for potential issues in the production of carbohydrate enzymes required for the breakdown of sugars such as lactose derived from dairy produce[41] and onwards the effect this may have for presented symptoms in cases of autism. Further studies are awaited in this area.

Increased intestinal permeability

Another issue inferred by the opioid-excess hypothesis is the means by which dietary-derived opioid peptides are able to enter general circulation to exert an effect beyond the confines of a normally well-shielded GI tract. Speculation centred on a possible role for the gut mucosal barrier as playing some part in this process[42]. Drawing again on the example of CD, where modified gluten peptides are able to gain access to the lamina propia, part of the gut mucosa, the suggestion was that abnormal porosity of the intestinal barrier may facilitate transport of these opioid peptides[43] or their effects into the wider central nervous system.

In contrast to the research history of opioid peptides and their detection, findings of abnormal intestinal permeability, commonly referred to as leaky gut, are accumulating in the autism research literature. de Magistris *et al.*[44] have provided one of the most comprehensive analysis of the leaky gut and autism so far based on their dataset looking at permeability measures for both children with autism and their extended family. Alongside other studies[45,46] evidence is accumulating to suggest that abnormal intestinal permeability is a finding for a proportion of people on the autism spectrum and may well be influenced by the implementation of a GFCF diet. Further questions are being asked about this area of investigation insofar as the nature of the permeability present and, as is noted in cases of CD, how tight-junction proteins may be implicated in this process.

The gastrointestinal immune system

Immune involvement in cases of autism is a hugely diverse area of investigation[47]. The whole process of immune system functioning and malfunctioning is seemingly implicated across many cases of the broad spectrum that is autism, ranging from findings of hypoimmunity[48] to autoimmunity[49] and various complementary issues in-between. The concept of immune-related GI symptoms being present in cases of autism has been suggested[50] based on reports of specific and diffuse immunopathology present in the gut mucosa[51]. As a result of some of this collected work, various suggestions have implicated issues such as GI

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inflammation as being connected to immune reactivity to dietary proteins[52].

Immune reactivity to dietary proteins such as gliadin has recently emerged as an important feature in some cases of autism[45,53,54]. Data pointing to elevated levels of IgG anti-gliadin antibodies has been a particularly consistent finding, complemented by elevated antibody titres to deamidated gluten peptides and other serological markers more commonly associated with CD. The biological picture being built up suggests immune system exposure to dietary proteins, potentially also implicating the previously described issues with intestinal permeability. Similar processes have also been described in cases of other behaviourally defined conditions such as schizophrenia[55] hinting at some biochemical overlap.

The gut microbiota and autism

Hosting trillions of bacteria from a wide variety of species, the digestive tract represents an important ecosystem, with a growing research interest in its functions outside of purely being one of metabolising foods[56]. Allied to intestinal barrier function and the GI immune system, this triad of variables represent an important biological interface which some have speculated to be crucial not just to biological functions but also psychological development too[57].

Examinations of the gut microbiota in relation to autism have begun to reveal a complex pattern of communities to be presented[58] although with still much to do regarding individual species being causally linked to autism. Emerging evidence based on the specific mouse models of autism have, for example, implicated aspects of the gut microbiota to be potentially important to some cases of autism. Hsiao *et al.*[59] observed GI issues to be present in a murine model of maternal immune activation associated with cases of autism. They recorded gut barrier defects in maternal immune activation offspring mice, which were corrected following oral administration of the human commensal *Bacteroides fragilis*. Behavioural changes were also noted in treated mice. Such evidence while still preliminary and requiring further independent replication outside of animal models, hints at the potentially important relationship between the gut microbiota and behaviour. The possibility that probiotic therapy might also impact on some autism also represents an area in need of further investigation.

Conclusions

The concept of a more plural definition for autism, the autisms, represents an increasingly important shift in our understanding of the ways that this complex and ill-understood condition comes about and manifests. Implicit to the idea of the autisms is the suggestion that various different variables, be they genetic or biological, can variably impact on development and behaviour including some role for dietary components for some people on the spectrum. The gut–brain interface provides an appealing research starting point when it comes to identifying those potential best-responders to something like dietary change including the use of a GFCF diet as an intervention option. Examination of this important connection may also provide further intervention avenues outside of rigorous dietary change which may be more appealing and less invasive.

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Conflicts of Interest

Paul Whiteley is a director of ESPA Research, a UK subsidiary organisation that carries out research into ASD including investigations on the use of a GFCF diet as an intervention for autism and related conditions. He is also a director and shareholder of Analutos Ltd. in the UK, which provides mass spectrometric and other analytical services to various sectors of the healthcare, chemical and pharmaceutical industries. He is a shareholder in The Autism Food Club, a website providing information on the use of a GFCF diet.

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