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Autism Spectrum Disorder and Associated Gastrointestinal Issues

Winston Tan, MB BChir Student [1]*

[1] School of Clinical Medicine, University of Cambridge, Cambridge, United Kingdom CB2 0SP

*Corresponding Author: wwwt3@cam.ac.uk

Abstract

Introduction and Definition: Autism spectrum disorder (ASD) is a "collection of conditions regarding brain development"; it presents with a diverse spectrum of characteristics and severity. It is well documented that people with ASD face gastrointestinal (GI) issues at a much higher frequency than the neurotypical population. This can drastically reduce their physical quality of life as well as hinder many social situations. The etiology is complex with multiple factors centred around the gut-brain axis.

Presentation & Impact: The GI issues faced by those with ASD commonly include nausea, chronic constipation, diarrhoea, gastroesophageal reflux disease (GERD), chronic flatulence, gut inflammation, ulcers, and more. These problems carry extra baggage as they often lead to further distressing reactions. For example, posturing, self-harm, and outbursts are regularly reported – especially as those with ASD struggle to articulate the pain/issue. In the long term, GI issues affect mood, learning, as well as sleep (which can exacerbate the previous behaviours, particularly aggression). From a social perspective, this can impede on the social life of those with ASD.

Etiology: The gut-brain axis – the two-way influences between the gut microbiome and the brain – seems to be at the core of most GI issues. People with ASD often have gut dysbiosis: an imbalance in their gut bacteria. While there is an excess of pathogenic bacteria, there is a lack of beneficial ones as well as a decrease in bacterial diversity. Other issues commonly associated with ASD contribute to this: digestive enzyme deficiencies (such as absence of lactase), selective eating (for example, with eating sensory issues), medication, and more. The issue of selective eating itself causes many of the GI symptoms; an unbalanced diet can cause diarrhoea, constipation, reflux, and intestinal motility issues.

Treatment & Management: Treatments are usually behavioural. For children, clinicians work with parents to incorporate more balanced meals. Therapy is also used to overcome sensory issues and mealtime-related anxiety. However, specific medications such as laxatives or probiotics can be administered to relieve persistent symptoms.

Keywords: autism spectrum disorder; gastrointestinal issues; gut-brain axis

Introduction

The following encyclopedia entry aims to outline the strong links between autism spectrum disorder (ASD) and gastrointestinal issues. In summary, this seems to stem from imbalances with the gut microbiota and the subsequent consequences though this is greatly affected by a patient's own lifestyles of restrictive eating habits, individualised medication, and other physiological factors. This explains the wide variance in presentation; effective therapy is achieved when administered with a personalised, multi-disciplinary approach.

ASD is a neurodevelopmental condition that is extremely variable amongst the ASD population, though is characterised with several key features. Difficulties with social interactions, repetitive behaviours, and restrictive interests [1, 2] are some of the distinctive aspects of ASD. Although it is classified as a "disorder", it is a condition that does not need to be cured [3]. Much is unknown about ASD, from its etiology to its complex presentation – research into ASD and its many associated conditions has only grown in prominence in the last 20 years [4]. However, it is well established that ASD has a wide range of lifelong effects that range from very severe to mild. These include difficulty understanding social cues, increased sensitivity to sensory stimuli, and a need for routine [5, 6]. Each of these symptoms are unique to each person. It is also recognised that certain physiological issues correlate with ASD. This article will aim to focus on the high prevalence of gastrointestinal (GI) issues in the ASD population – a common physiological comorbidity [7–9]. Whilst the exact cause is unclear, much of the evidence seems to point towards involvement of the gut-brain axis as well as the complex considerations of the sensory issues, selective eating routines, and medications that people with ASD have [10]. Unfortunately, GI issues in people with ASD can extend beyond the physiological [11, 12] and often affect

many other aspects of the patient's life. Treatment is rarely pharmacological and often focuses on behavioural therapy, targeting the restrictive eating patterns and/or the sensory issues associated with feeding. (However, drugs are occasionally administered when symptoms are severe and persistent [10].) This area of research is currently expanding as the gut microbiome is being increasingly associated with contributing to many of the other characteristic symptoms of ASD and neurodevelopment [13].

Body

Presentation

Although GI issues are a common occurrence in the ASD population (~25% of children diagnosed with ASD experience at least one GI issue) [14], its presentation can vary wildly.

Common chronic manifestations include gastro-esophageal reflux disease (GERD), constipation, diarrhoea, vomiting, chronic flatulence, and inflammatory bowel disease [13–17]. These symptoms impair digestion; prolonged periods of handling these symptoms can also exert body-wide detrimental effects. Such GI issues can negatively influence absorption of vitamins, minerals, and other nutrients. It has been consistently found that ASD patients with GI issues have deficiencies in various ions and vitamins. Over a sustained period of time, this can lead to malnourishment and stunted growth [14]. The wider physiological impacts broaden beyond nutritional issues: seizures, sleep disorders, and psychiatric problems [16] are common issues associated with GI symptoms in the ASD population. For example, behavioural changes may be observed with individuals on a carbohydrate-free diet; this diet leads to a reliance on ketones which decreases mitochondrial activity and energy levels [16]. An umbrella symptom that accompanies almost all these issues is abdominal pain and discomfort. Since ASD is a condition that intrinsically involves communication difficulties, this abdominal pain can present unusually. Firstly, it may sadly go unrecognised [13] if the patient struggles to express the nature and/or location of the pain. Therefore, GI patients with ASD may express their discomfort with behaviours such as sighing, moaning, screaming, rubbing the abdomen, curling up, swallowing or tics [11]. These vocal and motor presentations can be troubling but are important to recognise to allow rapid diagnosis and treatment.

Impact on Patient's Wider Life

Many of these symptoms are chronic and since they relate to feeding – a constant, daily event of life – these issues can persist into other areas of life. Studies have shown that children with ASD and GI issues are more irritable, argumentative, aggressive, destructive and/or hyperactive than ASD children without GI issues [11, 16, 18, 19]. Physical discomfort underlies these behaviours, but other factors may contribute. As mentioned before, difficulties communicating their symptoms can be incredibly frustrating for patients [18].

These behaviours can lead to social withdrawal. As well as the social difficulties associated with ASD in general, GI issues can compound this with added feelings of anxiety, hyper-sensitivity to sensory information, and embarrassment [11, 17]. Moreover, there are lots of social expectations and etiquettes at mealtimes that may not accommodate GI issue patients with ASD [14].

For children, GI issues can be especially impactful on schooltime activities. Firstly, these chronic health issues can drastically affect attendance which impairs academic performance and makes it more difficult for the child to maintain friendships. In class, the aforementioned symptoms can reduce the patient's attention; they may lose motivation to fully participate in class and group activities. Amongst peers, patients may try to avoid group gatherings that involve food [17].

GI issues can be very disruptive to sleep quality [12, 13, 18] Abdominal pain and symptoms such as chronic diarrhoea can interrupt sleep. If not treated properly, poor sleep can act in a vicious cycle to exacerbate the other problems. Assessments of families with children with ASD have found positive correlations with sleep difficulties and aggressive/stereotyped behaviours in the daytime. These can also present at mealtimes, making feeding balanced, nutritional meals a challenge. In addition, poor sleep can emphasise other general symptoms of ASD since sleep is crucial for learning, adaptive functioning, memory, and neuroplasticity [12]. Poor sleep for children with ASD can impact parental sleep, increasing parental stress. This is important since it has been reported that the success of behavioural interventions of ASD is closely linked to parental stress [12].

The GI issues can penetrate a patient's life and be very debilitating. Consequently, treatment is essential and should be both rapid and effective. To fully reach effective treatment, the underlying mechanisms of the link between GI symptoms and ASD should be uncovered thoroughly.

Etiology

There are many factors which play a part in producing the symptoms experienced by GI issue sufferers; it is still relatively unclear how all of these components fit together, however, the gut microbiome seems to be key [18]. The gut microbiome consists of a complex network of microorganisms: the microbial gut flora. This flora is crucial to many functions – hunger regulation, energy uptake, intestinal motility, and immune responses [14]. It is also one half of the gut-brain axis, an important link between the nervous system and the gut which influences much of the whole body's physiology [10, 13–15, 17, 19]. Altered microbiota can arise from a range of issues.

Deficiencies in enzymes involved with carbohydrate metabolism have been associated. This possibly alters the carbohydrate composition in the intestines, providing different growth substrates for the gut flora. As an example, fatty-acid and gas-producing microflora can use non-

absorbed sugars as substrates for growth, resulting in increased flatulence and bloating [20].

External factors can also alter the microbiome composition. For example, use of broad-spectrum antibiotics also decreases the diversity of gut flora [15]. Pathogenic bacteria – such as *Clostridium bolteae* – can invade the microbiome, leading to GI problems [15, 21, 22]. More commonly, feeding selectivity can drastically reduce the nutritional value of a diet which can reduce gut flora diversity. Studies have shown that children with ASD are up to five times more likely to develop feeding disorders than neurotypical children [16]. This relates directly to the hyper-/hyposensitivity and preference to routine that is characteristic of ASD. This results in children with ASD often rejecting certain foods [14, 23]. Food may be rejected due to aversions of smell, texture, appearance, and/or warmth: sensory avoidances. This is very common and there have been many reports that wholegrains, fresh fruit and vegetables, and lean proteins are often rejected since they have stronger textures and tastes. Patients may also restrict their diet to avoid specific fears such as choking or vomiting. Finally, eating may be disrupted due to a lack of interest [10, 14]. From a social perspective, children with ASD often have a disinclination to try a wider range of foods, leading to parents' frustration. This may make mealtimes difficult, emphasising the issue as parents may keep serving the same meals, in a vicious cycle [10]. This directly links to symptoms such as chronic constipation and diarrhoea, and also reduces the diversity of the gut microbiome [17].

An altered microbiome can greatly alter the gut-brain axis. This is not only harmful to the gut processes itself, but also impacts the nervous system, resulting in many of the outward behaviours of ASD.

The gut-brain axis is a bidirectional relationship which comprises the gut, the enteric nervous system (ENS), and the central nervous system (CNS), and involves neural and hormonal pathways. Direct communication is via the vagus nerve and spinal afferents, with some gut bacteria initiating communication. The *Lactobacillus rhamnosus* bacteria can activate vagal pathways as an example, influencing neurotransmitter release in the brain. On the other hand, indirect communication involves signalling between the ENS and the CNS with intermediate hormonal and immune pathways. Studies have identified specific examples of gut microbial imbalance (dysbiosis) affecting physiological processes. For example, many of the metabolites produced by gut bacteria affect enteroendocrine cells. The enteroendocrine cells produce hormones which can signal to the CNS via the vagus nerve. Hence, dysbiosis can impact the release of hormones which are important for appetite, mood, and GI motility. Dysbiosis can also increase the production of pro-inflammatory cytokines. When concentrations are high, these enter the bloodstream and cross the blood brain barrier, inducing neuroinflammation. This can exacerbate many of the behaviours associated with ASD [13].

The overall effect of an imbalanced gut-brain axis worsens both symptoms in the gut and behavioural symptoms. The pain and discomfort are detrimental to treatment progress and without intervention can lead to vicious cycles [19].

Treatment & Management

Managing and treating GI issues in people with ASD is an ongoing process that is monitored and adapted over time. Due to the complex interacting factors that play into the symptoms, a multi-disciplinary approach is ideal. Whilst the GI symptoms themselves can be treated much in the same way as when treating GI symptoms in a neurotypical patient [17], specialist psychiatrists and/or neurologists may also be needed to assess the unique presentations of discomfort in ASD patients [14]. Many treatments aim to restore the imbalance of the gut microbiome [10, 13, 15]. Therapy can be additive; a diverse repertoire of beneficial bacteria can be administered via probiotics [24] or via fecal microbial transplantation [25]. Probiotics can also strengthen the gut wall, reducing gut leakiness and neuroinflammation. Therapy can be subtractive, targeting harmful bacteria in the gut. Therapy can also be modulatory, involving lifestyle changes such as diet and increased exercise [13, 15].

However, it has been discussed how a healthy diet is often difficult to achieve due to hyper-sensitivity and other social factors. As a result, behavioural therapies are crucial to management. This could include conditioning therapy or systemic desensitisation, in the hopes of widening the patient's diet [26]. Sensory-friendly environments like quiet eating spaces in school or temperature-appropriate food may also help remove some external sensory stresses. This allows the patient to focus more on eating, encouraging healthier eating habits [17, 27]. Clinicians should be mindful that ASD presentation is so variable; therefore, treatment that is tailored to each individual's needs would be most effective [14].

Future Implications

Work on understanding the gut-brain axis in the ASD population has opened potential insights into the causes of wider ASD characteristics. Inflammation in the gut can lead to a "leaky" gut. This is due to the release of pro-inflammatory cytokines that alter the tight junctions between the epithelial cells (that make up the lining of the gut wall), with the aim of increasing its permeability to give immune cells access [17, 28]. Abnormal short chain fatty acids (produced by the imbalance of gut bacteria) can leak out into circulation and reach the brain, contributing to neuroinflammation and the neurological symptoms of ASD. However, further evidence is required to warrant this theory [29]. Neuroinflammation is not the only consequence of gut dysbiosis. Dysbiosis can reduce absorption of certain amino

acids from food, such as tryptophan. This reduction in tryptophan is thought to be connected to a worsening of repetitive behaviours [14]. The potential causal relationship between gut dysbiosis and neurological symptoms of ASD has been supported by experiments on mice. In studies on gestating mice, gut dysbiosis was induced; in the pups, it was observed that sociability synaptic plasticity in the ventral tegmental area was reduced [16]. Decreased maturity and function of microglia have also been observed in similar mice studies [10]. Targeting the imbalance of the gut microbiome seems promising and key to future treatments. Furthermore, since the unusual composition of the gut microbiome appears to be characteristic of ASD, potential biomarkers may be discovered to support ASD diagnosis [17].

List of Abbreviations
ASD: autism spectrum disorder
CNS: central nervous system
ENS: enteric nervous system
GERD: gastroesophageal reflux disease
GI: gastrointestinal

Conflicts of Interest
The author declares that they have no conflicts of interest.

Authors' Contributions
WT: contributed to literature search, generated prompts for OpenEvidence 2.7.9 and Perplexity 2.63.1, drafted the manuscript, edited the manuscript and gave final approval for the version to be published.

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