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Gastrointestinal alterations in autism spectrum disorder: What do we know?

Geir Bjørklund[a,h,*], Lyudmila Pivina[b,c,h], Maryam Dadar[d,h], Nagwa A. Meguid[e,f,h], Yuliya Semenova[b,c,h], Mona Anwar[e,h], Salvatore Chirumbolo[f,g,h]

[a] Council for Nutritional and Environmental Medicine (CONEM), Mo i Rana, Norway
[b] Semey Medical University, Semey, Kazakhstan
[c] CONEM Kazakhstan Environmental Health and Safety Research Group, Semey Medical University, Semey, Kazakhstan
[d] Razi Vaccine and Serum Research Institute, Agricultural Research, Education and Extension Organization (AREEO), Karaj, Iran
[e] Department of Research on Children with Special Needs, Medical Research Division, National Research Centre, Giza, Egypt
[f] CONEM Egypt Child Brain Research Group, National Research Centre, Giza, Egypt
[g] Department of Neurosciences, Biomedicine and Movement Sciences, University of Verona, Italy
[h] CONEM Scientific Secretary, Verona, Italy

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ABSTRACT

There is an emerging body of evidence associating children having autism spectrum disorder (ASD) with gastrointestinal (GI) symptoms, such as abdominal pain, chronic diarrhea, constipation, vomiting, gastroesophageal reflux, intestinal infections, and increased intestinal permeability. Moreover, in many studies, large differences in the composition of intestinal microbiota and metabolic products between ASD patients and controls were reported. Deepening the role and the biology of the gut microbiome may be fundamental to elucidate the onset of GI symptoms in ASD individuals and their etiopathogenetic causes. The gut-brain axis may affect brain development and behaviors through the neuroendocrine, neuroimmune, and autonomic nervous systems.

1. Introduction

Autism spectrum disorder (ASD) is a heterogeneous neurodevelopmental disorder that is characterized by impairment in social reciprocity, language and communication abnormalities, and repetitive, ritualistic, restrictive and stereotypical patterns of activities, interests, and behaviors (Constantino and Marrus, 2017; Moeschler, 2019; Varghese et al., 2017). ASD has been known as one of the main challenges of modern medicine with puzzling increased prevalence. Currently, about 1–68 children have been recognized as suffering from ASD, according to the prevalence estimated from the recent CDC's Autism and Developmental Disabilities Monitoring Network (Yenkoyan et al., 2017). Significantly, the prevalence of ASD in children is higher in boys (23.6 per 1000) compared with girls (5.3 per 1000) (Christensen et al., 2018). It is possible to find many different well-defined biological disturbances in ASD patients after its first description by the Austrian-American psychiatrist and physician Leo Kanner in 1943 (Kanner, 1943, 1968). Numerous recent studies indicated a significant relationship between GI disorders, irritability, and mood problems in ASD patients (Mazefsky et al., 2014).

Symptoms of a disorder of the gastrointestinal system are quite common in children with ASD. However, the mechanisms of such disorders are not yet fully understood. It is hypothesized that gut microbiota and its metabolites may contribute to the ASD pathophysiology (Li et al., 2019a, 2017; Margolis et al., 2019). Different articles have revealed the key role of the gastrointestinal modification as well as the gut microbiota on the animal central nervous system (CNS) and proposed the influence of the gut microbiome brain axis (GMBA) (see further on) (Bienenstock et al., 2015; Lam et al., 2017; Mayer et al., 2015). GMBA and communication between the gut and brain function probably play an important role in ASD, in as much the prevalence of GI symptoms in ASD children ranges from 23 to 70 % (Chaidez et al., 2014).

Moreover, the presence of GI symptoms is associated with the ASD severity (Adams et al., 2011; Gorrindo et al., 2012), indicating that the gut is involved in the behavior and etiology of ASD (Liu et al., 2019; van de Wouw et al., 2017). This article discusses the evidence of abnormal GI function in ASD, their relationship to autism severity, and the possible role of GI abnormalities in the ASD pathology. Before outlining the role of GMBA in GI disorders in ASD, we will try to have a thorough description of GI impairments in ASD.

* Corresponding author at: Council for Nutritional and Environmental Medicine, Toften 24, 8610 Mo i Rana, Norway.
E-mail address: bjorklund@conem.org (G. Bjørklund).

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2. Gastrointestinal (GI) disorders in ASD: a perspective on the reliability of symptoms

GI inflammatory symptoms in ASD children have high prevalence (Rossignol and Frye, 2012a; Wakefield et al., 2005). Correlation between ASD and GI symptoms was first described in the early 1970s. In a cohort of 15 ASD children, Goodwin and co-workers reported GI issues in more than half of the subjects (Goodwin et al., 1971). According to different authors, the prevalence of GI symptoms in the population with ASD can range from 17 to 86 % (Erickson et al., 2005; Geier et al., 2012; Gorrindo et al., 2012; Isaksson et al., 2017; Klukowski et al., 2015). It has been reported that in children with ASD, the severity of diarrhea, irritable bowel syndrome, and chronic constipation has been correlated with the degree of GI microbial dysbiosis (McElhanon et al., 2014b; Sanctuary et al., 2019). A recent meta-analysis of research investigating GI symptoms among children with ASD was performed and indicated that insufficient data were available to determine whether GI symptoms often linked with organic pathologies, such as gastroesophageal reflux, gastroenteritis, food allergies, and inflammatory bowel disease, are more common among children with ASD (McElhanon et al., 2014a). In another large prospective cohort study, conducted during ten years in Norway, the maternally reported GI symptoms were more often persistent and more common during the first three years of life in children with ASD as compared to children with typical development or developmental delay (Bresnahan et al., 2015). Also, it was reported that GI problems are common in individuals with ASD, and changes in commensal gut bacteria were involved in certain behavioral abnormalities in a mouse model of ASD (Sampson and Mazmanian, 2015; Wang and Kasper, 2014). Therefore, disruption of gut microbiota could stimulate the over-colonization of neurotoxin-producing bacteria that contribute to symptoms of ASD (Frye et al., 2015). There is a correlation of gastrointestinal symptoms with autism severity, indicating that children with more severe ASD are likely to have more severe gastrointestinal symptoms and vice versa. Symptoms of ASD may be exacerbated due to the underlying gastrointestinal problems (Adams et al., 2011). Although gastrointestinal problems have been implicated in some people with ASD, there are many discrepancies on this topic. However, most of the studies confirm this correlation as significant when compared to healthy, age-matched controls (Adams et al., 2011; Parracho et al., 2005) (Table 1).

Further evidence of the relation between GI symptoms and ASD is the improvement in behavioral symptoms, including aggression, self-harm, and anxiety, after gastrointestinal pathology has been treated in patients with ASD (Buie et al., 2010). The potential common mechanisms of action for inflammation and gut microbiota on the neural profile of ASD have been considered (Doenyas, 2018). Chronic ileocolonic lymphoid nodular hyperplasia (LNH) and enterocolitis, causing mucosal inflammation of the colon, stomach, and small intestine has been reported (Furlano et al., 2001; Uhlmann et al., 2002; Wakefield et al., 2005). In some ASD children, the gastrointestinal inflammatory symptoms have characteristics similar to inflammatory bowel disease (IBD) (Ashwood et al., 2004; Balzola et al., 2005; Furlano et al., 2001; Lee et al., 2018; Torrente et al., 2002). This condition has been proposed to be a new variant of the IBD and called "pan-enteric IBD-like disease" (Balzola et al., 2005).

Patients with ASD often have a disturbance of the quantitative composition of bacterial flora in colon and rectum (Liu et al., 2019). There is a large enhancement of the production rate of propionic acid by the colonic microflora at the expense of butyric acid. This leads to enhancement of the uptake rate of propionic acid in the brain, leading in turn to severe disturbance of cerebral mitochondrial function, which is attended by enhanced oxidative stress (Liu et al., 2019; MacFabe et al., 2011; Shultz et al., 2015). Reproducing this biochemical disturbance in animal experiments causes the animals to display behavioral disturbances very similar to what is observed in ASD individuals (MacFabe, 2013, 2012). Moreover, it was revealed that GI

Table 1
Characteristics of gastrointestinal (GI) symptoms prevalence in children with autism spectrum disorder (ASD).

Country, year of publication	Research characteristics				
	Study description	Characteristics of the study groups	GI symptoms in ASD patients	GI symptoms in healthy controls	Reference
USA, 2019	Parent-report screen using the 35-item Gastrointestinal Symptom Inventory (2005)	Of the 131 children with ASD, 43.4 % were non-verbal	Seventy-six ASD children with at least one GID: functional constipation 35.1 %, GERD 29.8 % and functional diarrhoea 5.3 %. 20.6 % had ≥ 1 newly recognized GID. Total with any GID 58 %, Functional constipation + GERD 9,2%, Functional diarrhoea + GERD 3,1%	No control group	Margolis et al. (2019)
USA, 2002	Parents survey (112 children with ASD and their neurotypical and age-matched siblings)	The study group included 112 children with ASD (5.4 ± 2.3 years old). The control group consisted of 44 healthy siblings (6.1 ± 3.1 years old)	The most common GI sings were diarrhoea (27.6 %), constipation (9.5 %), gaseousness (60.3 %), bloating (37.9 %), abdominal pain (37.9 %), reflux (15.5 %), stool impaction (19 %), and belching (25 %). No symptom: 19.8 %, one symptom: 16.4 %, two symptoms: 24.1 %, three symptoms: 25 %, four or more symptoms: 14.7 %	Diarrhoea: 0 %, constipation: 13.6 %, gaseousness: 20.5 %, bloating: 6.8 %, abdominal pain: 15.9 %, reflux: 4.5 %, stool impaction: 0%, belching: 6.8 %. No symptom: 70.5 %, one symptom: 18.2 %, two symptoms: 4.5 %, three symptoms: 4.5 %, four or more symptoms: 2.3 %	Horvath and Perman (2002)
Canada, 2008	Retrospective chart parent's review	160 children with ASD, median age six years	Of the ASD children, 81 (51 %) had long-term food intolerance, 94 had GI dysfunction (28 % of them exhibited constipation), 36 had diarrhea, and GERD was reported in 18 children. Endoscopic studies revealed nodular lymphoid hyperplasia, colitis, ulcerative colitis, or hiatal hernia in eight children	No control group	Ming et al. (2008)
USA, 2011	In-home structured retrospective medical history interviews by parent recall	The study group included 589 children with idiopathic ASD, and the control group included 163 of their healthy siblings	GI problems in the study group were registered in 249 children (42 %) ($p < 0.001$). Of these, 116 (20 %) had constipation, and 111 (19 %) had chronic diarrhea	In the ASD group, 20 (12 %) of the children had GI disorders	(Wang et al. (2011b)

abnormalities can be a risk factor for sleep disorders in ASD children compared to children without gastrointestinal dysfunctions (McCue et al., 2017). Because a wide range of studies on ASD children have no control groups or inadequate controls or were subject to referral biases, different GI abnormalities were reported in ASD children. Evaluation of gastrointestinal symptoms is also complicated by the lack of appropriate diagnoses in the medical records of patients with ASD or incorrectly conducted parental surveys (memory mistakes related to the past incident). Violation of verbality in children with ASD makes it difficult to recognize GI symptoms. On the other hand, non-standardized GI evaluation, which should identify GI problems differently among the various studies, may create concern about the reliability of some research (Mannion et al., 2013). Differences between studies can also be connected to non-standardized GI surveys, which recognize GI symptoms differently among the wide range of studies.

The relationship between GI symptomatology and ASD may cause further disturbances, such as sleep disorders (Klukowski et al., 2015; Yang et al., 2018). In this perspective, therefore, new therapeutic approaches, for example, probiotics, to address GI disorders in ASD, are fundamental (Arnold et al., 2019).

3. Abnormal intestinal permeability

Protein structures that regulate intestinal permeability create an intestinal barrier (Ulluwishewa et al., 2011) that does not allow intestinal contents to enter the bloodstream, preventing the activation of immune response, subsequent inflammatory reactions and gastrointestinal tract disorders (Viggiano et al., 2015; Wang and Kasper, 2014). Thus, the integrity of the intestinal barrier causes a decrease in inflammatory reactions. This is proved by the fact that abnormal intestinal permeability was reported in 36.7 % of ASD patients and their relatives (21.2 %) in comparison with control children (4.8 %) (de Magistris et al., 2010a). A higher antigenic load of the gastrointestinal tract could be induced by an elevated intestinal permeability (Li et al., 2017). Reports of ASD children with "leaky gut" have been documented (Esch and Carr, 2004; Sajdel-Sulkowska et al., 2019; Samsam et al., 2014). For instance, there is a study that reported the unknown GI problems in 21 ASD patients, nine of which (43 %) revealed impaired intestinal permeability in comparison with 40 normal controls without permeability issues (D'Eufemia et al., 1996). A study with 90 ASD children showed that abnormal intestinal permeability was present in 36.7 % of children with ASD compared with 21.2 % first-degree relatives, 4.8 % adult controls, and none of the child controls. This suggests that a subgroup of children with ASD may indeed show a "barrier function deficit" and may, therefore, benefit from a gluten-free diet (de Magistris et al., 2010b). Also, it was investigated whether gut permeability is increased in ASD by evaluating gut permeability in children with ASD compared with age- and intelligence quotient-matched typically developing controls (Dalton et al., 2014). In their study, 103 children aged 10–14 years, were subcategorized for comparison into those without (n = 20) and the ASD group (n = 83). Both groups were given an oral test dose of mannitol and lactulose and urine collected for six hours. Gut permeability was assessed, and results showed no statistically significant group difference in small intestine permeability in a population cohort-derived group of children with ASD compared with a control group (de Magistris et al., 2010a). Also, another study revealed that there is no statistically significant difference in small intestine permeability in a population cohort-derived group of ASD children and a control group with age- and intelligence quotient-matched controls without ASD but with special educational needs (Dalton et al., 2014). In a study by Esnafoglu et al. (2017), the serum levels of zonulin were evaluated, which regulates tight junctions between enterocytes and serves as a physiological modulator controlling intestinal permeability (Esnafoglu et al., 2017). The study group included 32 patients with ASD, while the control group was comprised of 33 healthy subjects, and the severity of ASD symptoms was also evaluated (Esnafoglu et al., 2017). Serum zonulin levels were significantly higher in patients with ASD, and there was a positive correlation between zonulin levels and ASD severity. The authors concluded that zonulin might have a critical role in the development of ASD symptoms (Esnafoglu et al., 2017). It has been revealed that increased zonulin is related to social dysfunctions and hyperactivity in children with attention deficit hyperactivity disorder (Özyurt et al., 2018).

4. The role of gastrointestinal immunity

Gut microbiota makes critical contributions not only to metabolism but also to the maintenance of immune homeostasis and controlling the CNS activities through neural, endocrine, and immune pathways, the so-called "gut-brain axis" (Dinan and Cryan, 2015; Sampson and Mazmanian, 2015). It has been proposed that the modulation of gut microbiota, particularly butyrate-producing bacteria such as *Eubacterium, Ruminococcaceae, Erysipelotrichaceae, and Lachnospiraceae* can be a promising strategy in the search for alternative treatment of ASD (Liu et al., 2019).

The microfold cells of the intestinal mucosa belong to a group of cells forming the gut-associated lymphoid tissue. They can pass their engulfed material to the antigen-presenting cells such as macrophages and dendritic cells in the subepithelial tissue that are in cross-talk with lymphocytes, the B cells, for antibody production. The largest source of lymphoid tissue in the immune system is the GI tract, which is a significant site for immune modulation and even for influence on mood and behavior (Carabotti et al., 2015; Turner and Goldsmith, 2009; Zhu et al., 2017). Therefore, it is arguable that abnormalities of the mucosal immune system and its tolerant mechanisms could play an important role in ASD children with GI problems. The findings of immunohistochemical studies in the ASD children with GI symptoms revealed an elevated level of CD8 T cells in colonic and duodenal samples with particular affection of epithelium (Furlano et al., 2001; Torrente et al., 2002) and increased in γδ T cells in transverse colon samples (Furlano et al., 2001).

Moreover, declines in peripheral T cell numbers were reported in ASD children with GI problems (Ashwood et al., 2003), probably because of numbers of T cells translocating to the GI mucosa in this subset of ASD patients. In ASD individuals has been evidenced a more counter-regulatory response, presenting increased lymphocytes and pro-inflammatory cytokines, including TNF-α (Guloksuz et al., 2017) and interferon-γ (IFN-γ), and lesser amounts of the anti-inflammatory cytokine IL-10 (Ashwood et al., 2004; Torrente et al., 2002). Also, it has been reported that interleukin 6 (IL-6) and IL-17a play an important role as key cytokines in the maternal immune activation (MIA) induced ASD (Wang et al., 2019). In other cases, patients have shown evidence of an eosinophilic infiltrate of the gastrointestinal mucosa (Ashwood et al., 2003). Children with ASD frequently present an enhanced production of serum antibodies against gliadin and casein peptides resulting in autoimmune reactions (Vojdani et al., 2003). For example, ASD children produce not only more pro-inflammatory cytokines such as TNF-α, IL-1ß, and IL-6 (Jyonouchi et al., 2001; Ricci et al., 2013), but also at least 25 % of ASD individuals make serum IgG, IgM, and IgA antibodies against gliadin, which can also cross-react with cerebellar peptides (Vojdani et al., 2003). Other results of immunohistochemical studies revealed an accumulation of IgG and complement C1q colocalized on the basolateral enterocyte membrane in GI of ASD samples (Ashwood et al., 2003; Torrente et al., 2002), indicating a promising autoimmune component to GI abnormalities of ASD individuals. Other studies have demonstrated an increased number of Paneth cells in ASD children with GI problems (Horvath et al., 1999b; Horvath and Perman, 2002; Torrente et al., 2002) which secrete antimicrobial peptides that act as mediators of host-microbe interactions including innate immune protection from enteric pathogens (Clevers and Bevins, 2013). Focal autoimmunity may cause gut dysfunction resulting in failure to detoxify neuroactive substances originating from the flora and contribute to

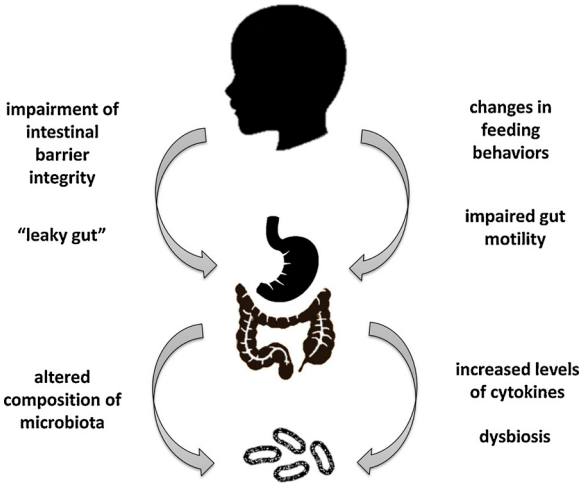

Fig. 1. Multilevel pathways in the gut–brain axis may lead to gastrointestinal disorders in children with autism spectrum disorder (ASD). Possible pathophysiological mechanisms that link ASD and gastrointestinal disturbances include altered feeding behaviors, impaired gut permeability, and increased biodiversity of the gut microbiome.

altering cognitive functioning as is seen in hepatic encephalopathy (Weber, 1996). The target for an autoimmune response could also be expressed in both the brain and gut, with pathological abnormalities in both sites.

Regulatory T cells (Treg) induced by Clostridia play a major role in inhibiting inflammatory and allergic reactions in the colon. The short-chain fatty acid butyrate produced in the large intestine induces Treg differentiation, which prevents colitis and improves immunologic homeostasis (Furlano et al., 2001; Furusawa et al., 2013).

Inflammatory and oxidative mediators are upregulated in neutrophils of children with ASD. Also, it has been reported that the expression of IL-17A and IL-17R are significantly increased in neutrophils of ASD patients. In addition, inflammatory signaling pathways, including ROS generating enzymes, i.e., NOX2/iNOS, and phospho-NFκB, are increased in neutrophils of patients with ASD as compared to control subjects (Nadeem et al., 2019).

The gut microbiota has a significant function in human pathology and physiology (Li et al., 2017). On the other hand, brain-gut abnormalities have been increasingly implicated in several processes of disease, including ASD (Israelyan and Margolis, 2019). In this regards, the results of atypical intestinal microbiota composition in ASD patients with elevated findings of *Clostridium* species in stool samples could reveal GI symptoms, and mucosal immune responses in some ASD children with GI dysfunctions particularly since bacteria are capable of transferring across the permeable intestinal barrier (Finegold et al., 2010, 2004; Finegold et al., 2002). Short-chain fatty acids such as acetate and propionate produced by *Bacteroides thetaiotaomicron* and butyrate produced by a *Clostridium tyrobutyricum* can influence the expression of the tight-junction proteins (claudin-5, occludin, ZO-1) which are associated with blood-brain barrier permeability and therefore may have a secondary impact on the brain function (Braniste et al., 2014). A study conducted by Liu et al. (2019) revealed that *Dialister, Bifidobacterium, Veillonella*, *Blautia, Turicibacter,* and *Prevotella* were consistently declined, while *Desulfovibrio*, *Lactobacillus, Clostridium,* and *Bacteroides* were increased in ASD patients compared to healthy subjects (Liu et al., 2019).

Researchers have wondered about the role of the gut-brain axis in the immune regulation of ASD (Luna et al., 2016; Sajdel-Sulkowska et al., 2019). The mucosal composition of the gut is a major issue related to immune disorders in ASD subjects. For example, a fundamental increase in several mucosa-associated *Clostridiales* was recently reported in ASD children with functional gastrointestinal disorders, whereas a marked decrease in Dorea and *Blautia*, as well as *Sutterella*, was described (Luna et al., 2017).

Recently, the abnormality of gut microbiota-associated epitopes composition in the gut of ASD children was revealed that was related to altered gut microbiota composition and the abnormal gut IgA levels (Wang et al., 2019). A fundamental issue is to comprehend the mechanisms underlying immune tolerance in the gut in ASD individuals, its relationship with the brain-gut axis, and the dietary and nutritional profiles of children with ASD. Exposure today includes food-derived xenobiotics as well as possible immunogenic antigens, which are also associated with various pathogenic threats and include viruses, pathogenic bacteria, pathogenic fungi, multicellular parasites, and tumor cells (Ghaisas et al., 2016; Samsam et al., 2014; Vela et al., 2015).

Furthermore, it has been reported that approximately 23 % of mothers of ASD children produce distinct patterns of autoantibodies to fetal brain proteins that have been recognized in only 1 % of mothers of typically developing children, indicating that autism-specific maternal anti-fetal brain autoantibodies are connected with conditions of metabolic pathways (Krakowiak et al., 2017; Van de Water et al., 2018).

A wide range of research is demanded to find the association between GI/immune/brain axes (Israelyan and Margolis, 2019; Li et al., 2017; Luna et al., 2017, 2016). In numerous studies, the association between GI inflammation in CNS function and altering behaviors has been evaluated. In one study, AKR mice infected by the parasite *trichurs muris* were evaluated by brain biochemistry, GI inflammation, and altered behaviors related to anxiety. The results of this study revealed that chronic GI inflammation stimulates anxiety-like behavior in AKR mice (Bercik et al., 2010). ASD patients may have elevated neuroinflammation (Ghaisas et al., 2016; Krakowiak et al., 2017), changes in the blood-brain barrier (Van de Water et al., 2018), and GI symptoms associated with elevated stress response (Bercik et al., 2010). Research on the role of the gut/brain axis and gut immunity in ASD is in progress and highlighted some important concerns, though therapeutic approaches are still far to be planned based on the more recent investigations. An altered gut microbiome seems to be at the beginning of the pathogenesis and exacerbation of ASD (Strati et al., 2017). According to the most recent opinions, this imbalance should affect the brain-gut axis and the regulation of immune tolerance, where the corticotrophin-releasing factor also exerts a role (Liu et al., 2015; O'Mahony et al., 2015; Rodiño-Janeiro et al., 2015). The possible pathways in the gut–brain axis leading to gastrointestinal disorders in children with ASD are presented in Fig. 1.

5. The possible role of impaired metabolism

It is revealed that intestinal microbes could produce some metabolites that play an important role in health and disease. Therefore, the utilization of fermentation products or fermentation processes could be changed in ASD children compared with children without ASD (Ding et al., 2017). The exact prevalence of inborn errors of metabolism in ASD is unknown. Many individuals with ASD also appear to have underlying metabolic conditions (Simons et al., 2017). Metabolic conditions such as mitochondrial disease and dysfunction and abnormalities in cerebral folate metabolism may affect a substantial number of children with ASD. In contrast, other metabolic conditions, have been associated with ASD, such as disorders of creatine, cholesterol, pyridoxine, biotin, carnitine, γ-aminobutyric acid, purine, pyrimidine, and amino acid metabolism and urea cycle disorders (Frye, 2014), or also histidinemia, dihydropyridine dehydrogenase deficiency, 5′-nucleotidase superactivity, phosphoribosyl pyrophosphate synthetase deficiency (Page, 2000). Several research studies have revealed the presence of other inborn errors of metabolism in ASD, including phenylketonuria (Lowe et al., 1980), adenylosuccinate lyase deficiency (Jaeken and Van den Berghe, 1984), disorders of mitochondrial metabolism (Shoffner et al., 2010; Weissman et al., 2008), and defects in the metabolism of purines and pyrimidines, and disorders of cerebral

glucose transport (Schaefer and Lutz, 2006; Shoffner et al., 2010). It has also been reported that the enteric bacterial metabolic product (propionic acid) can change the relevance to ASD in juvenile rats regarding reduced social behavior (Shams et al., 2019).

Recent studies have implicated physiological and metabolic abnormalities in ASD and other psychiatric disorders, particularly immune dysregulation or inflammation, oxidative stress, and environmental toxicant exposures (Rossignol and Frye, 2012b). Also, defects in the metabolism of phosphoinositide, important modulators of many cellular functions and critical components of lipid membranes, were recently reported in ASD patients (Gross, 2017).

Also, it is demonstrated that the GI problems are common in individuals with co-occurring ASD and mitochondrial disease, indicating the mitochondria as very sensitive to exogenous and endogenous environmental stressors, which could act as a biological connection between neurometabolic abnormalities associated with ASD and environmental stressors (Frye et al., 2015). However, not all children with ASD are affected by the aforementioned metabolic abnormalities (Campistol et al., 2016). ASD is a heterogeneous etiologic entity caused by many different diseases occurring in the CNS at an early stage in life. Several metabolic defects have been associated with symptoms of ASD. However, inborn errors of metabolism can probably account for less than 5 % of these individuals (Manzi et al., 2008). Therefore, although metabolic testing could reveal a diagnosis of urea cycle disorder, it is not cost-effective for non-syndromic ASD individuals (Campistol et al., 2016).

6. Treatment outcomes of GI disorders and ASD

Special diets such as gluten-free and/or casein-free have proved to help to lower the production of TNF-α in the colonic mucosa (Ashwood et al., 2004) and to decrease the incidence of eosinophilic infiltration of the mucosa (Ashwood et al., 2003), offering promising results. The α-amylase/trypsin inhibitors in wheat are strong activators of innate immune responses in monocytes, macrophages, and dendritic cells (Junker et al., 2012). As a result, epithelial cell damage occurs, leading to antigen increased intestinal permeability (Rostami et al., 2017). While supporting this link between inflammation and ASD, normal anti-inflammatory treatments have improved ASD symptomatology (Wakefield et al., 2002; Wang et al., 2019). For example, improvements in speech and developmental milestones were reported in a child who developed ASD and autoimmune lymphoproliferative syndrome (Shenoy et al., 2000). After being treated with steroids, the child's symptoms resolved. In another case of pervasive developmental disorder, significant improvements ameliorating abnormal behaviors such as hyperactivity, tantrums, impaired social interaction, echolalia, and stereotypes were achieved after treatment with corticosteroids (Stefanatos et al., 1995). Antibiotic therapy is also involved in the modulation of gut microbiota in the management of psychiatric disorders. Based on a combination of antibiotics applied to murine specimens, Desbonnet et al. (2015) demonstrated reduction and diversity of the gut microbiota that also influenced behaviors as it reduced anxiety and induced cognitive deficits (Desbonnet et al., 2015). Some studies have examined the second-generation tetracycline, minocycline as a treatment for depression, as it has neuroprotective activities (Miyaoka et al., 2012; Soczynska et al., 2012). In another small study, 11 children affected by ASD have been treated with vancomycin for eight weeks. This led to improvements of such ASD symptoms as communication and reduction of GI symptoms as well (Sandler et al., 2000). In addition, a small open-label clinical trial revealed the influences of microbiota transfer therapy (MTT) on gut microbiota composition and changes in the gut ecosystem of 18 ASD-diagnosed children, indicating promising approaches for improvement of gastrointestinal and ASD symptoms (Kang et al., 2017). Moreover, a population-based cohort study revealed an abnormal composition of microbiota in ASD children who were treated with antibiotics such as vancomycin, aiming to remove deleterious microbes (Luna et al., 2016; Sandler et al., 2000; Son et al., 2015).

The use of various kinds of antibiotics during pregnancy as a potential risk factor for ASD/infantile autism has been highlighted by Atladóttir et al. (2012). Furthermore, the gut microbiota of infants can be influenced by the early feeding pattern and is related to ASD (Li et al., 2017). In another study of ASD children with GI symptoms, eight weeks with oral human immunoglobulin (IG) treatment reduced the GI severity in 50 % of the patients. However, the advantages of the therapy were not stable at the 30 days of follow up. Also, behavioral improvements were reported from baseline at the end of treatment (Schaefer and Lutz, 2006).

7. Nutrition and gastrointestinal immunity

Numerous research on the gut-brain axis is expanding, and different ASD models revealed GI dysfunction (Nithianantharajah et al., 2017; Wang et al., 2011b). Many of the GI symptoms reported in ASD children have motivated some researchers to focus on the possible role of nutritional imbalance in some of the GI disorders. However, examining studies for revealing the link between nutritional supplements and its effect on ASD could not support this hypothesis (Levy et al., 2007). It has been revealed that short-chain fatty acids (SCFAs) have critical effects on GI disorders and ASD pathogenesis (Liu et al., 2019).

Moreover, some ASD symptoms, such as resistance to change and repetitive behaviors, can have an important role in nutrition and feeding behaviors in ASD children (Erickson et al., 2005). In general, these studies reported that since ASD children tend to have elevated food selectivity but that selectivity approaches do not induce malnutrition, and therefore, nutrient intake is sufficient in ASD children (Ahearn et al., 2001; Pivina et al., 2019; Raiten and Massaro, 1986; Shearer et al., 1982). Also, some documents regarding elevated rates of food allergies among ASD populations have been demonstrated (Horvath and Perman, 2002). It is revealed that ASD children had more responses to food allergens as evaluated by positive pinprick reactions (Lucarelli et al., 1995). Recently, it was established that the utilization of nutraceuticals in ASD patients can reveal a successful integrative approach with current treatment, which helped to reach the desired outcomes (Alanazi, 2013). Patients with ASD could also experience leaky gut syndrome, which is induced by inflammation, damaged intestinal mucosa, and abnormal overgrowth of bacteria (Horvath and Perman, 2002). In addition, a subset of ASD children showed high levels of microbial metabolites on proteinaceous substrates. However, the combination of gut barrier integrity, microbiota composition, specific protein intakes, and poor digestion in the ASD subjects represented a phenotypic pattern (Sanctuary et al., 2018). In another study, the elevated levels of IFNγ and TNFα were reported in the response of peripheral blood mononuclear cells (PBMC) to dietary proteins in the ASD children and normal siblings and children with the known dietary intolerances (Jyonouchi et al., 2002). Also, this study identified a significant association between increased IFNγ and TNFα responses with dietary proteins and increased response to LPS in ASD children (Jyonouchi et al., 2002). This result suggests that an abnormal immune system may play a role in GI dysfunction.

8. Abnormalities in the digestive enzymes (disaccharidase activities)

It has been assessed 36 children with ASD (age: 5.7 ± two years, mean ± SD), who had frequent gastrointestinal complaints (chronic diarrhea, gaseousness, and abdominal discomfort and distension). They found a decreased activity of one or more disaccharidases or glucoamylase was found in 21 children (58.3 %); 10 children had decreased activity in 2 or more enzymes. The most frequent finding was a low lactase level, which was present in 14 patients (Horvath et al., 1999a). Another study established the incomplete digestion of dietary casein

and gluten in the small intestine and, therefore, elevated absorption of incompletely hydrolyzed peptides that could affect the nervous system (Kawicka and Regulska-Ilow, 2013). Horvath and his colleagues (1999) suggested that gastrointestinal abnormalities might contribute to some of the behavioral problems frequently described in these children (Horvath et al., 1999b).

Moreover, it has been proposed in a double-blind, randomized clinical trial on 101 ASD children aged from 3 to 9 years that digestive enzymes are promising approaches for managing ASD symptoms (Saad et al., 2015). Also, it is highlighted that ASD children who have symptoms of gastrointestinal disorders had mild levels of mucosal inflammation on intestinal biopsy, while disaccharidase activity was not different in individuals with ASD and neurotypical persons (Kushak et al., 2016; Ming et al., 2008). Also, numerous studies have reported increased levels of circulating antibodies against streptokinase (SK) in children with ASD as compared to healthy controls (Vojdani et al., 2003). The presence of esophagitis correlated well with the reported symptoms and may, in part, explain the sudden irritability, aggressive behavior, or nighttime awakenings in many of these children. Diarrhea and gaseousness may be the consequence of decreased disaccharidase activity and may contribute to behavioral problems.

9. Abnormalities in digestive hormone (secretin)

This hormone, secretin, produced by the small intestine, is a part of a family of hormones that also have some receptors in the brain (e.g., hypothalamus, hippocampus) (Francis, 2005). It has been reported the impaired secretion of secretin in patients with ASD, who within five weeks of receiving intravenous secretin infusions exhibited marked diminution of GI symptoms and improvements in behavior, including the expansion of expressive language (Horvath et al., 1999a). Similarly, two male patients (seven and nine years old) who have ASD with associated gastrointestinal symptoms received multiple doses of intravenous secretin for six months were subject to the assessment of several specific outcomes to evaluate drug efficacy. Besides improving eating behaviors, the administration of secretin led to significant and lasting reduction of associated problems, such as difficulties with toileting, sleeping and/or eating; laughing, crying or giggling at inappropriate times; improved the response to touch, light, sound, taste or smells; diminished unawareness of pain, heat or cold (Pallanti et al., 2005). However, when several research teams attempted to replicate these results in their trials with larger numbers of patients, a beneficial effect of secretin was not seen (Levy et al., 2003; Lightdale et al., 2001; White, 2003; Williams et al., 2012), except for a double-blind placebo-controlled trial by Kern et al. (2002). This study found that children with chronic, active diarrhea showed a reduction in aberrant behaviors when they were treated with secretin but failed to do this when treated with placebo. Children with no GI problems were unaffected by neither secretin nor placebo (Kern et al., 2002).

10. Behavior and gastrointestinal dysfunction

Some studies reported behavioral symptoms associated with GI abnormalities in ASD patients and indicated that those with sleep problems were also more likely to have GI abnormalities (Maenner et al., 2012; Mannion et al., 2013; Ming et al., 2008). In a study on 2973 children with ASD enrolled in autism treatment network, it was revealed that ASD children with GI abnormalities had higher levels of anxiety and sensory over-responsivity (Mazurek et al., 2012). It was also proposed that there is a link between these three symptoms that involved the hypothalamic-pituitary-adrenal (HPA) axis and amygdala-based circuits (Herman and Cullinan, 1997; Mazurek et al., 2012). The HPA axis also modulates immune function, which indicates a link between behavior in ASD patients and mucosal immune irregularities. Various research using human and animal models has studied how increased peripheral cytokines induce a striking modification in behavior (Patterson, 2009). However, it remains unclear if a similar phenomenon can involve mucosal inflammation or not. Although it is believed that GI abnormalities could be relatively common in ASD, the accurate prevalence of these abnormalities is unknown (Buie, 2005; Campbell et al., 2009; Hughes et al., 2018). Also, it is not clear if these abnormalities are more regular in ASD persons in comparison with the typically developing individuals. However, a novel, well-controlled prospective study through a structured interview, demonstrated a considerably elevated prevalence of GI abnormalities in ASD patients as compared to controls (Valicenti-McDermott et al., 2006). Parents often report some GI symptoms in their children, such as food intolerance, constipation, diarrhea, bloating, abdominal pain/discomfort, gas, and a history of reflux (Horvath et al., 1999b; Quigley and Hurley, 2000). While many children with ASD reveal common GI abnormalities, others may present self-injurious behavior (SIB) and aggression, facial grimacing, chest tapping, and seeking of abdominal pressure (Bauman, 2010). It has been revealed that ASD patients could exhibit gastroesophageal reflux disease (GERD), colitis, esophagitis, gastritis, Crohn's disease, inflammatory bowel disease, and celiac disease, while treatment of these abnormalities could lead to improved behavior and better developmental progress (Bauman, 2010). Moreover, it has been reported that disrupted MET gene signaling, as a pleiotropic receptor with an important role in both GI repair and brain development, may be involved in the elevated risk for ASD and familial GI abnormalities (Campbell et al., 2009). Different functional pathways in the gene promoter of MET receptor tyrosine kinase have been related with ASD, and the expression of MET protein has been decreased in temporal lobe cortex in postmortem brain tissue of individuals with ASD. Therefore, the recognition of medical abnormalities in ASD patients, particularly in the case of GI problems, may not only affect the quality of life for those affected with ASD but also could result in the improvement of genetic and phenotypic subtypes in this complex heterogeneous abnormality.

11. Insights on the role of GMBA in the GI symptomatology of ASD

Since a few years ago, the role of GMBA in ASD and GI symptoms has been quite dismissed as a peculiarity, whereas GMBA is currently considered a key factor in GI disorders in ASD, often caused by gut dysbiosis (Ding et al., 2017). Intestinal microbiota directly interacts with the enteric nervous system (ENS), which has considerable autonomy related to the other parts of the nervous system (CNS, sympathetic, and parasympathetic nervous system). ENS includes at least 0.5 million neurons (more than all peripheral ganglia) (Rao and Gershon, 2016), as well as auxiliary cells such as astroglia (enteroglia), which provide a diffusion barrier between intestinal capillaries and ENS ganglia; ganglia have a protective effect against ENS neurons and provide them with nutrients (Sharkey and Savidge, 2014). The ENS has significant similarities with the structure of the CNS. Almost all types of neurotransmitters presented in the CNS function in ENS (Rao and Gershon, 2016). The important role of microbiota for the normal functioning of the ENS is evidenced, for example, by the fact that the ENS of germ-free mice have a reduced ability to respond to various stimuli; this ability is restored by colonizing the intestines of mice with a probiotic strain of Lactobacillus reuteri (Parashar and Udayabanu, 2016). In general, the axis of the microbiota – intestine – brain includes the entire intestinal microbiota, ENS, parasympathetic and sympathetic nervous system, and CNS. These structures carry out functional interaction with the endocrine and immune systems through the involvement of cytokines, neuropeptides, and numerous other signaling molecules. The bi-directional nature of the interaction between different links in the microbiota – intestine – brain axis has been established. The microbiota directly affects various aspects of the functioning of the nervous system and especially the brain (for example, the activity of microglia), the permeability of the blood-brain barrier, neurogenesis, and synthesis as well as excretion of non-transmitters. The effect of the

CNS on the gastrointestinal tract and its microbiota is significant. This is most dramatic when brain damage occurs. Thus, cerebral stroke leads to a change in the composition of the intestinal microbiota, which especially affects the bacteria of the families Peptococcaceae and Prevotellaceae (Westfall et al., 2017).

The influence of the microbiota of the digestive tract on the human body and its neuro-psychic status is mediated by exposure to the hypothalamus-pituitary-adrenal system. Modification of this system function by microbial neuroactive compounds predisposes to the occurrence of depression, anxiety, bipolar disorder (intermittent periods of mania and depression), burnout syndrome, and chronic fatigue syndrome (Lach et al., 2018). Recovery intestinal microbiota, especially with probiotics, reduces the risk of neuropsychic activity disorders. In the feces of children with ASD, there is an increased accumulation of the genera Clostridium, Desufovibrio, and Bacteroidetes. These bacteria produce significant amounts of SCFA, primarily propionic acid, which is associated with the pathogenesis of ASD (MacFabe, 2012). In patients with ASD, in addition to intestinal dysbiosis and cognitive defects, clinical manifestations of gastrointestinal disorders are often found, including constipation, increased permeability of the intestinal wall, problems of digestion and assimilation of carbohydrates, and proliferation of lymphoid tissue of the small intestine (Sampson and Mazmanian, 2015). Children with ASD have gastrointestinal disturbances 3–4 times more often than healthy children (Rao and Gershon, 2016). It was found that patients developed or worsened signs of ASD after a long stay in the hospital with symptoms of gastric discomfort (MacFabe, 2012). The role of the microbiota of the gastrointestinal tract in the pathogenesis of ASD is indicated by the fact that the successful administration of antibiotics to patients with ASD at least briefly improves their mental state (Bercik et al., 2012). The increase in the frequency of psychic disorders of the autism spectrum throughout the world in recent decades is associated with changes in the composition of the intestinal microbiota under the influence of both a change in diet and lifestyle, as well as stressful effects on the host organism and its microbiota (MacFabe, 2012). Administration to healthy mice of 4-ethyl phenyl sulfate, which is secreted by the mouse microbiota and is present in an increased concentration in the blood serum of individuals with ASD, leads to the development of autism-like symptoms (Sampson and Mazmanian, 2015).

Bacteria genotypes and different strain population or bacterial turn over in the gut microbiome (GM) plays a major role in elucidating the influence of GMBA in ASD (Ding et al., 2017). Gut bacteria colonize the distal part of the small intestine and mainly the colon (Dieterich et al., 2018). Goblet cells in the intestinal mucosa produce mucins that prevent the majority of gut bacteria from penetrating through the intestinal epithelial barrier, and Paneth cells are the main supplier of antimicrobial defensins. In this microenvironment, the complex interplay gut microbiome local immunity is fundamental (Tosoni et al., 2019; Zurita et al., 2019). The regulation of this cross-talk might be fundamentally exerted by the tuning of the balance Th17/Tregs, from which gut release its immune modulators and the innate resident population its cytokines, such as IL6, IL33, IL-17 and IL-23 (Omenetti and Pizarro, 2015).

There is a growing interest in the role of the gut in the pathogenesis not only of ASD but also of a range of chronic conditions, especially those with a strong inflammatory component. In this perspective, great attention is being paid to the large bowel microflora in both a negative and protective light (Xu et al., 2019). Furthermore, research into the microbiome has been reviewed in the context of a range of neurological diseases (A Kohler et al., 2016; Castillo-Álvarez and Marzo-Sola, 2019; Klukowski et al., 2015; Mulak and Bonaz, 2015). This should suggest that for ASD, pathogenesis, the role of an impaired GMBA may be fundamental (Jin et al., 2019; Li et al., 2019b; Sharon et al., 2019; Wang and Kasper, 2014).

Alterations in gut bacterial population and dysbiosis are the main causes of GI symptoms and exacerbation in ASD. Previously reported data have shown that children with ASD have a lower relative amount of *Bifidobacterium* species, particularly of the mucolytic bacterium *Akkermansia muciniphila* (Wang et al., 2011a). Furthermore, recent studies have outlined that ASD children have an abundance of the gut microbiota species *Sutterella spp* and *Ruminococcs torques* in feces (Chatrchyan et al., 2013). Differences in the gut microbiota bacterial composition affect bacteria-derived metabolites, which can trigger impairments in gastrointestinal activity and GMBA (Samsam et al., 2014; Wang et al., 2014). The case of short-chain fatty acids (SCFAs) has moved great attention to ASD-causing GI disorders (Morris et al., 2017). Wider spectra of actions were attributed to lipids in this perspective (Russo et al., 2018). SCFAs are in the spotlight because some reports have outlined their ability to modulate gut-related immunity, so suggesting a role in possibly solving GI pathology in ASD (Ratajczak et al., 2019). Particularly in the case of propionic acid, produced mainly by clostridia, bacteroides, and desulfovibrio bacteria, the involvement of SCFA in GMBA appears very important (MacFabe, 2015). Further research is needed to elucidate how SCFA may address GI symptoms in ASD subjects.

12. Concluding remarks

Many studies with different designs from randomized, double-blind placebo-controlled to open-label trials have been conducted to examine the possible role of GI abnormalities in ASD behavior symptoms. The evidence indicates that GI abnormalities, in many cases, are a part of the ASD pathology. The mechanisms for how GI abnormalities contribute to the pathophysiology of ASD is not fully known. More research is needed to understand better the relationship between GI disorders and irritability, behavior, and mood problems in ASD patients, including the function of neuroactive metabolites. Future studies should examine novel approaches for the possible therapeutic management of GI dysfunction in ASD.

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