The Egyptian Journal of Otolaryngology

ORIGINAL ARTICLE Open Access

Screening of gastrointestinal symptoms and celiac disease in children with autism spectrum disorder

Eman Ahmed[1], Amira Mansour[2*], Ayman Amer[2], Tarek Barakat[3] and Hemmat Baz[2]

Abstract

Background: This study aimed to evaluate the GIT manifestation in Autistic children and relate it to the degree of autism to demonstrate the possible connection between celiac disease and autism. An observational cross-sectional study with analytic component was carried out on 114 children with autism spectrum disorder above 3 years who visited to Phoniatric Unit, Mansoura University Hospitals and were separated into three groups according to DSM-V each of them contained 38 children, group I (children with level I ASD), group II (children with level II ASD), and group III (children with level III ASD).

Results: Fifty percent of ASD children in the studied groups showed at least one GIT symptom. Constipation was the most common symptom. The existence of gastrointestinal signs was shown to have a substantial link with the severity of autism. None of the youngsters had celiac disease.

Conclusion: Gastrointestinal issues are frequent in ASD children and may lead to ASD behavioral symptoms. It is possible that children with more severe autism are more prone to suffer from gastrointestinal issues, and the other way around. This research found no evidence to demonstrate a connection between autism spectrum disorder and celiac illness.

Keywords: Autism spectrum disorder, Celiac disease, Gastrointestinal dysregulation

Background

Autistic people have a number of medical complications. Because of their documented incidence and association with the severity of core autism-related behavioral problems, gastrointestinal (GI) disorders are of special concern [1].

It is now clear that gastrointestinal (GI) problems are common in many children with ASD. An approximated 50% or more of these youngsters are impacted, with signs 4 times more common than in children without ASD. Chronic constipation, diarrhea, and stomach discomfort are the most often reported symptoms. Furthermore, GI microbial dysbiosis, defined as an imbalance in the organisms that comprise the gut microbiota, has been reported in many investigations of children with ASD [2].

Clinical manifestations of digestive system disorders in children with ASD may vary from children with average progress, and diagnosing a GI issue in children may be more challenging and time-consuming. The incidence of GI tract signs varied from 9 to 84% in children with ASD, whereas it ranged from 9 to 37% in children without ASD [3–5]. Because of basic ASD symptoms such as difficulty in verbal and nonverbal communication and a changed sense of pain, subjective symptoms such as pain, discomfort, heartburn, or nausea are difficult to detect and understand.

The connection of ASD with a high incidence of GI symptoms has prompted a thorough investigation of the

*Correspondence: dr.amira_mohamed95@yahoo.com

[2] Phoniatric Unit, ORL Department, Faculty of Medicine, Mansoura University, Mansoura, Egypt
Full list of author information is available at the end of the article

ASD gut microbiome [6]. In recent times, there has been a surge of interest in the function of gut bacteria in brain progress and behavior, particularly in the formation of brain circuitries that govern learning, emotion, and social behavior. Autism spectrum disorder is one neurodevelopmental condition that exhibits this relationship, with a growing number of GI issues and changed gut microbiota composition (ASD). Furthermore, children with ASD have altered gut microbial composition, with decreased gut bacterial variety and underestimation of potentially helpful bacteria such as Bifidobacterium, Prevotella, and Desulfovibrio, as well as a decrease in short-chain fatty acids. These results suggest that the gut-brain axis may play a role in ASD [7].

Celiac disease (CD) is classically defined as an immune-mediated chronic enteropathy in the small intestine, which is usually caused by gluten ingestion from wheat, rye and bar-ley in patients whom are genetically predisposed, CD is considered as a multisystem disorder, often presented by extra-intestinal manifestations and could affect any organ or body system, including the nervous system [8].

It is suggested that CD might be involved in ASD pathogenesis. This is based on the leaky-gut hypothesis [9]. The association between ASD and CD is still a matter of debate. Some studies reported no evidence for the existence of an ASD-CD link, whereas others suggested a possible connection, or a higher prevalence of CD in ASD children than in general pediatric population. While the etiology and pathogenesis of ASD are still unknown, there is evidence that a substantial number of ASD children display an increased immune reactivity against gluten [10]. So, the aim of this study was to evaluate the GIT manifestation in autistic children and relate it to the degree of autism to demonstrate the possible connection between celiac disease and ASD.

Methods

The authors run an observational cross-sectional study with analytic components to evaluate the prevalence of gastrointestinal manifestation and celiac disease among children with autism spectrum disorder and evaluate the correlation between autism and the GIT symptoms.

The participants were 114 children with ASD above 3 years who went to the outpatient clinic at the Phoniatric Unit, Mansoura University Hospitals. They were separated into three groups according to DSM-V (group I (level I ASD), group II (level II ASD), and group III (level III ASD)). Each group consisted of 38 children. Children with known neurological, psychiatric, immunological disorders, or delayed language development due to other causes than ASD were excluded from the study.

The 4th Arabic edition of the Preschool Language Scale and the Stanford Binnet Intelligence Scale Arabic version were used to evaluate each child's ability to communicate in both English and Arabic [11]. The authors performed the Child Autistic Rating Scale "CARS" [12] for the ASD children to categorize them into their degrees of severity. A symptomatology checklist was constructed to determine if or whether there are any GIT symptoms and other common chronic symptoms suggestive of celiac disease among children with ASD. Anxiety, bloating, diarrhea, and constipation, as well as vomiting, sensitivity to food, trouble swallowing and blood in the stool are all signs of irritable bowel syndrome (IBS) [13], some of the most common symptoms of celiac disease include growth and weight loss; constipation; vomiting; abdominal bloating; and fatigue and irritability [14].

Laboratory detection of tissue transglutaminase (IgA and IgG) and serum IgA were done only for cases having multiple chronic gastrointestinal manifestations suggestive of celiac disease. The centrifuged blood samples were kept at − 20 °C until they were needed. Turbidimetric immunoquantification was used to rule out people with an IgA deficiency (COBAS MIRA, Roche Diagnostic Systems). ELISA was used to determine the presence of anti-transglutaminase antibodies of both IgA and G types (IgA-tTG and IgG-tTG). The manufacturer's instructions state that the typical range has a maximum of 20 arbitrary units. This is the highest limit of that range. Gastrointestinal endoscopy was performed on all individuals who had anti-transglutaminase test results above normal.

Finally, endoscopy was only performed on patients with numerous chronic gastrointestinal symptoms that were consistent with celiac disease and positive laboratory findings. All patients having endoscopy were fasted for 6 h and sedated with general anesthesia or midazolam and fentanyl, depending on the physician's option. All endoscopic treatments were carried out by a skilled endoscopist using high-resolution endoscopes (GIF 160, Olympus Corporation, Tokyo, Japan). Biopsies taken using cold forceps from the duodenal bulb and distal duodenum at least five times. Formalin-fixed, paraffin-embedded, 5-mm-thick sections, and hematoxylin-and-eosin-stained biopsy samples were sent to a pediatric gastroenterologist, who used the Marsh categorization system to determine whether or not the samples included CD diagnostic features.

Results

Descriptive and comparative analysis

Comparative and descriptive analysis of study groups

None of the comparisons yielded statistically significant results in age and gender between all studied groups. However, male predominance was apparent in all three

levels of ASD. There was a significant decrease in language age and IQ, with a significant increase in CARS scores associated with ASD severity (Table 1).

Comparative and descriptive examination of the symptomatology

Descriptive and comparative analysis of recurrent symptoms Regarding the presence of the recurrent symptoms asked in the questionnaire in the whole study population, it was found that 50% of the total population was suffering from at least one recurrent symptom, while multiple symptoms were observed at about Twenty-nine percent of the whole population. Also, recurrent constipation was the most prevalent recurrent sign with a percentage of 33%, followed by bloating with a percentage of 26%, while the minor recurrent symptom was blood in stool with a percentage of 2%. One symptom was not reported, which is blood in vomitus (Table 2).

Table 2 The percentage of each of the recurrent symptoms in the whole population of the study

Presence of	All patients ($n = 114$)
Recurrent symptoms	50% (57)
Multiple recurrent symptoms	29% (33)
Abdominal pain	5% (6)
Bloating	26% (30)
Diarrhea	7% (8)
Constipation	33% (38)
Pain with stool	12% (14)
Vomiting	4% (5)
Food sensitivity	3% (3)
Difficult swallowing	3% (3)
Blood in stool	2% (2)
Blood in vomitus	0%

Data are expressed as percentage (number)

When compared between the three studied groups, the highest number of cases suffering from recurrent GIT symptoms were of level III ASD while the lowest number was of level I ASD. Also, constipation was the most common symptom, with the highest percentage in level III ASD with the smallest proportion in level I. Concerning diarrhea, only reported cases were found in group III. Significant statistical differences between the groups were also shown as painful stool as no reported cases were found in group I; however, the highest percentage was found in group III. Lastly, vomiting was statistically significant as only reported cases were found in group III (Tables 3 and 4).

Chronic symptom descriptive and comparative analysis Regarding the presence of the chronic symptoms asked in the questionnaire in the whole study population, it was found that 36% of the total population was suffering from at least one recurrent symptom, while multiple symptoms were observed at about 12% of the whole population. Also, chronic irritability was the most common chronic symptom with a percentage of 23%, followed by chronic bloating with a percentage of 11% and constipation with 10%, while the minor chronic symptoms were diarrhea with or without blood and abdominal pain with a percentage of 1%. It was found that 14 children had multiple chronic symptoms; none of them was in the group, only four children with a percentage of 10.5% in group II and I while the majority of them was in group III (10 children) with a percentage of 26.3%. Between groups I and III, there was a statistically significant difference (P value = 0.001) (Tables 5, 6, 7, and 8).

Out of the 14 children with multiple chronic symptoms, only 2 children from group III were positive for lab

Table 1 Demographic data analysis, both descriptive and comparative, CARS, IQ, and language age in study groups

Variables		Level I ASD ($n = 38$)	Level II ASD ($n = 38$)	Level III ASD ($n = 38$)	*P* value
Age (month)		62.4 ± 18 months	70.8 ± 25.2 months	60 ± 24 months	0.07[1]
Gender	**Male**	71% (27)	68% (26)	71% (27)	1[2]
	Female	29% (11)	32% (12)	29% (11)	
CARS		30.2 ± 0.7	33.9 ± 1.1	40.7 ± 3.1	< **0.0001**[1]
IQ		77.1 ± 8.7	58.4 ± 6.5	48.4 ± 82	< **0.0001**[1]
Language age (month)		21.9 ± 7.1	14.4 ± 3.5	8.3 ± 1.9	< **0.0001**[1]

Data are expressed as mean ± SD or percentage (number)

[1] *P* value was generated by Kruskal–Wallis one-way test

[2] *P* value was generated by Cramer's V chi-square test

P-value is significant when < 0.05

Table 3 Description and comparison of the recurrent symptoms among the three groups of the study

Presence of	Level I ASD ($n = 38$)	Level II ASD ($n = 38$)	Level III ASD ($n = 38$)	*P* value
Recurrent symptoms	24% (9)	40% (15)	87% (33)	< **0.0001**
Multiple recurrent symptoms	0%	21% (8)	66% (25)	< **0.0001**
Abdominal pain	3% (1)	0%	13% (5)	0.07
Bloating	11% (4)	29% (11)	40% (15)	0.06
Diarrhea	0%	0%	21% (8)	< **0.0001**
Constipation	11% (4)	26% (10)	63% (24)	< **0.0001**
Pain with stool	0%	11% (4)	26% (10)	**0.002**
Vomiting	0%	0%	13% (5)	**0.010**
Food sensitivity	0%	0%	8% (3)	0.11
Difficult swallowing	0%	0%	8% (3)	0.11
Blood in stool	0%	0%	5% (2)	0.33
Blood in vomitus	0%	0%	0%	–

Data are expressed as a percentage (number)

The *P* value was generated by Cramer's V chi-square test

P value is significant when < 0.05

Table 4 Post hoc analysis of the incidence of recurrent symptoms in the groups of the study

Presence of	P1	P2	P3
Recurrent symptoms	0.22	< **0.0001**	< **0.0001**
Multiple recurrent symptoms	**0.005**	< **0.0001**	< **0.0001**
Diarrhea	–	**0.005**	**0.005**
Constipation	0.14	< **0.0001**	**0.002**
Pain with stool	0.12	**0.001**	0.14
Vomiting	–	**0.020**	**0.020**

Data are expressed as percentage (number)

The *P* value was generated by the chi-square test

P1 is generated by comparing mild and moderate autism

P2 is generated by comparing mild and severe autism

P3 is generated by comparing moderate and severe autism

P value is significant when < 0.05

Table 5 The percentage of each of the chronic symptoms in the whole population of the study

Presence of	All patients ($n = 114$)
Chronic symptoms	36% (41)
Multiple chronic symptoms	12% (14)
Growth retardation	2% (2)
Weight loss	2% (2)
Chronic diarrhea	1% (1)
Blood with chronic diarrhea	1% (1)
Chronic bloating	11% (12)
Chronic vomiting	2% (2)
Chronic constipation	10% (11)
Chronic pain	1% (1)
Chronic fatigue	2% (2)
Irritability	23% (26)

Data are expressed as a percentage (number)

investigation. These two children went for endoscopy for sure diagnosis of celiac disease, but none of them were confirmed as celiac patients (Table 9).

Discussion

There are many new issues in GID and ASD that need more and more research [15]. The existing trials are tiny and short-term, making it unable to say definitively if supplements for a healthy diet interventions are beneficial for children with ASD [16].

Many children with ASD have gastrointestinal (GI) problems, as has lately been shown. More over half of these children have ASD, and the incidence of signs is 4 times greater than in children without the disorder [2].

The signs of the current observational cross-sectional study were constructed to evaluate gastrointestinal symptoms and other common chronic symptoms suggestive of celiac disease among children with autism spectrum disorder. Additionally, it is critical to realize the correlation between gastrointestinal symptoms and the severity of autism spectrum disorders. According to Mannion et al. [17], who conducted a research on the relevance of autism spectrum disorder in children and adolescents, the relevance of comorbid psychiatric illnesses, sleep issues, gastrointestinal symptoms, as well as epilepsy was much lower, there was an agreement between both

Table 6 Description and comparison of the chronic symptoms among the three groups in the study

Presence of	Level I ASD ($n = 38$)	Level II ASD ($n = 38$)	Level III ASD ($n = 38$)	*P* value
Chronic symptoms	0%	45% (17)	63% (24)	˂ **0.0001**
Multiple chronic symptoms	0%	11% (4)	26% (10)	**0.002**
Growth retardation	0%	0%	5% (2)	0.33
Weight loss	0%	0%	5% (2)	0.33
Chronic diarrhea	0%	0%	3% (1)	1
Blood with chronic diarrhea	0%	0%	3% (1)	1
Chronic bloating	0%	16% (6)	16% (6)	0.05
Chronic vomiting	0%	5% (2)	0%	0.33
Chronic constipation	0%	11% (4)	18% (7)	**0.015**
Chronic pain	0%	0%	3% (1)	1
Chronic fatigue	0%	3% (1)	3% (1)	1
Irritability	0%	21% (8)	47% (18)	˂**0.0001**

Data are expressed as percentage (number)

The *P* value was generated by Cramer's V chi-square test

P value is significant when < 0.05

Table 7 Post hoc analysis of the incidence of the chronic symptoms of the groups in the study

Presence of	P1	P2	P3
Chronic symptoms	˂ **0.0001**	˂ **0.0001**	0.17
Multiple chronic symptoms	0.12	**0.001**	0.14
Chronic constipation	0.12	**0.012**	0.52
Irritability	**0.005**	˂ **0.0001**	**0.029**

Data are expressed as a percentage (number)

The *P* value was generated by the chi-square test

P1 is generated by comparing mild and moderate autism

P2 is generated by comparing mild and severe autism

P3 is generated by comparing moderate and severe autism

P value is significant when < 0.05

Table 8 The percentage of children having multiple chronic symptoms in the three groups who submitted to lab investigation

Level I ASD (38)		Level II ASD (38)		Level III ASD(38)	
No.	**%**	**No.**	**%**	**No.**	**%**
0	0	(4)	10.5%	(10)	26.3%
$p_1 = 0.115$, $p_2 = 0.001^*$, $p_3 = 0.076$					
$\chi^2(^{MC}p) = 12.805^*(0.002^*)$					

Data are expressed as a percentage (number)

$|^2$Chi square test, *MC* Monte Carlo

^{p} *p* value for comparing between the studied groups

^{p1} *p* value for comparing between group 1 and group 2

^{p2} *p* value for comparing between group 1 and group 3

^{p3} *p* value for comparing between group 2 and group 3

* Statistically significant at $p \leq 0.05$

Table 9 The percentage of children with positive lab results

Level II ASD (38)		Level III ASD (38)	
No.	**%**	**No.**	**%**
(0)	0%	(2)	5.3%
$\chi^2(^{FE}p) = 2.054(0.493)$			

Data are expressed as a percentage (number)

$|^2$Chi-square test, *FE* Fisher exact

^{p} *p* value for comparing between the studied groups

studies in that constipation is one of the most common present symptoms. However, the percentage of presence of at least one GIT symptom as was reported 79.3% in their study and of this study was 50%, and this may be contributed to the difference in the number of the participants in both studies 87 against 114 and also that their participants included both children and adolescents, while this study only included children.

Another research, carried out by Ibrahim et al. [18] to demonstrate that autistic children are more likely to suffer from gastrointestinal issues, has shown that 77.2% of the studied 121 patients suffered at least one GIT symptom among them, 50.3% experienced diarrhea, 44.9% experienced abdominal discomfort and irritability, and 33.9% experienced constipation. This study estimates constipation (33%) is again in good agreement but is much lower for diarrhea and abdominal pain. Valicenti-McDermott et al. [19] also studied the incidence of GIT signs among 50 autistic children and found that 70% of the studied group suffered at least one symptom and that constipation has the highest incidence, as this study showed with a percentage of 44%.

A meta-analysis carried out. There were 15 studies that encompassed 2215 children with ASD to provide the most accurate evaluation of existing information on this issue, according to McElhanon et al. [20]. There were tight inclusion criteria, consistent data collecting, and a variety of statistical methods employed in the study. ASD children had a higher likelihood of experiencing general gastrointestinal symptoms than their typically developing peers, indicating that they may be more sensitive to experiencing symptoms such as abdominal pain, constipation, and diarrhea.

As shown in these previous studies and this current study, constipation was the most common symptom that ASD children suffer from. This may be referred to several causes. Constipation may be triggered or exacerbated in children with ASD who have nonorganic toileting concerns, such as a lack of or a delay in learning to bowel train and higher rates of problem behaviors when the toileting pattern changes. Sensory stimuli, sensory processing impairments, and motor difficulties may all contribute to the development of fecal retention in children with autism spectrum disorders (ASD). Constipation may also be linked to food selectivity in this group, as people with ASD tend to eat a lot of processed foods and less fiber-rich fruits and vegetables, both of which have a laxative impact and shorten transit time through the intestines [20].

In children with ASD, gastrointestinal comorbidities are prevalent and impact between 9 and 91% of patients, with signs 4 times more common than in children without ASD. This wide range is attributable to the wide variety of signs covered in diagnosis and the limited number of research measuring the prevalence of gastrointestinal symptoms. Because many of the children in this study are nonverbal or have trouble talking, these symptoms are typically underreported by their caregivers, who may not recognize the signs in their children. The most prevalent complaints, however, are persistent constipation, diarrhea, and stomach discomfort. Children with autism spectrum disorder (ASD) have a higher probability of food allergies than their age-matched peers, and they may be under-diagnosed for similar reasons. Autism spectrum disorder (ASD) sufferers report that some meals worsen their gastrointestinal and behavioral symptoms. Youngsters with ASD have different gut flora, immune systems, and digestive capacities than normally developing children; however, this has not been shown to cause their bad reactivity to certain meals [21].

These findings might be explained by a shared genetic basis for gastrointestinal and behavioral disorders. In line with our findings, Wang et al. [22] observed that the severity of autism signs was linked to a greater risk of gastrointestinal disorders and that this increased risk was also connected with an increased severity of autistic signs. There is also a linkage between the severity of an individual's ASD and their gastrointestinal problems, according to Fattorusso et al. [23]. Whether or whether there is a link between ASD and CD is still up in the air. Some studies found no evidence of a correlation between ASD and CD, whereas others found a greater frequency of CD in ASD children than in the general pediatric population [24].

On the other hand, Chandler et al. [25] and Williams et al. [26] reported that the presence of GI difficulties did not vary by gender, ASD subtype, race, or IQ in the ASD group; however, these findings were not supported by additional researches. There was no difference in the intensity of symptoms, demographic features, or measures of adaptive functioning between individuals with and without gastrointestinal disorders, according to Nikolov et al. [27].

Also, Pavone et al. [28] has performed a case-control study to search for a link between Autism and CD and failed to prove the existence of a connection between them. Among the 120 CD patients studied, they identified no instances of autism, and none of the CD patients had any cases of autism. Researchers from around the country have conducted yet another investigation on the link between celiac disease and an increased chance of developing an autism spectrum disorder was carried out by Ludvigsson et al. [29] and illustrated no association between both.

The etiology of these GI issues is unknown. Furthermore, the reasons seem to be related in part to aberrant gut flora and probably to the overuse of oral antibiotics, which might affect gut flora. Oral antibiotics kill practically all normal gut microbiota, which aids in the digestion of plant polysaccharides, promotes gastrointestinal motility, maintains water balance, produces certain vitamins, and competes with harmful bacteria. Loss of normal gut flora may lead to an expansion of pathogenic flora, which could also lead to constipation and other issues [30].

A rise in the number of ASD cases may be linked to specific habits (such as a poor diet, medication use, and excessive personal hygiene) that alter the composition of the gut microbiota that in turn affects ASD gastrointestinal pathophysiology, according to the prevalence of GI signs in autistic subjects. The bacterial gut microbiota of ASD individuals has been found to be altered, even though the variations observed in these investigations were discordant, which might be owing to variations in sampling tactics and methodology utilized [30]. Because gut microbiota may play a role in the modification of intestinal microbial community structure in

ASDs, it opens the door to new possible therapeutic options targeted at relieving digestive symptoms [30].

The presence of GI disorders in children with ASD poses the question about a possible association between GI disorders and severity of ASD symptoms. Behavior characteristics hypothesized to be expressions of GI problems are common in children with ASD. Facial grimacing, teeth gritting, excessive chewing (of food or items) belong to frequently observed facial expressions of GI symptoms in children with autism. Accompanying vocal behaviors such as sobbing, screaming, or delayed echolalia may also be present. Motor behaviors such as the child placing pressure on the stomach with their own hands or objects, including chairs or tables, may be associated with the abdominal area and are commonly reported by parents and/or caregivers. Such behaviors may be collectively described as abdominal behaviors [31]. Facial expressions and abdominal behaviors may be present as separate entities or coexist with general motor behaviors. General motor behaviors typical for this group of children include self-injuries, increased repetitive/stereotypic movements, unusual posturing, or tapping/twitching. Stomach pain or abdominal discomfort in children with ASD may be indicative of motoric excitation which in turn may have an effect on the general state of the child expressed as irritability, oppositional behavior, or sleep disturbances. Children with abdominal pain are more likely to present with these psychological disorders, anxiety, behavioral problems, or other psychological symptoms [31].

GI problems including feeding problems, dysphagia, nausea, bloating, profound constipation, or diarrhea can reflect functional GI dysmotility (oropharyngeal, esophageal, and bowel dysmotility). The enteric nervous system, described as a "second brain", autonomic nervous system (ANS) that directly controls the GI system being involved in gut motility, local secretion, and absorption. Dysautonomia is the disorder of the autonomic nervous system (ANS) associated with several diseases, also with ASD, but often misdiagnosed and left untreated. Dysautonomia encompasses abnormal reflex adaptive reactions of control mechanisms in the brain and/or peripheral distribution of the sympathetic and parasympathetic nervous systems. It is hypothesized that limbic system control of the ANS is affected, especially damage to the amygdala (e.g., by seizures). In children with autism, dysautonomia may manifest in many ways: it may be expressed in behaviors such as "hand flapping" or usage of peripheral vision which may be explained as attempts to avoid "unpleasant autonomic sensations" caused by stimulation of visual pathways that disturb sympathetic/parasympathetic homeostasis [31].

Among 147 people with autism spectrum disorders, the rate of celiac disease was not higher than the prevalence documented in a cohort of 2034 healthy children from the same geographical region by Batista et al. [32]. ASD prevalence in 211 CD patients was 0.95%, which is not substantially different from the prevalence of 0.9% seen in general US population. As a result, the researchers came to the conclusion that there is no statistically significant link between CD and ASD.

As discussed before, Constipation and feeding concerns selectivity are often caused by behavioral factors. Data imply that the greater occurrence of these gastrointestinal issues in children with autism may be due to a neurobehavioral instead of a main organic gastrointestinal etiology.

Barcia et al. [33], on the other hand, analyzed a big sample of 150 randomly chosen ASD patients retrospectively and discovered an elevated incidence of intestinal biopsy-confirmed CD in ASD children (3.3%) compared to the usual population (0.9%).

According to Quan et al. [34], there is insufficient data to show a link between ASD and celiac illness. Several research design features, rather than the absence of this comorbidity, may explain these results. More population-based research is needed to accurately analyze the link between these two illnesses.

Conclusion

Children with autism spectrum disorders (ASD) often have digestive problems, which may be linked to their behavioral symptoms. More severe autism is associated with an increased risk for severe gastrointestinal problems, whereas the opposite is true for children with milder autistic symptoms. According to this study, there is no indication of a relationship between autism and celiac disease.

Acknowledgements
Not applicable.

Consent to participate
The parents of children signed a written informed consent form.

Authors' contributions
EA performed the experiments, collected the data, and contributed data and analysis tools. The AM was a major contributor in writing the manuscript. AA contributed to clinical evaluation of ASD children, and analyzed and interpreted the data. TB provided key/unique reagents, and analyzed and interpreted the data. HB conceived, designed and supervised the study, and contributed to data analysis and interpretation. All authors read and approved the final version of the manuscript and they all contributed substantially in the research.

Funding
No funding.

Availability of data and materials
Available (The datasets used and/or analyzed during the current study are available from the corresponding author).

Declarations

Ethics approval and consent to participate
This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the institutional research board of Mansoura University. The parents of children signed a written consent form.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no conflict of interests.

Author details
[1]Phoniatric Unit, ORL Department, Mansoura Specialized Hospital, Mansoura, Egypt. [2]Phoniatric Unit, ORL Department, Faculty of Medicine, Mansoura University, Mansoura, Egypt. [3]Gastroenterology and Hepatology Unit, Pediatric Department, Faculty of Medicine, Mansoura University, Mansoura, Egypt.

Received: 24 January 2022 Accepted: 17 June 2022
Published online: 15 July 2022

References

1. Hsiao EY (2014) Gastrointestinal issues in autism spectrum disorder. Harv Rev Psychiatry 22:104–111
2. Sanctuary MR, Kain JN, Chen SY, Kalanetra K, Lemay DG, Rose DR, Yang HT, Tancredi DJ, German JB, Slupsky CM (2019) Pilot study of probiotic/colostrum supplementation on gut function in children with autism and gastrointestinal symptoms. PLoS One 14:e0210064
3. Buie T, Campbell DB, Fuchs GJ, Furuta GT, Levy J, Vandewater J, Whitaker AH, Atkins D, Bauman ML, Beaudet AL (2010a) Evaluation, diagnosis, and treatment of gastrointestinal disorders in individuals with ASDs: a consensus report. Pediatrics 125:S1–S18
4. Black C, Kaye JA, Jick H (2002) Relation of childhood gastrointestinal disorders to autism: nested case-control study using data from the UK General Practice Research Database. BMJ 325:419–421
5. Levy SE, Souders MC, Ittenbach RF, Giarelli E, Mulberg AE, Pinto-Martin JA (2007) Relationship of dietary intake to gastrointestinal symptoms in children with autistic spectrum disorders. Biol Psychiatry 61:492–497
6. Liu F, Li J, Wu F, Zheng H, Peng Q, Zhou H (2019) Altered composition and function of intestinal microbiota in autism spectrum disorders: a systematic review. Transl Psychiatry 9:43
7. Isaksson J, Pettersson E, Kostrzewa E, Heijtz RD, Bölte S (2017) Brief report: association between autism spectrum disorder, gastrointestinal problems and perinatal risk factors within sibling pairs. J Autism Dev Disord 47:2621–2627
8. Green PH, Jabri B (2006) Celiac disease. Annu Rev Med 57:207–221
9. Buie T, Fuchs GJ, Furuta GT, Kooros K, Levy J, Lewis JD, Wershil BK, Winter H (2010b) Recommendations for evaluation and treatment of common gastrointestinal problems in children with ASDs. Pediatrics 125:S19–S29
10. Józefczuk J, Konopka E, Bierła J, Trojanowska I, Sowińska A, Czarnecki R, Sobol L, Józefczuk P, Surdy W, Cukrowska B (2018) The occurrence of antibodies against gluten in children with autism spectrum disorders does not correlate with serological markers of impaired intestinal permeability. J Med Food 21:181–187
11. Abu-Hasseba A (2011) Standardization, translation, and modification of the preschool language scale-4. MD thesis of phoniatrics. Cairo, Egypt: Faculty of Medicine, Ain Shams University.
12. Melika L (1998) Stanford Binet Intelligence Scale (4th Arabic version). Victor Kiorlos Publishing, Cairo
13. Schopler E, Reichler RJ, Renner BR (1988) The childhood autism rating scale (CARS). Western Psychological Services. Los Angeles
14. Chaidez V, Hansen RL, Hertz-Picciotto I (2014) Gastrointestinal problems in children with autism, developmental delays, or typical development. J Autism Dev Disord 44:1117–1127
15. Rubio-Tapia A, Hill ID, Kelly CP, Calderwood AH, Murray JA (2013) ACG clinical guidelines: diagnosis and management of celiac disease. Am J Gastroenterol 108:656
16. Dawson G (2017) Questions remain regarding the effectiveness of many commonly used autism treatments. Pediatrics 139:e20170730
17. Mannion A, Leader G, Healy O (2013) An investigation of comorbid psychological disorders, sleep problems, gastrointestinal symptoms, and epilepsy in children and adolescents with an autism spectrum disorder. *Research in Autism Spectrum Disorders,* 7**,** 35-42. 16- IBRAHIM S H, VOIGT R G, KATUSIC S K, WEAVER A L & BARBARESI W J(2009) Incidence of gastrointestinal symptoms in children: A population-based study. Pediatrics 124:680
18. Ibrahim SH, Voigt RG, Katusic SK, Weaver AL, Barbaresi WJ (2009) Incidence of gastrointestinal symptoms in children: A population-based study. Pediatrics 124:680
19. Valicenti-MCDERMOTT M, MCvicar K, Rapin I, Wershil BK, Cohen H, Shinnar S (2006) Frequency of gastrointestinal symptoms in children with autistic spectrum disorders and association with family history of autoimmune disease. J Dev Behav Pediatr 27:S128–S136
20. MCelhanon BO, MCcracken C, Karpen S, Sharp WG (2014) Gastrointestinal symptoms in autism spectrum disorder: a meta-analysis. Pediatrics 133:872–883
21. Sanctuary MR, Kain JN, Angkustsiri K, German JB (2018) Dietary considerations in autism spectrum disorders: the potential role of protein digestion and microbial putrefaction in the gut-brain axis. Front Nutr 5:40. ISO 690
22. Wang LW, Tancredi DJ, Thomas DW (2011) The prevalence of gastrointestinal problems in children across the United States with autism spectrum disorders from families with multiple affected members. J Dev Behav Pediatr 32:351–360
23. Fattorusso A, Di Genova L, Dell'isola GB, Mencaroni E, Esposito S (2019) Autism spectrum disorders and the gut microbiota. Nutrients 11:521
24. Chandler S, Carcani-Rothwell I, Charman T, Pickles A, Lucas T, Meldrum D, Simonoff E, Sullivan P, Baird G (2013) Parent-reported gastrointestinal symptoms in children with autism spectrum disorders. J Autism Dev Disord 43:2737–2747
25. Williams KC, Fuchs GJ, Furuta GT, Marcon MA, Coury DL (2010) 511 Clinical Features Associated With GI Symptoms in Autism Spectrum Disorders (ASD). Gastroenterology 138:S-74
26. Nikolov RN, Bearss KE, Lettinga J, Erickson C, Rodowski M, Aman MG, MCcracken JT, MCdougle CJ, Tierney E, Vitiello B (2009) Gastrointestinal symptoms in a sample of children with pervasive developmental disorders. J Autism Dev Disord 39:405–413
27. Pavone L, Fiumara A, Bottaro G, Mazzone D, Coleman M (1997) Autism and celiac disease: failure to validate the hypothesis that a link might exist. Biol Psychiatry 42:72–75
28. Ludvigsson JF, Reichenberg A, Hultman CM, Murray JA (2013) A nationwide study of the association between celiac disease and the risk of autistic spectrum disorders. JAMA Psychiat 70:1224–1230
29. Adams JB, Johansen LJ, Powell LD, Quig D, Rubin RA (2011) Gastrointestinal flora and gastrointestinal status in children with autism–comparisons to typical children and correlation with autism severity. BMC Gastroenterol 11:22
30. Strati F, Cavalieri D, Albanese D, De Felice C, Donati C, Hayek J, Jonsson O, Leoncini S, Renzi D, Calabrò A (2017) New evidences on the altered gut microbiota in autism spectrum disorders. Microbiome 5:24
31. Wasilewska J, Klukowski M (2015) Gastrointestinal symptoms and autism spectrum disorder: links and risks–a possible new overlap syndrome. Pediatr Health, Med Therapeut 6:153
32. Batista IC, Gandolfi L, Nobrega YKM, Almeida RC, Almeida LM, Campos Junior D, Pratesi R (2012) Autism spectrum disorder and celiac disease: no evidence for a link. Arq Neuropsiquiatr 70:28–33
33. Barcia G, Posar A, Santucci M, Parmeggiani A (2008) Autism and coeliac disease. J Autism Dev Disord 38:407–408
34. Quan J, Panaccione N, King J, Underwood F, Windsor J, Coward S, Gidrewicz D, Kaplan G (2019) A257 association between celiac disease and autism spectrum disorder: a systematic review. J Can Assoc Gastroenterol 2:502–550

Publisher's Note