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Original Article

Evaluation of functional gastrointestinal disorders in children aged 4-10 years with autism spectrum disorder

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ABSTRACT

Background. Gastrointestinal system disorders are known to be prevalent among children with autism spectrum disorder (ASD). Some ASD-associated comorbidities are abdominal pain, constipation, diarrhea, gastroesophageal reflux, sleep disturbances, epilepsy, and psychiatric problems. Nonetheless, there is still limited information about the presence of functional GI disorders (FGIDs) among children with ASD, especially in Türkiye. Using the Rome criteria, we aimed to investigate FGIDs in children with ASD.

Methods. The sample of the study consisted of 68 children aged 4-10 years, diagnosed with ASD according to the DSM-5 diagnostic criteria and had scores greater than 30 on the Childhood Autism Rating Scale (CARS-2) and an age-sex matched control group (n=78). The Rome III criteria were used to evaluate FGIDs.

Results. The frequency of FGIDs in the ASD group was higher (76.5%) compared to the control group ($p<0.001$). Compared to the control group, abdominal migraine frequency increased 10 times ($p=0.012$), functional constipation 7 times ($p<0.001$), and fecal incontinence 6 times ($p<0.001$) in the ASD group. Stool retention was not present in most children in the ASD group who were found to have fecal incontinence.

Conclusion. In this study, the most common FGIDs in the ASD group were abdominal migraine, functional constipation, and non-retentive fecal incontinence. The finding that most children with ASD who had fecal incontinence did not show stool retention implicated social, psychological, and behavioral factors as the causes of incontinence. Raising awareness of healthcare professionals about the frequency of FGIDs in children with ASD will improve many areas in the daily lives of these children.

Key words: autism spectrum disorder, functional gastrointestinal disorders, constipation, abdominal migraine, fecal incontinence, stool retention.

Gastrointestinal (GI) problems are common clinical conditions in autism spectrum disorder (ASD).[1-3] These conditions are prevalent but often overlooked.[4] It is thought that GI problems that are not treated in children with ASD are associated with behavioral, psychiatric, and sleep disorders.[5,6] GI problems were noticed in children with ASD for the first time with the demonstration of nutritional disorders.[7] Children with ASD have been found to be five times more likely to display nutritional issues such as food refusal, neurodevelopmental food selectivity, and inadequate oral intake compared to healthy peers.[8-10] In subsequent studies, GI disorders have been seen very frequently in ASD patients, in line with nutritional selection.[2,10,11]

The prevalence of children with ASD who also have GI problems have been reported as 9-91%.[1-4,11,12] It has been stated that these children are more than five times as likely to

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develop GI problems as those without ASD, and the most common problems seen in children are abdominal pain, constipation, and diarrhea.[4,11] Seizures, sleep disorders, psychiatric disorders, and GI problems are considered to be the four main comorbidities in children with ASD.[12,13] It has been shown that these disorders are also related to each other and are correlated with the severity of ASD.[14-16]

It has been found that children diagnosed with ASD who also have flatulence, diarrhea, abdominal pain, and constipation are more irritable, more likely to display social withdrawal, and more hyperactive in comparison to those who do not have GI problems.[15,16] It is known that argumentative, oppositional, defiant, and destructive behaviors are more common in children with ASD who have GI problems.[6]

Studies related to functional GI disorders (FGIDs) among children diagnosed with ASD are limited in Türkiye. We aimed to evaluate the status of FGIDs in children with ASD based on the Rome criteria and raise awareness regarding this issue among healthcare professionals interacting with ASD patients.

Methods

This cross-sectional study was performed from November 2021 to March 2022 with the participation of patients followed-up in the "Pediatric Gastroenterology" and "Child and Adolescent Psychiatry" outpatient clinics at Dokuz Eylul University Hospital.

The institutional review board approved this study (E-74660883-604.01.01-148935). Parental informed consent was obtained from all patients and controls participating in the study.

Children with a diagnosis of ASD based on the diagnostic criteria of DSM-5 in the Child and Adolescent Psychiatry outpatient clinic and who scored over 30 on the Childhood Autism Rating Scale - 2nd Edition (CARS-2) were included in the study.[17] CARS consists of 15 items, and it is an instrument of behavioral rating created to distinguish between children with intellectual disabilities and children with symptoms associated with ASD. CARS allows determining the clinical severity of ASD as mild-moderate and moderate-severe. According to scoring children who score between 15 and 29.5 do not show autistic symptoms. Children who score between 30 and 36.5 points are clinically mild to moderately autistic, and those who score between 37 and 60 points are severely autistic. In our study, children with mild and moderate autism were evaluated. The children to be included in the control group were selected from among those with non-GI complaints and normal physical examination results, who presented to the general pediatrics outpatient clinic and had similar age and sex distributions.

All cases in the autism and control groups were included in the study in our pediatric gastroenterology outpatient clinic after organic pathologies related to their complaints were excluded. The sample of the study included 68 children in the ASD group and 78 in the control group, aged between 4 and 10. Data were collected by asking questions to the parents by the pediatrician (FGIDs survey questions prepared according to the Rome III criteria, the validity and reliability of which are in Turkish).[18]

Statistical analysis

The collected data were analyzed with the IBM SPSS Statistics 2010 program. The normality of the distributions of the continuous variables was examined using the Kolmogorov-Smirnov test. The categorical variables in the study are presented with frequency (n) and percentage (%) values, and the continuous variables are presented with median (IQR: 25th-75th percentile) values since parametric test assumptions were not met. The categorical variables were analyzed with Pearson's chi-square and Fisher's exact tests, and Yates's correction was performed. Since parametric test assumptions were not provided, the Mann-Whitney U test was used for the comparison of the two groups. The level of statistical significance was accepted as $p<0.05$.

Results

In the study, the children in the ASD and control groups had similar characteristics in terms of age and sex distributions. Male sex was dominant in both groups (Table I). Some of the patients were receiving risperidone, valproic acid, and zuclopenthixol treatments due to autism-related irritability (including aggression, anger, tantrums, self-harming behaviors). Additionally, there were patients receiving melatonin treatments for autism-related insomnia disorder. The frequency of FGIDs in the ASD group was 76.5%, and this was found to be significantly higher in comparison to that of the control group (39.8%) (p<0.001) (Table I). The rate of functional constipation was approximately 7 times higher in the ASD group (38.2%) when compared to that of the control group (5.1%) (p<0.001, Table I).

In the evaluation of bowel movements, it was determined that the ASD group had a stool retention behavior rate of 61.8% and a painful defecation rate of 38.2%, which were significantly higher than the rates in the control group (p=0.001).

The rates of fecal incontinence were 29.4% in the ASD group and 5.1% in the control group (p<0.001) (Table I). The behavior of stool retention was found in 60% of the children with fecal incontinence in the ASD group, and this rate was significantly higher than that in the children with fecal incontinence in the control group (p=0.002). Moreover, when the rectal examination of the cases diagnosed with fecal incontinence was performed, there was no fecal retention in the entire autism group. In the control group, this rate was 50%, but it was not evaluated statistically because the number of cases was small.

The frequency of abdominal migraine (AM) was 13.2% in the ASD group and 1.3% in the control group (p=0.012) (Table I).

There was no significant difference in the frequencies of functional dyspepsia, functional abdominal pain, irritable bowel syndrome, cyclic vomiting disorders, or reflux between the two groups. However, postprandial distress was observed in all functional dyspepsia patients with ASD (n=9). On the other hand, in the control group, this rate was 25% (n=2) (p<0.001).

Table I. Characteristics of the autism spectrum disorder (ASD) group and the control group and comparisons based on the Rome III criteria in terms of functional GIS diseases Data presented as n (%), except when indicated otherwise.

Characteristics	Control N=78	ASD N=68	p-value
Gender			
Girl	19 (24.4)	13 (19.1)	0.532
Boy	59 (75.6)	55 (80.9)	
Age (months), median (IQR)	85 (65-99)	84 (60-108)	0.769
3-7 years old	38 (48.7)	39 (57.3)	0.335
8-10 years old	40 (51.3)	29 (42.7)	
Dyspepsia	8 (10.3)	9 (13.2)	0.785
Abdominal Pain	17 (21.8)	20 (29.4)	0.412
Irritable bowel syndrome	3 (3.9)	8 (11.8)	0.141
Constipation	4 (5.1)	26 (38.2)	**<0.001**
Abdominal migraine	1 (1.3)	9 (13.2)	**0.012**
Fecal incontinence	4 (5.1)	20 (29.4)	**<0.001**
Cyclic vomiting	1 (1.3)	3 (4.4)	0.341
Reflux	8 (10.3)	13 (19.1)	0.210
All GI Disorders	31 (39.8)	52 (76.5)	**<0.001**

Discussion

The broad range of GI symptoms (9-91%) observed in children diagnosed with ASD can be attributed to the respondent characteristics (e.g., doctor, parent) and the variations in the techniques used across research to determine GI symptomatology.[1,2] Functional GI diseases are diagnosed subjectively using the Rome criteria, which provide specific standards based on symptoms. Proven and objective indicators are not available for an accurate diagnosis. A complete anamnesis and physical examination are extremely important. When necessary, comprehensive examinations should be performed, and organic causes should be excluded. Physicians should examine patients meticulously to test the presence of any potentially concerning symptoms or signs. The Rome criteria are defined as the diagnostic criteria for FGIDs. From these criteria, questionnaires adapted to the current language were created, and these questionnaires are still the gold standard in the diagnosis of FGIDs. The Rome III criteria, which have been tested for validity and reliability in Turkish, were used in this study.[2,18]

In our study, we found the frequency of FGIDs in the children with ASD to be 76.5%, which was approximately two times the frequency in the healthy control group. This information supports studies that have found the frequency of FGIDs among children diagnosed with ASD to be 3-4 times higher than those in healthy populations.[4,19,20] The medication used in the ASD group may change the outcome, however, it should not be forgotten that the disease score was stable in our study. In our study, children with mild and moderate autism (children with a CARS score of 30-36.5 points) were evaluated.

In the literature, it has been reported that the most common disorder in children with ASD is functional constipation, and it is observed in 40% of cases.[11,16,21] In our study, in the ASD group was functional constipation at a rate of 38.2%, and it was approximately 6 times more common than the rate in the control group.

In our study, in the ASD group, we found the rate of fecal incontinence to be 29.4%, and this rate was 6 times higher than that in the control group. It was determined that stool retention behavior was observed at a rate of 61.8%, and painful defecation was observed at a rate of 38.2% in the ASD group, and these rates were higher than those in the control group. This made us think that the causes of incontinence in children with ASD may be social, psychological, and behavioral.[11,21]

Furthermore, in our study, the frequency of functional abdominal pain was 29.4%, the frequency of gastroesophageal reflux was 19.1% in the ASD group, and these rates were similar to those reported in the relevant literature.[11,21]

The prevalence of AM in children has been reported to range between 0.2% and 4.1%.[22] It is most commonly seen in children aged 4–15 years. The average age at diagnosis is between 3 and 10 years, with the peak incidence at 7 years of age. Most previous studies have demonstrated that AM is more prevalent in girls than in boys, similar to cephalic migraine and other FGIDs.[23] Equal prevalence has been reported in girls and boys in a few studies.[24] Using the Rome II and III criteria, a 2008 study examined the prevalence of various FGIDs in children diagnosed with chronic, idiopathic abdominal pain.[25] When the Rome III criteria were used, the frequency of diagnosis of AM in patients with chronic abdominal pain rose from 5% to 23%. This result showed that the Rome III criteria had a higher positive predictive value (100%) and a lower negative predictive value (7.7%). According to the authors, this difference between the diagnostic values of the two sets of criteria might have resulted in an incorrect diagnosis of other functional abdominal pain disorders, such as AM.[25] There have been no new studies reported so far that looked at the prevalence and other epidemiological characteristics of AM based on Rome IV criteria released in 2016. The frequency of AM among children in Türkiye is unknown. In the study performed by Paydaş[26] in Konya, 8.12% of patients who applied to the pediatric gastroenterology outpatient clinic

with chronic abdominal pain were diagnosed with AM. Additionally, in a study conducted in a child psychiatry clinic in our country, the frequency of AM in children with autism was found to be 1%.[27] Ninety-seven children who applied to Ankara Bilkent City Hospital Child and Adolescent Psychiatry outpatient clinic and were diagnosed with ASD due to gastrointestinal symptoms were included in the study after their organic pathologies were evaluated and excluded. In the study, FGID diagnoses were made using the data of the Pediatric Functional Diagnostic Questionnaire and Gastrointestinal Disorders Parent Report Form (prepared according to QPGS-RIII-Rome III criteria) filled out by the parents.[27]

The finding in our study that the frequency of AM in the ASD group was 13.2%, ten times higher than in the control group, was novel and had not before been reported in the literature. Recent postmortem studies in ASD, the presence of minicolumnopathy and its association with both serotonergic abnormalities and a hyperexcitable cortex were demonstrated.[28] Similarities in clinical histories and laboratory test results also suggest a presumed association between autism and migraine is also suggested by similarities in clinical histories and laboratory evidence. Some commonalities include the presence of neuroinflammation, sensory overstimulation (e.g., flickering of fluorescent lights), "food allergies," benefits from similar diets, and the role of nitric oxide.[28]

In our study, although the frequency of functional dyspepsia did not increase in children with ASD, the presence of postprandial distress syndrome in these children is noteworthy. Even though the pathophysiology of postprandial distress syndrome is not clear, gastric electrical rhythm abnormalities, delayed gastric emptying, poor gastric expansion response to feeding, and antroduodenal dysmotility are thought to be the causes. This finding suggests that these symptoms may develop due to autonomic nervous system disorders in children with ASD.

In studies, a clear and convincing link between autism and GI disorders has not yet been found. Intestinal permeability, dysbiosis, immune reactivity, GIS neurotransmitters, and genetic factors have been put forward as the cause. Changes in the gut-brain axis are thought to show a two-way interaction.[21,29,30]

It has been suggested that the absorption of poorly digested food particles or certain toxins as a result of increased intestinal permeability triggers the secretion of antibodies, resulting in inflammatory response and subsequently facilitating the development of dysbiosis by causing a drop in immunoglobulin levels.[21,29,30]

The knowledge that GI symptoms in ASD are associated with multiple pathways of the gut-brain axis has been associated with the autonomic nervous system, which affects parasympathetic activity (abnormal dynamics of neurohormones including GABA and serotonin) and sensitivity to stress, as well as the microbial and immune components.[21]

In addition, several links were found between the genetic abnormalities described in autistic cases and GI comorbidities that could explain the clinical findings. In studies, nucleotide polymorphisms of c-Met proto-oncogene encoding MET receptor tyrosine kinase, *CHD8* mutation, 5-HT transporter (SERT) gene (*SLC6A4*) variants causing serotonin elevation phenotype subtype have been reported in all cases in a subgroup of individuals diagnosed with ASD who also have additional GI disorders.[31,32]

Evidence presented by numerous studies has revealed that GI dysfunctions are particularly important and the presence of several abnormalities, including parasympathetic activity dysfunctions and elevated endocrine stress response along the nerve connections between the gut and the central nervous system. As a result, the most frequently encountered GI abnormalities, including gastroesophageal reflux, constipation, abdominal pain, diarrhea, and food selectivity are likely to be associated

with typical symptoms such as stereotypy, repetitive and ritualistic behaviors, and social withdrawal.[1,21,33,34]

It is important to note that untreated GI disorders in children with ASD have a bidirectional relationship with many problems such as sleep, behavioral, and psychiatric disorders.[1] GI problems negatively affect the quality of life, social adaptation, and treatment of children with ASD. It is thought that ASD severity and GI problems are related. It has been argued that there is a strong relationship between GI problems and psychiatric disorders such as anxiety, social withdrawal, regression in verbal abilities, and sleep problems in ASD.[1,2]

Psychiatric disorders occur in 70% of children with ASD. Anxiety is the most common diagnosed psychiatric disorder associated with ASD, while other common disorders include attention deficit/hyperactivity disorder (ADHD) and oppositional defiant disorder.[13] Anxiety is closely linked to chronic GIS problems in children with ASD.[15] As such, functional GIS disorders in children with ASD are among the comorbidities that do not vary significantly after the age of four, along with schizophrenia, epilepsy, and sleep disorders.[20] Our study was limited in this sense; by including children with mild and moderate autism, a diagnostic correlation with FGIDs could not be made across a wide range of disease severity. In the future, the correlation between CARS scores and comorbid psychiatric disorders of children with ASD diagnosed with FGIDs can be investigated.

Consequently, in our study, the rate of functional GIS disorders in children diagnosed with ASD was 76.5%. The most frequently identified conditions were functional constipation, AM, and non-retentive fecal incontinence. The finding in this study that the majority of the children with ASD who had fecal incontinence did not show fecal retention indicated that the causes of incontinence are social, psychological, and behavioral. It should not be forgotten that increasing awareness about the recognition of functional GIS disorders in children with ASD is important for the improvement of behavioral findings as well as improving many parameters in the daily lives of these children.

Ethical approval

The local ethics committee of Dokuz Eylul University approved the study (Number: E-74660883-604.01.01-148935, Date: November 29 th 2021). Parental informed consent was obtained from all patients and controls participating in the study.

Author contribution

The authors confirm contribution to the paper as follows: Study conception and design: YÖ; data collection: ÖGA, KA, GŞ, YG, SK; analysis and interpretation of results: ÖGA, YÖ; draft manuscript preparation: ÖGA, YÖ. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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