Gastrointestinal disturbances in patients with autistic spectrum disorders

Problemy gastroenterologiczne pacjentów z zaburzeniami ze spektrum autyzmu

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ABSTRACT

Gastrointestinal problems occur in patients with Autistic Spectrum Disorders (ASD) more often than in their peers without developmental problems. The most prevalent include abdominal pain, impaired peristaltic reflexes and eating disorders. The study objective was to determine the incidence of gastrointestinal disorders in ASD children with gastrointestinal complaints. **Methods:** 30 patients with ASD suffering from gastrointestinal complaints were analyzed. **Results:** All the children had upper gastrointestinal tract endoscopy and four of them colonoscopy. The nutritional condition was normal in 60% of them, 17% displayed malnutrition and 23% were overweight. Chronic abdominal pain was observed in 80% of patients. Impairment in peristaltic reflexes was noted in almost all autistic children. Histopathology of the duodenum revealed changes in 70% of cases. Colitis chronica indeterminata was recognized in all examined children. **Conclusions:** Autistic children with gastrointestinal disturbances should be looked after also by a gastroenterologist. Higher incidence of gastrointestinal pathologies in ASD may have influence on the behavioral patterns of these sufferers.

Key words: Autistic Spectrum Disorders, chronic abdominal pain, chronic inflammation of duodenum, colitis chronica indeterminata.

STRESZCZENIE

Problemy gastroeneterologiczne dzieci z zaburzeniami spektrum autyzmu (ASD) występują częściej niż u ich rówieśników. Do najczęstszych należą bóle brzucha, zaburzenia motoryki w obrębie przewodu pokarmowego, problemy żywieniowe. Celem badania było określenie częstości występowania schorzeń gastroenterologicznych u pacjentów ASD zgłaszających dolegliwości ze strony przewodu pokarmowego. **Pacjenci i metoda:** przeanalizowano 30 pacjentów ze zdiagnozowanymi zaburzeniami ze spektrum zaburzeń autystycznych u których występowały istotne dolegliwości gastroenterologiczne. **Wyniki**: U wszystkich badanych pacjentów stwierdzono wskazania do endoskopii górnego odcinka przewodu pokarmowego, ponadto u czterech z nich do kolonoskopii. U 60% stwierdzono prawidłowy stopień odżywienia, 17% pacjentów z grupy badanej było niedożywionych, natomiast 23% z nadwagą lub otyłych. Przewlekłe bóle brzucha obserwowano u 80 % z nich. U prawie wszystkich pacjentów z zaburzeniami autystycznymi stwierdzono zaburzenia motoryki w obrębie przewodu pokarmowego. U 70 % pacjentów badanie histopatologiczne wycinka błony śluzowej dwunastnicy uwidoczniło zmiany zapalne, natomiast u dzieci, u których wykonano kolonoskopię, badanie histopatologiczne wykazało nieswoiste zapalenie jelita grubego. **Wnioski**: Pacjenci z ASD, u których występują dolegliwości ze strony przewodu pokarmowego, powinni być konsultowani gastroenterologicznie. Występowanie zaburzeń gastroenterologicznych może predysponować do nasilania zaburzeń zachowania.

Słowa kluczowe: zaburzenia spektrum autyzmu, przewlekłe bóle brzucha, przewlekłe zapalenie dwunastnicy, nieswoiste zapalenie jelita grubego.

According to ICD – 10 Autism belongs to a group of pervasive developmental disorders. Symptoms occur before 3 years of age and consist of abnormal function in three spheres of development: social interaction, communication behavioral patterns, and interests. If abnormal and/or impaired development is exhibited past the age of 3yrs, and/or if symptoms concerning one or two of the areas necessary to recognize infantile autism are missing, Atypical Autism is diagnosed. Both Infantile Autism (IA) and Atypical Autism (AA) are referred to as Autistic Spectrum Disorders (ASDs). The range of disabilities seen among children in ASD is considerable. ASDs do not have any etiological factor in common. A hereditary basis is supported in many cases by a high concordance in monozygotic twins, a broader autistic phenotype in the families of probands and association with a number of genetic disorders. In ASDs patients abnormal levels of neurotransmitters have been observed, including gamma-aminobutyric acid, opiates, glutamine acid and cat-

echolamines. The concept of disorders in serotonergic transmission is the most prevalent and best investigated; platelet hyperserotonemia has been detected in 25-60% of autistic children [1].

The incidence is estimated at 7 per 10,000 children, and 20 per 10,000 for Atypical Autism [2]. According to The USA Department of Health and Human Services Centers for Disease Control and Prevention the average ASD prevalence was about 1 in 150 children in some communities [3].

Besides the main abnormalities, autistic children display numerous neurophysiological disorders – in reception of sensoric stimuli, motor activity planning, and circadian rhythm regulation. Over the last years attention has been paid to the higher incidence of gastrointestinal problems in autistic children compared to that of the healthy child population. The most prevalent include abdominal pain, impaired peristaltic reflexes and eating disorders [4–9].

The Study Objective was to determine the incidence of gastrointestinal disorders in ASD children with gastrointestinal complaints and undertake to link them with pathology observed in endoscopic examinations.

PATIENTS AND METHOD

During last 6 years we hospitalized 30 patients: typical autism (17 children) or autistic features (13 children), all suffering from gastrointestinal complaints such as abdominal pain, impaired peristaltic reflexes and/or bleeding; 4 of the children had already had surgical intervention for alimentary tract problems.

The patients were aged 3yrs up to 13yrs (mean: 7 years 6 months); there were 12 girls (40%) and 18 boys (60%). In the children, subject to the study, infections were excluded, (based on physical examination and biochemical parameters of inflammatory conditions), and so were organic changes within the abdominal cavity (ultrasound). Their physical development was assessed according to Cole's index. Diagnostic immunological tests for the presence of celiac disease were performed (EmA and tTG) in IgA class, or IgG class in the case of IgA deficiency. The children with atopic dermatitis underwent tests for the presence of food allergy (via interview, total IgE, specific IgE).

All the children had upper GI tract endoscopy performed, and 4 of them in addition to that, colonoscopy. Histological evaluation of all the bioptates was performed by the same histopathologist. At the time of the investigations 4 children were partaking in a low gluten and milk-free diet.

RESULTS

The nutritional condition was normal in 18 (60%) of the studied children; 5 (17%) displayed malnutrition and 7 (23%) were overweight. Chronic abdominal pain was observed in 24 (80%) patients and was most frequently located intra-abdominally. Impairment in peristaltic reflexes was noted in 29 (97%) of the autistic children diagnosed in our hospital - in 17 (57%) cases it took the form of diarrhea and 20 (67%) suffered from constipation; some had alternating bouts of diarrhea and constipation. Vomiting and/or regurgitation were reported by 10 (33%) parents of the children. Bleeding episodes from the gastrointestinal system were reported by parents in 6 (20%) cases: 2 from the upper and the remaining 4 from the lower GI tract (none of the children was brought to hospital as an emergency). In 23 (77%) cases occurred sudden irritability episodes, in 19 (63%) eating disorders, and in 12 (40%) cases children refused to eat for several days. Moreover, 4 children had previously undergone surgical procedures affecting the alimentary tract: 2 had had a surgical anti-reflux procedure, 1 a procedure due to Hirschsprung's disease, and 1 owing to a relapse of the rectal mucosa.

The medical histories of 14 (47%) children revealed symptoms of atopic dermatitis, at the time of the study this was observed in 11 (37%) patients. Five children manifested elevated concentrations of total serum IgE (121 – 2000 IU/ml) and 4 the presence of specific IgE antibodies (in 2 cases against cow's milk protein, 2 against soya protein and 1 against egg protein). The presence of auto-immunological disorders was noted in the family histories of 7 patients.

It was only in one case that an immunological test for celiac disease showed elevated tTG levels with negative endomysial antibodies and an abnormal histological picture of the duodenal mucosa (chronic duodenitis with a moderate degree of lymphocytic and plasmatic inflammatory infiltration in lamina propria, accompanied by normal architectonics of intestinal villi and Marsh's index at 12/100).

As many as 10 (33%) patients in turn were found to have IgA deficiency. In no child did we find a pathological condition of the liver or pancreas.

Endoscopic examinations of the upper GI tract revealed macroscopic changes in the form of mucosal reddening in the lower esophagus of 4 (13%) children, LA erosion type A (7-8 mm) in 1 child, inflammation within the lowest third of the esophagus with the presence of numerous "scutes" in yet another child; in 1 patient incompetence of the cardiac orifice was observed. However, with the exception of two cases where eosinophil infiltration was detected, the outcomes of histological tests of taken bioptates were normal.

Four 4 (13%) children with a confirmed Helicobacter Pylori infection exhibited nodules of the mucous membrane in the antrum of the stomach. In 2 patients irregular mucosal reddening was discovered in the same area; yet another patient displayed histopathological features of chronic superficial inflammation. In none of the studied children did macroscopic examination of the descending duodenum reveal any changes. However, in 21 (70%) cases microscopic histopathological changes were found in the form of chronic inflammation of the mucous membrane. This number includes 12 (40%) cases of mild eosinophilic infiltration (Grade 0 according to the scale of Whitington), 2 cases of lymphocytic and plasmatic infiltration, and 1 of eosinophilic duodenitis (Whitington Grade III) with no features of villous atrophy.

Slight disorders in the architectonics of the villi, in the form of their bases being wider were observed in 3 patients. Chronic inflammation of the mucous membrane with an

increased number of intraepithelial lymphocytes was recognized in bioptates of 5 (17%) children. Two patients presented 40/100 enterocytes with normal architectonics of the villi and heights of the crypts (Marsh I); 4 children with pain in the hypogastrium, 2 of whom with bleeding underwent colonoscopy. In a macroscopic assessment 1 patient displayed decreased vascular markings; histologically, however, mild colitis chronica indeterminata was recognized in all of the children.

DISCUSSION

Gastrointestinal complaints constitute one of the most common conditions of the developmental period of , so called, a healthy child. Abdominal pain is annually reported even by 44% of children; on a weekly basis it is a problem of 17% [10]. Around 50% of the number complained about a chronic character of the ailment. Chronic functional abdominal pain is noted in 20-25%. According to Campo et al. 80% of the developmental age patients with chronic functional abdominal pain are found to have neurotic disorders, whereas 43% suffer from depression [11].

Over the last years researchers have focused on a greater incidence of GI tract pathologies in children with developmental problems, mainly from the group of Autistic Spectrum Disorders (ASDs), compared to the population of healthy children. Some autistic children may display features of hyperactivity, concentration difficulty, affective disorders, sleeping disorders including nighttime awakening, sudden irritability episodes, anxiety, aggression, anorexic reactions and, finally, eating disorders which are commonly but erroneously treated as a component of autistic syndrome. According to the already conducted observations and studies all these disorders may mask the discomfort of an autistic child. Because of disturbances and difficulties in verbal communication with this type of patient, gastrointestinal symptoms can remain unrecognized and may, in turn, exacerbate behavioral disorders. The vast majority of the patients (80%) suffer from chronic abdominal pain. Only a few of them are able to report the complaint spontaneously, in most cases the information is gained by the parents when observing the child.

In our study eating disorders were reported by 63% of the parents; 1/3 of the patients refused to take food over several days. The literature suggests that feeding problems concern as many as 46–89 % families with autistic children. A number of reasons have been suggested for the prevalence of nutritional problems in patients with ASD. When we think about fear of novelty, sensory impairments or concentration on detail, we cannot forget about biological food intolerance [12,13]. In most cases patients select food on their own, which may result in conditions of deficiency. Despite possible difficulties, physical development of most studied children was normal and malnutrition was observed less frequently than a tendency for overweight or obesity.

Problems of the digestive system were demonstrated by all the studied children and were the indication that the tests should be performed. Almost all the children (96%) were found to suffer from impaired peristaltic reflexes, a disorder manifested by regurgitation/vomiting, diarrhea, constipation, or these symptoms occurring alternately. In 1/3 of the patients disorders had the form of regurgitation and vomiting, suggesting gastro-esophageal reflux. Since the patients could not co-operate the incidence of these conditions was not assessed by means of pH-metry. Endoscopic examinations, in turn, revealed macroscopic features of esophagitis in 6 (20%) children. Histological tests did not confirm this pathology; however, medical histories show that 2 (7%) children had undergone an antireflux procedure in their infancy, and in their cases endoscopy did not reveal any changes. In studies by other authors gastro-esophageal reflux was detected more frequently (Howard et al) [3]. Macroscopic changes of the gastric mucosa were discovered in 6 (20%) children; in 4 of these cases Helicobacter Pylori infection was recognized (which corresponds with the population frequency) and in a further 2 we only observed irregular mucosal reddening of the antrum (1 of these patients: presenting single petechiae, chronic superficial gastritis was histologically recognized).

Endoscopy did not detect macroscopic changes in the duodenum, yet in 21 (70%) patients chronic inflammation of the duodenal mucosa was found in histological tests. Twelve 12 (40%) children were diagnosed with chronic duodenitis with eosinophil infiltration assessed as Grade 0 according to the scale of Whitington, but possibly suggesting food allergy. Eosinophilic duodenitis was recognized in 1 patient. The parents of 18 (60%) children reported symptoms of food allergy, and 11 (37%) patients presented features of atopic dermatitis when in hospital, in 1 case accompanied by pollen allergy. High total serum IgE concentrations found in 5 (17%) children may indicate IgE-dependent allergy. Trajkovski et al. has found significantly higher levels of total IgE, and also specific IgE, IgG and IgM antibodies to food antigens in ASD patients [14]. Such a high incidence of food allergy may be connected with total IgA deficiency: noted in our study and known to occur in autistic children much more often than in the rest of the population [15]. According to Ming et al. in ASD patient's food intolerance is markedly associated with gastrointestinal dysfunction [16].

Although thus far the collected evidence does not attest the connection between autism and celiac disease, in view of increasingly frequent occurrences of oligosymptomatic, atypical or latent forms of the latter, we conducted all the diagnostic tests necessary for its recognition both immunological and histological ones. The presence of anti-tTG IgA antibodies was only noted in one girl with normal architectonics of intestinal villi and slightly elevated number of intraepithelial lymphocytes. A latent form of celiac disease can be considered in her case; consequently, systematic observation for this disease is recommended. Increased numbers of intraepithelial lymphocytes that are not joined with the immunological indicators of celiac disease, a condition found in 16% of the patients, may suggest a different type of pathology within the intestines.

Disorders of the lower GI tract manifested by pain in this area or constipation were observed in 2/3 of the studied group. Generally, constipation is a common problem of the

developmental period. The literature on autistic children suggests that this condition is found in about 30–40%; in the observed group, though, it was noted in 57% of the children [9]. This may be affected by appetite problems, eating disorders, and pathology of the alimentary tract resulting from disorders in both the digestive and nervous systems. Nonetheless, in autistic children constipation may lead to a relapse of the rectal mucosa more frequently than in their non-autistic peers [8]. One of our patients was diagnosed as having a rectal prolapse demanding surgical intervention.

The colonoscopy performed in 4 children revealed the presence of non-specific chronic inflammation of the mucous membrane. When carrying out endoscopic examinations of the lower digestive system in children displaying developmental disorders, also autism, Wakefield et al. recognized various inflammatory conditions referred to as *enterocolitis autistica* in nearly all the patients enrolled in their study. The presence of chronic entorocolitis in autistic children is also indirectly proved in the observation by Anthony et al., who found increased excretion of calprotectin in feces [17]. This observation was demanded by Fernell et al. – the use of two markers of inflammatory reactions in the gut (i.e. rectal NO and fecal calprotectin) were not able to disclose a link between ASD and active intestinal inflammation [18].

The frequency of gastrointestinal bleeding in autistic children seems to be slightly higher than in the population at large. In our research episodes of bleeding were observed in 6 (20%) children, primarily from the lower alimentary tract. As the children were not hospitalized as a result, the causes remain unknown; whether they were caused by constipation or inflammation requires further investigation.

Hypothetical pathogenesis of autism allows for some other functional disorders of the digestive system: increased intestinal barrier permeability, intestinal dysbacteriosis, disaccharide intolerance observed in 58% autistic patients studied by Horwath et al., and a role of opioid peptides obtained from incompletely decomposed proteins (mainly gliadmorphine and bovine caseomorphine) [4,6,19,20]. This last hypothesis is the reason for introducing elimination diets, mainly deprived of gluten and milk, after which in some cases we could observe improved communication with a child. Knivsberg et al. have done a single blind study of dietary intervention in ASD: they proved a positive effect of gluten and casein free diets (10 patients, 1 year of observation) [21]. However, in our studied group the parents of 4 (13%) children applied only a low gluten and milk-free diet, which still, in their opinion, resulted in improved contact. Unfortunately, up till now there have not been great randomized studies` and the effectiveness of such treatment is not proven [22].

What should also be taken into consideration is the impact of immunological disorders on the function of the digestive system in autistic children. The literature provides descriptions of disorders in cell immunity (depression of CD4 cells, anti-CD2+ and BCD20+ T-cells decline) and humoral immunity (increase in INF gamma, IL-1, IL-6, TNF alfa). Jyonouchi et al. discovered a correlation between primary immunological disorders within the intestinal mucosa of autistic patients and gastrointestinal symptoms with regard to autistic patients who did not report such complaints [23]. The findings of their research indicate also the presence of non-allergic hypersensitivity in the first group of patients [24]. Immune aberrations consistent with a dysregulated immune response and gastrointestinal *dysmotility* in ASD patients could result in microbiological gut dysbiosis [25].

IgA deficiency has also been detected: Wakefield et al. observed it in 25% of their study subjects and in our research it was present in almost one third of the group. Besides, other auto-immunological problems, such as the presence of antibodies against neuronal cells, neurophilaments, Purkinje cells, serotonin receptors, and endothelial cells, may cause damage to the brain and intestines, both directly and as a result of systemic disorders. What is also taken into account in ASD is the dysfunction of the gut-brain axis [17,26-29]. Perhaps in autistic children, disorders of the immunological etiology may influence the function of the gut-brain axis; this prognostication is open to further research. Additionally, according to Valicenti–McDermott et al an association between children with ASDs and language regression, a family history of autoimmune disease and gastrointestinal symptoms was observed [30,31].

The presence of auto-antibodies against serotonin receptors discovered in autistic children is a particularly interesting phenomenon, the more so as serotonin is one of the transmitters common to the central nervous system, enteric nervous system, endocrine system and immune system. Serotonin plays an important role in mediating visceral sensation and homeostasis in the processes of sensation, motor activity and excretory function. The roles of serotonin receptors types 3 and 4 ($5HT_3$ and $5HT_4$) present in visceral neurons, are also essential [32]. Serotonin constitutes the main transmitter of the sensation of pain, also visceral pain, and serotonergic drugs may be applied in the treatment of irritable bowel syndrome.

Ming et al. in their analysis group of 160 patients with ASD found strong associations between gastrointestinal dysfunction and food intolerance; sleep disorders and gastrointestinal dysfunction, and sleep disorders and mood disorder. Regarding their and our results there is a question - if one concurrent disorder may be responsible for the other or do they stem from a common pathology? [16].

There is a consensus report on evaluation, diagnosis and treatment of gastrointestinal disorders in individuals with ASDs, and up till now, standard of care in the diagnostic workup and treatment of gastrointestinal concerns should be given as for patients without ASDs [31].

CONCLUSIONS

1. Higher incidence of gastrointestinal pathologies in autistic children may influence disorders of behavioral patterns.
2. Autistic children should also be looked after by a gastroenterologist.

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