

Gastrointestinal abnormalities in children with autistic disorder

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Objectives: Our aim was to evaluate the structure and function of the upper gastrointestinal tract in a group of patients with autism who had gastrointestinal symptoms.

Study design: Thirty-six children (age: 5.7 ± 2 years, mean \pm SD) with autistic disorder underwent upper gastrointestinal endoscopy with biopsies, intestinal and pancreatic enzyme analyses, and bacterial and fungal cultures. The most frequent gastrointestinal complaints were chronic diarrhea, gaseousness, and abdominal discomfort and distension.

Results: Histologic examination in these 36 children revealed grade I or II reflux esophagitis in 25 (69.4%), chronic gastritis in 15, and chronic duodenitis in 24. The number of Paneth's cells in the duodenal crypts was significantly elevated in autistic children compared with non-autistic control subjects. Low intestinal carbohydrate digestive enzyme activity was reported in 21 children (58.3%), although there was no abnormality found in pancreatic function. Seventy-five percent of the autistic children (27/36) had an increased pancreatico-biliary fluid output after intravenous secretin administration. Nineteen of the 21 patients with diarrhea had significantly higher fluid output than those without diarrhea.

Conclusions: Unrecognized gastrointestinal disorders, especially reflux esophagitis and disaccharide malabsorption, may contribute to the behavioral problems of the non-verbal autistic patients. The observed increase in pancreatico-biliary secretion after secretin infusion suggests an upregulation of secretin receptors in the pancreas and liver. Further studies are required to determine the possible association between the brain and gastrointestinal dysfunctions in children with autistic disorder. (*J Pediatr* 1999;135:559-63)

Autistic disorder belongs to the group of pervasive developmental disorders as defined by both the American (*Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*)¹ and international (*International Classification of Diseases, Ninth Revision*) diagnostic systems. Autistic disorder implies severity of disturbance in multiple areas of development reflected in a marked lack of development of social interaction and communication; restricted, repetitive, and stereotyped patterns; and typical prelinguistic communicative behaviors. In addition to the abnormalities in communication and language skills, these children frequently have aggressive and self-injurious behaviors. Sudden unexplained irritability or aggressive behavior, nighttime awakening, and pushing on the abdomen are usually considered part of the behavioral problems associated with autism.

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Many parents report gastrointestinal symptoms in their autistic child; however, until recently, gastrointestinal symptoms of these children received little attention. In 1996, D'Eufemia et al² reported increased intestinal permeability in 9 of 21 (43%) patients with autistic disorder. The report of Wakefield et al³ represents the first effort to evaluate the gastrointestinal tract in children with autism. In a recent case report we described 3 chil-

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dren with autistic spectrum disorder and chronic diarrhea who had an increased pancreatico-biliary secretory response after secretin injection, suggesting that gastrointestinal dysfunction might be associated with this pervasive developmental disorder.⁴

This report describes several gastrointestinal abnormalities in low-functioning autistic children and underlines the importance of comprehensive gastrointestinal evaluations.

PATIENTS AND METHODS

Children diagnosed with autistic disorder or pervasive developmental disorder, not otherwise specified by professionals with expertise in behavioral pediatrics were referred to our gastroenterology clinic for further evaluation.

Thirty-six children with one or more of the following symptoms including abdominal pain ($n = 25$), chronic diarrhea ($n = 21$), gaseousness/bloating ($n = 21$), nighttime awakening ($n = 15$), and unexplained irritability ($n = 18$) underwent esophagogastroduodenoscopy. The mean age of these patients was 5.7 years (5.7 ± 2 years, mean \pm SD; range, 2.5-10 years; 33 boys).

Their medical history revealed that 64% of these children were breast-fed for an average of 6.7 months, 36% had a history of cow's milk and/or soy protein intolerance, and 44.4% had allergy to foods according to the parents and care givers interviewed at the outpatient clinic. Seventeen (47.2%) children were on a casein-free and/or gluten-free diet at the time of evaluation.

Clinical Investigations

Patients fasted after midnight, and the procedures were performed the next morning with patients under general anesthesia. The full upper gastrointestinal workup included esophageal, gastric, and duodenal biopsies for his-

tology, measurement of the digestive enzymes of the small intestine (lactase, maltase, sucrase, palatinase, glucoamylase) and pancreas (lipase, amylase, trypsin, chymotrypsin, and carboxypeptidases A and B), and bacterial and fungal cultures. The normal values for intestinal enzymes were based on the measurements on 104 histologically normal intestinal biopsy tissues. The normal values for pancreatic enzymes were established by measurement on 215 specimens collected from children. Antibiotic and antifungal therapies were discontinued a week before the endoscopy to allow culture of the duodenal fluid. All fluids for cultures were obtained before pancreatic stimulation to avoid the dilution of juice resulting in falsely low quantitative counts. The pancreatic enzyme activities were measured from specimens collected before and after secretin stimulation.

For the collection of pancreatic juice, we stimulated the fluid secretion with secretin (Ferring Laboratories, Inc, Suffern, NY), 2 cat units (CU)/kg body weight, given intravenously within 1 minute. The pancreatico-biliary juice was collected after positioning the endoscope distal to the ampulla of Vater, and the fluid was collected by moving the tip into the outcoming fluid and suctioning it into a collector trap. In a few cases an endoscopic retrograde cholangiopancreatography catheter was placed into the channel of the endoscope, and fluid was suctioned into a syringe.

A basal sample was collected in the duodenum around the Vater papilla before the secretin injection and was sent for enzyme analysis and bacterial and fungal cultures. Three additional specimens were collected after the secretin injection within a 5- to 10-minute period. The pancreatic enzyme activities were measured in all collected aliquots. The volume of secreted fluid after secretin administration was measured and recorded in milliliters per minute. The normal fluid output was based on the data from 26 non-autistic patients who underwent the

same procedure. The duodenal biopsy specimens were obtained after the fluid collections to avoid blood contamination. Endoscopic grading of esophagitis was based on the description of Leape et al⁵ for pediatric patients.

Histology

The histologic grading of esophagitis followed the scores described by the Working Group on Gastro-Oesophageal Reflux Disease of the European Society of Paediatric Gastroenterology and Nutrition.⁶ The histologic criteria for reflux esophagitis included eosinophilic and/or polymorphonuclear infiltrate, basal layer thickening, and papillary hypertrophy.

Gastric biopsy specimens were stained with Giemsa stain to determine the presence of *Helicobacter pylori* infection.

The histology slides were examined by surgical pathologists and were further reviewed by 3 authors (J.P., C.D., and K.H.) in an observer-blinded fashion. In the intestinal specimens, the number of intraepithelial lymphocytes, lamina propria cell density, villus/crypt ratio, and mitoses in crypts were assessed. The number of Paneth's cells per crypt was counted in all 36 patients with autism and compared with 22 biopsy specimens from non-autistic pediatric patients (12 immunocompetent and 10 immunodeficient) who underwent endoscopy because of failure to thrive, chronic diarrhea, or suspected celiac disease.

Ethical Approval and Consent

The project for the examination of the effect of secretin injection was approved by the Internal Review Board of University of Maryland School of Medicine. Informed written consent was obtained from each parent before endoscopy and secretin infusion.

Statistical Analysis

Data were expressed as mean \pm SD. In all comparisons between groups the Student *t* test was used, and a *P* value of $<.05$ was considered significant.

was a statistically significant difference between patients with diarrhea ($n = 21$) and those without diarrhea ($n = 15$) (4.8 ± 2.3 mL/min vs 2.4 ± 1.3 mL/min; $P < .05$). An important clinical observation was that autistic children with chronic diarrhea showing the high fluid response with secretin had an improved stool consistency after the procedure, and it lasted for a few weeks or was sustained.

Duodenal Fluid Culture

There was no evidence of either fungal or bacterial overgrowth in the duodenum, even in those 12 patients who, on the basis of urine organic acid test results, were suspected of having such overgrowth.

DISCUSSION

Few studies have addressed gastrointestinal problems in children with autistic disorder. Goodwin et al⁷ studied 15 randomly selected children with autism and found that 6 had either bulky, odorous, or loose stools or intermittent diarrhea; one had celiac disease. In a recent study, 43% of the autistic patients without symptoms or evidence of any gastrointestinal disease had altered intestinal permeability.² Low concentrations of serum α_1 -antitrypsin were reported in children with typical autism,⁸ a finding that is indicative of intestinal protein loss. In a recent case report we presented gastrointestinal and behavioral observations on 3 children with autistic spectrum disorder.⁴

Although gastrointestinal symptoms frequently accompany the manifestations of autism, little attention has been paid to this aspect of this developmental behavioral disorder, and a gastrointestinal workup has not been part of the regular medical evaluations. Sudden unexplained irritability or aggressive behavior, mood change, discomfort, and nighttime awakenings in these children were considered to be part of the brain dysfunction and not manifesta-

tions of organic problems. A significant percentage of children with autistic disorder are reported to be low functioning and have only prelinguistic communicative behavior. A plausible reason for the paucity of gastrointestinal evaluation of these children may be their inability to verbalize and describe their abdominal pain or discomfort and a lack of cooperation in non-invasive studies, such as breath tests.

The upper gastrointestinal evaluations of children with autistic disorder support the presence of a chronic inflammatory process in the gut, as reported by Wakefield et al.³ They performed colonoscopy with histologic examinations in 12 children and reported that all had intestinal abnormalities, ranging from lymphoid nodular hyperplasia to aphthoid ulceration.³ In our study chronic inflammation of the esophagus, stomach, and duodenum was the major and most consistent finding.

The most frequently detected abnormalities in children with autistic disorder included a high prevalence of reflux esophagitis, hyperplasia of duodenal Paneth's cells, intestinal carbohydrate digestive enzyme deficiencies, and an unusual hypersecretory response to intravenous secretin administration.

A significant portion (25/36) of autistic children had gastroesophageal reflux and reflux esophagitis. There are no age-related data on the prevalence of gastroesophageal reflux disease in the 2.5- to 10-year-old group. The prevalence of reflux esophagitis is low (estimated 2%) in Western countries.⁹ It is known that both neural and humoral factors can have an effect on the lower esophageal sphincter. People under stress are more likely to have dysmotility and reflux. It is known that secretin has a suppressive effect on gastric secretion.¹⁰ Whether a low secretin level may contribute to the high prevalence of acidic reflux in these children warrants further investigation.

An elevation in the number of Paneth's cells was found in most of the studied patients. Reportedly, the aver-

age count of Paneth's cells in the crypts is about 5%, and there is no significant difference in the number of these cells between the healthy and inflamed duodenum¹¹ or in celiac disease.¹² Scott and Brandtzaeg¹² reported that the average number of Paneth's cells in healthy control subjects was 2 per crypt, which is similar to that of our control subjects. We observed an ~50% increase in the number of these cells in patients with autistic disorder. In normal crypt base cross-sections, the size of Paneth's cells is similar to that of the surrounding cells, and they are smaller than the goblet cells. Many patients with autistic disorder had enlarged Paneth's cells filled with huge granules. Hypertrophy and hyperplasia of the Paneth's cells have been reported in hamsters after ligation of pancreatic ducts,¹³ and a varying degree of increase in the number of Paneth's cells was described in patients with chronic pancreatitis.¹⁴ It is thought that absence of pancreatic fluid favors the multiplication of Paneth's cells. We did not find evidence of pancreatic insufficiency in our patients. However, the high secretory response to secretin might suggest the absence of regular secretin stimulation of the pancreas and biliary tract. There are no data available regarding the effect of secretin or cholecystokinin on Paneth's cells or local immune defense of the intestine. Studies indicate that Paneth's cells produce and release substances such as lysozyme, defensins,¹⁵ and α_1 -antitrypsin.¹⁶ The human intestinal defensin 5 (HD-5) has antimicrobial activities against bacteria and *Candida albicans*.¹⁷ Paneth's cell metaplasia is a typical finding in inflammatory bowel diseases involving the colon.¹⁸ Transmission electron microscopic studies in tissues from patients with Crohn's disease showed that Paneth's cells were increased in number and showed both focal granule extrusion and cytoplasmic lysosomal inclusions.¹⁹ Our studies revealed similar findings, including a greater

number of Paneth's cells and increased granule discharge into the lumen of crypts. However, although the presence of Paneth's cells represents a metaplastic change in Crohn's disease, these cells are normally present in the duodenum. The importance of this Paneth's cell activation in patients with autistic disorder is not known and warrants further investigation.

Children with autistic disorder frequently have loose, extremely foul-smelling stools and gaseousness. These symptoms are not associated with growth failure and cannot be explained by the limited diet preference of these children. In most of the cases, results of the routine stool tests are negative. Typically, parents claim that the gastrointestinal and behavioral symptoms are manifested in parallel. Our study showed that 58% of the examined children had disaccharidase/glucoamylase enzyme activities below the normal range. Carbohydrate malabsorption may result in gaseousness with crampy abdominal pain and may be the cause of chronic loose stools. The most frequent finding was a low lactase activity in 14 of the 21 children with pathologic disaccharidase results.

Children with autistic disorder and chronic diarrhea had a higher pancreatico-biliary fluid output after secretin stimulation. This high secretory response to secretin administration may indicate an upregulation of the secretin receptors in the ductal cells of the pancreas or in the bile-duct epithelium. In turn, this may occur in the absence of normal secretin stimulation, which can be the consequence of either a defect in secretin production or a problem of release from the intestinal S cells.

In summary, our findings suggest that gastrointestinal abnormalities may contribute to some of the behavioral problems frequently described in these children. 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. The diarrhea and gaseousness may be the consequence of decreased disaccharidase activity and may also contribute to the behavioral problems.

Our results suggest a possible upregulation of secretin receptors in the pancreas and the biliary tract and a high prevalence of reflux esophagitis and chronic duodenitis associated with Paneth's cell hyperplasia in a group of children with autistic disorder who have various gastrointestinal symptoms. Further gastrointestinal studies of children with autistic disorder may contribute to a better understanding of the etiology of this disorder.

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