Autistic disorder and gastrointestinal disease

Karoly Horvath, MD, PhD,* and Jay A. Perman, MD†

Autistic disorder is a pervasive developmental disorder manifested in the first 3 years of life by dysfunction in social interaction and communication. Many efforts have been made to explore the biologic basis of this disorder, but the etiology remains unknown. Recent publications describing upper gastrointestinal abnormalities and ileocolitis have focused attention on gastrointestinal function and morphology in these children. High prevalence of histologic abnormalities in the esophagus, stomach, small intestine and colon, and dysfunction of liver conjugation capacity and intestinal permeability were reported. Three surveys conducted in the United States described high prevalence of gastrointestinal symptoms in children with autistic disorder. Treatment of the digestive problems may have positive effects on their behavior.
Curr Opin Pediatr 2002, 14:583–587

*†Department of Pediatrics, *Division of Pediatric Gastroenterology and Nutrition, University of Maryland School of Medicine, Baltimore, Maryland, USA.

Correspondence to Karoly Horvath, MD, PhD, Division of Pediatric Gastroenterology and Nutrition, University of Maryland School of Medicine, 22 South Greene Street, N5W70, Box 140, Baltimore, MD 21201-1595; USA; e-mail: khorvath@pol.net

Current Opinion in Pediatrics 2002, 14:583–587

Abbreviations

AD	autistic disorder
GI	gastrointestinal
LNH	lymphoid nodular hyperplasia
L/M	lactulose/mannitol

ISSN 1040–8703

Recent epidemiologic data indicate that autistic disorder (AD), as defined by the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV) criteria, affects as many as 1 of 250 children [•1]. This represents significant change since the early 1990s when autism was diagnosed in 1 of 1000 to 2000 children. A gender difference is seen in AD; approximately 80% of the children are boys. Most of the recently diagnosed cases belong to the "late onset" group: normal development in the first year of life followed by regression in social and communication skills.

The focus in autism research has expanded from psychological studies to exploration of the biologic basis of this pervasive developmental disorder. Although the number of published metabolic, genetic, immunologic, and neuroimaging studies has significantly increased, we are still far from understanding the etiology of autistic disorder. It is likely that no single cause exists. A generally accepted consensus regarding the brain areas responsible for autism does not exist.

The gastrointestinal (GI) tract was a relatively neglected part of autism research until the late 1990s, although two studies published almost three decades ago suggested GI problems in children with AD. In 1971, a report of 15 randomly selected autistic cases described six children who had bulky, odorous, or loose stools, or intermittent diarrhea; one patient had celiac disease [2]. The other study described low serum concentrations of α-1 antitrypsin [3].

Two studies were published in 1998, which drew significant attention and initiated a new period in the investigation of the GI tract of children with AD. Wakefield *et al.* [4] described ileal-lymphoid-nodular hyperplasia and nonspecific colitis in 12 children with developmental disorders; for 9 of them the diagnosis was AD. The other study, which was a case report of three children with AD, reported the results of upper GI endoscopies. This paper described increased pancreaticobiliary secretory response following intravenous secretin administration, coinciding with a significant amelioration of the GI symptoms and improvement in eye contact, alertness, and expansion of expressive language [5]. This review summarizes the GI symptoms, and histologic and functional abnormalities reported in children with AD.

DOI: 10.1097/01.MOP.0000030221.71203.46

Gastrointestinal symptoms in children with autistic disorder

Population surveys can provide a picture of the magnitude of GI problems in children with AD. Three surveys (a total of 1280 subjects with AD) have been reported from Arizona [6], California [7], and the middle Atlantic region [8]. Agreement was found among the surveys that close to 20% of these children had chronic diarrhea. Our detailed survey in which children with AD were compared with their siblings found the following GI symptoms: diarrhea (three or more loose or watery stools per day, persisting longer than 2 weeks); constipation (two or fewer bowel movements per week, which were hard in consistency; foul smelling stools; gaseousness (two to three times per week); abdominal bloating (at least one time per week); abdominal discomfort (at least one time per week); and food regurgitation (more than once a week). Table 1 shows the prevalence of GI symptoms in 112 consecutively examined children with AD and their nonautistic, age-matched siblings living in the same household. Overall, 76% of the autistic patients had at least one GI symptom as compared with 30% of the healthy siblings. Most the children with AD (64%) had two or more symptoms. A high percentage of children more than 4 years of age with autism (48%) were not yet toilet trained, compared with 2% of their siblings.

Nongastrointestinal symptoms suggestive of digestive disease

Children with AD frequently have reflux esophagitis [9]. Infants and children with gastroesophageal reflux disease more frequently have sleep disturbance than the normal population [10]. Nighttime wake-up with pain, abdominal discomfort, or both is common feature of gastroesophageal reflux and reflux esophagitis in children. We found a higher prevalence of sleep disturbances and sudden irritability in children with AD who had GI symptoms.

Table 1. Comparison of the prevalence (%) of gastrointestinal symptoms in 112 children with AD and their siblings

	Children with AD (N = 112) 5.4 ± 2.3 years	Age-matched siblings (N = 44) 6.1 ± 3.1 years
Diarrhea	27.6	0
Constipation	9.5	13.6
Gaseousness	60.3	20.5
Bloating	37.9	6.8
Abdominal pain	37.9	15.9
Reflux	15.5	4.5
Stool impaction	19	0
Belching	25	6.8
Number of gastrointestinal symptoms per child		
No symptom	19.8	70.5
One symptom	16.4	18.2
Two symptoms	24.1	4.5
Three symptoms	25	4.5
Four or more symptoms	14.7	2.3

Sleep disturbances

Children with neurologic, neuropsychiatric, and developmental disabilities are predisposed to sleep disturbances. Sleep problems (interrupted sleep and limited hours of sleep) were reported in one third of handicapped children [11]. Another study of children with autistic disorder reported a 64% prevalence of sleep problems. The most common problem was difficulty falling sleep (41%), followed by frequent awakening (34%) and early morning awakening (20%) [12]. Our study found disturbed sleep with nighttime wake up in 52% of the patients with autism versus only 7% of the healthy siblings ($P < 0.001$). Children with AD and GI symptoms had a higher prevalence of sleep disturbances (55%) compared with those who did not have GI symptoms (14%). In our series of 36 children with autistic spectrum disorder, 61% of those with AD and reflux esophagitis had nighttime wake-ups compared with 13% of those without reflux esophagitis.

Sudden irritability or aggressive behavior

It is difficult to assess the cause of sudden irritability manifested as unexplained crying and aggressiveness in these nonverbal children with AD. More than one third of the parents reported these symptoms in their children. Although these features are not part of the DSM-IV criteria of autistic disorder, many experts consider them as autistic symptoms. We found that 43% of 28 children with esophagitis had daytime unexplained irritability versus 13% of those who had normal esophageal histology. Whereas 24-hour pH probe measurements are necessary to establish a close correlation between acidic refluxes and irritability, it is technically not feasible to perform this procedure in most of these children.

Functional gastrointestinal abnormalities

Disaccharidase activities

Low activities of disaccharidase enzymes (lactase, maltase, sucrase, palatinase, and glucoamylase) were present in 21 of the 36 children (58%) with AD [••9]. The most frequent finding was a low lactase level, which was present in 14 of 36 patients. Ten children had decreased enzyme activities in two or more enzymes. Children with low enzyme activities had loose stools, gaseousness, or both. Functional studies of carbohydrate malabsorption to prove the clinical significance of the disaccharidase findings would require that these children cooperate for breath hydrogen testing, which is not feasible in this population.

Pancreatic enzyme activities

Since our previous paper reporting GI abnormalities in 36 children with AD [••9], we performed pancreatic function tests with secretin stimulation during endoscopy in 53 additional children with AD. Only 1 of 89 children had stimulated duodenal enzyme values (amylase, lipase, trypsin, chymotrypsin, and carboxypepti-

dases) consistent with pancreatic insufficiency. This patient's sweat chloride test result was normal. For the remaining children, no difference was seen in the fasting pH of the duodenal fluid nor in the prestimulatory and poststimulatory enzyme activities between those who were autistic and those who were not.

Pancreaticobiliary fluid secretion

Because secretin has a secretory effect on both pancreatic duct cells and the biliary epithelium [13], the fluid response (mL/min) represents a combination of these two fluids. We observed increased volume of secreted fluid following secretin administration (2 cu/kg body weight [BW], intravenous, during endoscopy). Average pancreaticobiliary fluid output was significantly higher (3.8 ± 2.2 mL/min) for the autistic group compared with controls (1.46 ± 0.57 mL/min; $P < 0.05$) [••9]. Of the 36 children studied, 75% had a fluid output 1 SD above the values of the patients who were not autistic. Typically, the children with AD with chronic diarrhea had a higher fluid output compared with those without diarrhea (4.8 ± 2.3 *vs* 2.4 ± 1.3 mL/min; $P < 0.05$).Increased response to administration of a hormone is suggestive of the upregulation of the receptors for that hormone. The reason for the increased response warrants further investigation.

Intestinal permeability

D'Eufemia *et al.* [14] reported that 43% of the children with AD without evident GI symptoms had increased intestinal permeability (lactulose/mannitol [L/M] test) as compared with none of the 40 controls. We performed permeability studies by using L/M tests in 25 children with AD and GI symptoms [15]. Of the children, 76% (19/25) had a LM ratio above the cutoff value (0.03).

Sulfation deficit in the liver

Abnormal serum liver function tests have not been described in children with AD. Waring *et al.* [•16,17] studied the conjugation (sulfation and glucuronidation) process in the liver by using acetaminophen as substrate, and reported that the sulfate conjugation of acetaminophen was diminished in children with AD compared with those of age-matched children. We performed three acetaminophen tests on the same 26 children with AD. Of the 26 children, 22 (85%) had basal acetaminophen sulfate: glucuronide ratio less than 1. Although slight fluctuations were seen, the individual ratios stayed in the same range in the two repeat tests performed at 6-week intervals. These measurements suggest a persisting defect in the sulfation capacity of the liver (unpublished data). This decrease in the sulfation, if present in the brain and small intestine, may influence the activation and catabolism of certain hormones and neurotransmitters.

Histopathology of the gastrointestinal tract

Gross upper GI endoscopic findings (ulcers, erosions) are rarely found in these children. On routine histologic examination, reflux esophagitis (25/36; 69%) was the most frequent finding in 36 consecutive children with AD who had upper GI endoscopy [••9]. The clinical symptoms correlated well with the histologic findings. Of the children with reflux esophagitis, 93% had at least one of the following symptoms: signs of abdominal pain, nighttime wake-up, and sudden daytime irritability.

Chronic gastritis was reported in 15 of 36 children. Of the 36 children, 24 had chronic duodenitis. Although increased numbers of lymphoid aggregates and lymphocytic infiltrate in the mucosa with mild distortion of the surrounding glands were present in the stomach, none of the children had *Helicobacter pylori* infection. Only 2 of the 36 children had mild villous blunting in the duodenum, but the histologic features were inconsistent with celiac disease. We have tested the sera of more then 400 children with AD, and none of them had serologic evidence of celiac disease (unpublished data). A gluten- and casein-free diet is generally used in patients with AD. This practice is based on two hypotheses. The first is that autistic behavior can be partially caused by a dysfunction in the brain opioid system [18]. The second is based on the fact that both gluten and casein have potentially opioid segments called "gliadorphins" [19] and β-casomorphins [20], respectively. It is presumed that because of the "leakiness" of the intestine these peptides pass the intestine and reach the brain. However, scientific confirmation of these two hypotheses is warranted.

Routine histology showed increased staining at the base of crypts where Paneth cells are localized. Paneth cells produce many factors (*eg*, lysozyme, lactoferrin, defensin), which may play a role in local immune defense. A morphometric analysis of Paneth cells was performed on the biopsies of all the 36 children with AD and 22 age-matched controls who were not autistic. An elevated number of Paneth cells per crypt were found compared with the control group (3.09 ± 0.46 *vs* 2.07 ± 0.32; $P < 0.05$) [••9]. Our recent immunohistochemical studies combined with digital image analysis revealed that the lysozyme content was much higher in the Paneth cells of autistic subjects than in controls (unpublished data). No clear explanation exists for the changes in the Paneth cells in children with AD. It may be the consequence of either a dysfunction in local immune defense or in the digestive system.

Wakefield *et al.* [••21] obtained ileocolonic biopsies from 60 consecutive children with developmental disorders, 83% of whom had AD. Fifty-nine had one or more GI symptoms (*eg*, abdominal pain, constipation, diarrhea, changing stool consistency [constipation alternating with diarrhea], or bloating. All were well nourished with height and weight within the normal range. Colonic endoscopic findings included segmental swelling, hyperemia, superficial erosions, and nodularity. On histologic

examination, mild to moderate ileal lymphoid nodular hyperplasia (LNH) was described in 93% of the developmentally delayed and autistic children examined. In the colon, 30% had LNH. Histologic signs of chronic colitis were identified in 53 of 60 children (88%). An increase in the number of intraepithelial lymphocytes was present in 13% of the children. None of these findings was compatible with an inflammatory bowel disease.

The same research group performed immunohistochemical staining on transverse colonic biopsies of 21 children with AD and in four control groups: normal controls (n = 8), patients with LNH (n = 10), ulcerative colitis (n = 14), and Crohn disease (n = 15) [••22]. The main findings in children with AD were (1) a significant increase in the basement membrane thickness; (2) increase in the mucosal gamma/delta cell density; (3) increased number of CD8+ (suppressor cell) cells; and (4) intraepithelial lymphocytes. In addition, the density of CD3+ cells and plasma cells and the crypt proliferation ratio were higher in children with AD than in normal controls. Disruption of epithelial glycosaminoglycans was detected with special staining. The epithelium in children with autism was HLA-DR negative, which is suggestive of a predominantly type 2 T-helper response. These two studies concluded that a new variant of inflammatory bowel disease is present in children with autism and other developmental delays.

Torrente *et al.* [••23] reported IgG deposition on the basolateral surface of the intestinal epithelial cells in 23 of 25 autistic children. The IgG deposits were colocalized with complement C1q, which was not seen in patients with celiac disease or in normal controls. The IgG-C1q colocalization was accompanied by increases in mucosal lymphocyte density and crypt cell proliferation, which, together with the epithelial IgG deposition, are suggestive of an autoimmune process.

Histologic and immunohistochemistry studies performed on the intestinal biopsies of children with AD, thus, demonstrate the presence of chronic inflammation in the GI tract. As mentioned, a recent immunohistochemical study [23] raised the possibility of an autoimmune pathomechanism in the autistic gut. Also, serologic data indicate a possible autoimmune pathogenesis. Cell-mediated immune response of peripheral lymphocytes to the brain myelin basic protein was reported in 13 of the 17 patients with autism [24]. Antibodies to myelin basic and neuron-axon filament proteins were present in the sera of autistic patients [25], and patients with positive measles and herpes virus 6 antibody titers more likely had autoantibodies to these brain proteins. If the autoimmune process is proved, the described GI inflammation may be the consequence of a multiorgan inflammatory process.

Conclusions

Autism is a dysfunction of the brain areas responsible for communication, language, and social interaction. It is apparent that the children with AD have a high prevalence of various GI symptoms and dysfunctions. Future research should clarify whether digestive inflammation is part of a unique multiorgan, probably autoimmune, process. Pending answers, clinicians can treat most GI symptoms in children with autism by using conventional GI treatment options. In our experience, treatment of the GI problems (*eg*, reflux, colitis) often has beneficial effects on the behavior of children with autistic disorder.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:
- • Of special interest
- •• Of outstanding interest

1 • Bertrand J, Mars A, Boyle C, et al.: Prevalence of autism in a United States population: the Brick Township, New Jersey, investigation. Pediatrics 2001, 108:1155–1161.

This is a recent epidemiologic study reporting on a high prevalence of autism spectrum disorders (6.7 cases per 1000 children). The prevalence for children whose condition met full diagnostic criteria for autistic disorder was 4 cases per 1000 children.

2 Goodwin MS, Cowen MA, Goodwin TC: Malabsorption and cerebral dysfunction: a multivariate and comparative study of autistic children. J Autism Child Schizophr 1971, 1:48–62.

3 Walker-Smith J, Andrews J: Alpha-1-antitrypsin, autism, and coeliac disease. Lancet 1972, 2: 883–884.

4 Wakefield AJ, Murch SH, Anthony A, et al.: Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children. Lancet 1998, 351:637–641.

5 Horvath K, Stefanatos G, Sokolski KN, et al.: Improved social and language skills after secretin administration in patients with autistic spectrum disorders. J Assoc Acad Minor Phys 1998, 9:9–15.

6 Melmed RD, Schneider C, Fabes RA, et al.: Metabolic markers and gastrointestinal symptoms in children with autism and related disorders. J Pediatr Gastroenterol Nutr 2000, 31:S31–S32.

7 Lightdale J, Hayer C, Siegel B, et al.: Evaluation of gastrointestinal symptoms in autistic children before and following secretin infusion. J Pediatr Gastroenterol Nutr 2000, 31:s31.

8 Horvath K, Medeiros L, Rabsztyn A, et al.: High prevalence of gastrointestinal symptoms in children with autistic spectrum disorder (ASD). J Pediatr Gastroenterol Nutr 2000, 31:S174.

9 •• Horvath K, Papadimitriou JC, Rabsztyn A, et al.: Gastrointestinal abnormalities in children with autistic disorder. J Pediatr 1999, 135:559–563.

This paper describes upper gastrointestinal abnormalities found in 36 children with autism. Grade I or II reflux esophagitis was found in 25, chronic gastritis in 15, and chronic duodenitis in 24. An increase in the number of Paneth's cells was seen. Low intestinal carbohydrate digestive enzyme activity was reported in 21 children and 27 had an increased pancreaticobiliary fluid output after intravenous secretin administration

10 Ghaem M, Armstrong KL, Trocki O, et al.: The sleep patterns of infants and young children with gastro-oesophageal reflux. J Paediatr Child Health 1998, 34:160–163.

11 Clements J, Wing L, Dunn G: Sleep problems in handicapped children: a preliminary study. J Child Psychol Psychiatry 1986, 27:399–407.

12 Takase M, Taira M, Sasaki H: Sleep-wake rhythm of autistic children. Psychiatry Clin Neurosci 1998, 52:181–182.

13 Lenzen R, Alpini G, Tavoloni N: Secretin stimulates bile ductular secretory activity through the cAMP system. Am J Physiol 1992, 263:G527–G532.

14 D'Eufemia P, Celli M, Finocchiaro R, et al.: Abnormal intestinal permeability in children with autism. Acta Paediatr 1996, 85:1076–1079.

15 Horvath K, Zielke H, Collins J, et al.: Secretin improves intestinal permeability in autistic children. J Pediatr Gastroenterol Nutr 2000, 31:S30–S31.

16 Alberti A, Pirrone P, Elia M, et al.: Sulfation deficit in "low-functioning" autistic
• children: a pilot study. Biol Psychiatry 1999, 46:420–424.
This study examined acetaminophen sulfation by the liver in 20 "low functioning" autistic children. The autistic subjects showed significantly lower results than the control group ($P < 0.00002$).

17 O'Reilly B, Waring R: Enzyme and sulfur oxidation deficiencies in autistic children with known food/chemical intolerances. Journal of Orthomolecular Medicine 1993, 4:198–200.

18 Sahley TL, Panksepp J: Brain opioids and autism: an updated analysis of possible linkages. J Autism Dev Disord 1987, 17:201–216.

19 Graf L, Horvath K, Walcz E, et al.: Effect of two synthetic alpha-gliadin peptides on lymphocytes in celiac disease: identification of a novel class of opioid receptors. Neuropeptides 1987, 9:113–122.

20 Brantl V: Novel opioid peptides derived from human beta-casein: human beta-casomorphins. Eur J Pharmacol 1984, 106:213–214.

21 Wakefield AJ, Anthony A, Murch SH, et al.: Enterocolitis in children with de-
•• velopmental disorders. Am J Gastroenterol 2000, 95:2285–2295.
Colonoscopies were performed on 60 children with developmental delay, including 50 children with autism. Ileal lymphoid nodular hyperplasia (LNH) was reported in 93% and colonic LNH in 30% of the children. Histologic examination revealed reactive follicular hyperplasia in 88% and chronic colitis was identified in 88% of the developmentally delayed children.

22 Furlano RI, Anthony A, Day R, et al.: Colonic CD8 and gamma delta T-cell
•• infiltration with epithelial damage in children with autism. J Pediatr 2001, 138:366–372.
This study reported immunohistochemical studies of the transverse colon of 21 children with autism. The authors described lymphocytic colitis, basement membrane thickening, increased mucosal gamma delta cell, and CD8 (+) density and intraepithelial lymphocyte numbers. The epithelium was HLA-DR (–), which is suggestive of a Th-2 response.

23 Torrente F, Ashwood P, Day R, et al.: Small intestinal enteropathy with epi-
•• thelial IgG and complement deposition in children with regressive autism. Mol Psychiatry 2002, 7:375–382.
This study determined the density of intraepithelial and lamina propria lymphocyte populations, and studied mucosal immunoglobulin and complement C1q localization. IgG deposition was found on the basolateral epithelial surface in 23 of 25 autistic children, co-localizing with complement C1q.

24 Weizman A, Weizman R, Szekely GA, et al.: Abnormal immune response to brain tissue antigen in the syndrome of autism. Am J Psychiatry 1982, 139:1462–1465.

25 Singh VK, Lin SX, Yang VC: Serological association of measles virus and human herpesvirus-6 with brain autoantibodies in autism. Clin Immunol Immunopathol 1998, 89:105–108.