Autism and Gastrointestinal Symptoms

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

Address
Department of Pediatrics, University of Maryland School of Medicine, 22 South Greene Street, N5W70, Box 140, Baltimore, MD 21201-1595, USA.
E-mail: khorvath@umaryland.edu

Current Gastroenterology Reports 2002**, 4:**251–258
Current Science Inc. ISSN 1522–8037

Autism is a collection of behavioral symptoms characterized by dysfunction in social interaction and communication in affected children. It is typically associated with restrictive, repetitive, and stereotypic behavior and manifests within the first 3 years of life. The cause of this disorder is not known. Over the past decade, a significant upswing in research has occurred to examine the biologic basis of autism. Recent clinical studies have revealed a high prevalence of gastrointestinal symptoms, inflammation, and dysfunction in children with autism. Mild to moderate degrees of inflammation were found in both the upper and lower intestinal tract. In addition, decreased sulfation capacity of the liver, pathologic intestinal permeability, increased secretory response to intravenous secretin injection, and decreased digestive enzyme activities were reported in many children with autism. Treatment of digestive problems appears to have positive effects on autistic behavior. These new observations represent only a piece of the unsolved autism "puzzle" and should stimulate more research into the brain–gut connection.

Introduction

Autism may affect as many as one in 250 children, and approximately 80% of autistic children are male [1]. Most patients are diagnosed in the first 3 years of life. Our recent data (Unpublished) suggest that the majority of new patients belong to the late-manifesting group, defined as those who have normal development in the first year and who subsequently regress.

Diagnosis of autism is based on the presence of various behavioral symptoms. No single cause exists for the autistic spectrum of disorders. Diseases such as tuberous sclerosis, Down syndrome, cerebral palsy, fragile X, and congenital rubella are associated with an increased prevalence of autism. Because the cause of autism is unknown, many hypotheses have been suggested, and many different therapies have been implemented in autistic children.

In the last decade, the focus in autism research migrated from psychological studies to exploration of the biologic basis of this devastating disorder. Studies using neuroimaging and brain autopsy, as well as immunologic, genetic, metabolic, and gastrointestinal research efforts, have resulted in a significant amount of new information. However, this biologic research is still in the evolutionary stage, with many controversies, especially in brain and genetic research. For example, no consensus has been reached regarding the brain areas responsible for autism.

The gastrointestinal tract is an easier target for investigation than the brain. However, only two studies of gastrointestinal symptoms in autism were reported prior to 1996. In 1971, a report of 15 randomly selected autistic patients described six children who had bulky, odorous, or loose stools, or intermittent diarrhea, and one with celiac disease [2]. The second study described low serum concentrations of alpha-1 antitrypsin [3]. Little attention was given to these findings until several years ago when routine gastrointestinal evaluations of children with autism revealed an increased prevalence of gastrointestinal symptoms, histologic changes in the digestive tract, and gastrointestinal dysfunction, compared with control subjects. In the last 6 years, the number of reports describing gastrointestinal abnormalities in children with autism has increased. The purpose of this review is to summarize symptoms, histology, and functional abnormalities reported in children with autism.

Gastrointestinal Symptoms in Autism

Age of manifestation of autism and gastrointestinal symptoms

We have been evaluating children with autism and gastrointestinal symptoms since 1996 at our institution. To estimate the prevalence of gastrointestinal symptoms, we conducted a survey on 412 children with autism. The average age of manifestation of autistic behavior in our cohort was 18.0 ± 6.7 months, and the diagnosis was made at 29.4 ± 11.3 months. Only 21.1% of these patients had evident autistic features before their first birthday. In the preponderance of patients (40.5%), the first symptoms of autism appeared between 12 and 18 months. A recent trend is to define patients manifesting symptoms after 1 year of age as examples of late-onset autism. Parents did not have clear recollections regarding the age at which gastrointestinal symptoms manifested. Typically, they either reported that the gastrointestinal symptoms manifested at almost the same time as the behavioral symptoms or that they were present since birth.

Table 1. Comparisons of the prevalence of gastrointestinal symptoms between autistic children and their healthy siblings

	Autism, %	Sibling, %
Number of GI symptoms/subject		
No GI symptoms	17	72
One	10	16
Two	17	7
Three	15	0
Four or more	41	5
Specific symptom		
Abdominal discomfort	44	9
Gaseousness	54	19
Bloating	34	5
Belching	24	9
Reflux	16	5
Irritability*	44	2
Unexplained crying*	43	5
Sudden aggressive behavior*	33	2
Sleep problem*	51	7
Stool		
Number/d or wk		
3 or more/d	20	2
2–3/d	25	13
1–2/d	35	72
3–4/wk	7	2
1–2/wk	6	7
Consistency		
Loose/watery	32	2
Soft	18	21
Normal	13	81
Hard	10	12
Changing	23	0
Smell		
Foul smelling	49	0
Sour smelling	8	7
Normal smelling	43	93

* Symptoms can be associated with gastrointestinal abnormalities.
d—day; GI—gastrointestinal; wk—week.

Prevalence of gastrointestinal symptoms

The majority of young children with autism are nonverbal and unable to report abdominal discomfort. Parents and psychologists may consider some of their symptoms, such as sudden irritability, pushing on the abdomen, and aggressive behavior, as solely behavioral symptoms. Other symptoms, such as stool frequency and vomiting, can be evaluated more objectively.

In a survey conducted in Arizona, parents reported chronic diarrhea (71 of 379; 19%), constipation (78 of 379; 21%), and changing stool consistency (25 of 379; 7%) in their autistic children. The prevalence of diarrhea and constipation in the 40 surveyed nonautistic siblings was 8% and 10%, respectively [4]. Lightdale *et al.* [5] conducted a survey in 500 children with autism. Based on parental reports, 20% of these children had three or more stools per day, half of them had frequent flatulence and bloating, and one third had abdominal pain.

We collected detailed medical information on 412 autistic children aged 6.5 years ± 3.6 years with a four-page questionnaire. The questionnaires were sent to support groups in the eastern United States and given to patients attending autism clinics in Baltimore, MD and in Hershey, PA (Unpublished data). All of the children were diagnosed with autistic spectrum disorder (Pervasive Developmental Disorder, Not Otherwise Specified [PDD-NOS]) based on DSM-IV criteria. A section of the questionnaire was related to gastrointestinal symptoms. To verify the data, we interviewed the parents of 116 of the 412 children. Interviewed parents were asked to complete the same questionnaire for their healthy children. We were able to collect data from 43 healthy, age-matched siblings. The following gastrointestinal symptoms were evaluated:

- Diarrhea: three or more loose or watery stools per day persisting longer than 2 weeks
- Constipation: two or fewer bowel movements per week that are hard in consistency
- Foul-smelling stools
- Gaseousness occurring 2 to 3 times per week
- Abdominal bloating at least one time per week
- Signs of abdominal discomfort at least one time per week
- Food regurgitation
- Toilet training not achieved by 6 years of age

Overall, 84.1% of the autistic patients had at least one of the listed symptoms, compared with 31.2% of the healthy siblings ($P<0.0001$). The detailed results of this study are shown in Table 1. Thus, all three surveys conducted in the United States showed a high prevalence of gastrointestinal symptoms in children with autism.

Toilet training

Children with developmental disorders often have difficulty mastering toilet training. A retrospective survey including 100 parents of individuals with autism (mean age, 19.5 years) concluded that lower cognition and verbal levels were significantly correlated with age of accomplishment of bowel and urine training [6]. In our survey, a high proportion of children aged over 4 years with autism (57.2%) were not yet toilet trained.

Somatic development

An analysis of weight and height in 59 children with autism whom we evaluated demonstrated normal somatic development. The average weight percentile was 58.4% ± 30.5%, and the height percentile was 47.5% ± 29.0%. The average body mass index (BMI) of these 59 children was 63.2% ± 30.7%. Nineteen children (32.2%) had a BMI above the 85th percentile. The increased BMI may be explained partially by the fact that candy or cookies are used as reinforcement in many behavioral therapies for autistic children. Furthermore, these data suggest that there

Table 2. Summary of histologic findings in children with autism

Study	Subjects, *n*	Anatomic location	Finding	Prevalence, %
Horvath *et al.* [9••]	36	Esophagus	Reflux esophagitis	69.4
		Stomach	Chronic gastritis	41.6
			Helicobacter pylori infection	0
		Duodenum	Chronic inflammation	66.6
			Increased number of Paneth cells	80.5
			Villus blunting	5.5
			Celiac disease	0
Wakefield *et al.* [8••]*	60	Colon	Chronic inflammation	88
			Eosinophilic infiltrate	40
			Subepithelial apoptosis	50
			Increased IEL	13
	52	Ileum	Follicular hyperplasia	92
			Neutrophils–acute ileitis	8
			Aphtoid ulceration	4

*Fifty of 60 children had autism.
IEL—intraepithelial lymphocytes.

is no clinically significant malabsorption in the majority of these children.

Gastrointestinal symptoms and sleep disturbances

Sleep disorders, with nighttime awakening, were reported to us in half of the patients with autism, versus only 6.8% of the healthy siblings in our study. Although the mechanism of these sleep disturbances is difficult to ascertain, nighttime awakening with pain or abdominal discomfort is common with gastroesophaeal reflux and reflux esophagitis in children [7]. Figure 1 shows that autistic children with gastrointestinal symptoms have a higher prevalence of sleep disturbances, compared with those who do not have gastrointestinal symptoms and with their siblings (P=0.0001).

Taste function in autism

A small unpublished preliminary study conducted on 15 autistic subjects (age, 6 to 22 years) examined the taste function of the subjects compared with controls. Patients with autism showed hyposensitivity to salt (sodium chloride) and sugar (sucrose) and significant hypersensitivity to bitter (quinine sulfate) and sour (citric acid) tastes. (Taylor SA, Personal communication, 1999).

Endoscopic and Histologic Abnormalities in the Gastrointestinal Tract

In our experience, it is not difficult to perform upper gastrointestinal endoscopy or colonoscopy in children with autism who are under general anesthesia. Even the preparation for colonoscopy can be achieved in these children. However, safe and successful management during and immediately after the procedure is facilitated by an experienced pediatric anesthesiologist. Figure 2 summarizes the main gastrointestinal findings in children with autism.

Endoscopic findings

Gross endoscopic abnormalities (ulcers and erosions) are rarely found in the upper gastrointestinal tract in these patients. The most frequently noticed changes are distal esophageal swelling, hyperemia, and friability, whereas gastric (mostly antral) hyperemia, nodularity in the duodenal bulb, and friability of the duodenal mucosa are less frequently seen (Personal observation).

The colonic findings are also mild and include segmental swelling, hyperemia, superficial erosions, and nodularity. Wakefield *et al*. [8••] described mild to moderate ileal lymphoid nodular hyperplasia (LNH) in 93% of the examined developmentally delayed and autistic children. In the colon, 30% had LNH. Granularity, loss of vascular pattern, erythema, red halo signs, and superficial ulcers were also described. Although the inflammatory changes were patchy, they were distributed throughout the colon.

Histologic findings

Histologic findings in published studies are summarized in Table 2. In our series, approximately, 60% of the examined children with autism had inflammation consistent with gastroesophageal reflux disease [9••]. The clinical symptoms of these children correlated well with the histologic findings. Ninety-three percent had at least one of the following symptoms: signs of abdominal pain, nighttime awakening, and sudden daytime irritability.

Chronic gastritis was present in more than one third of the children with autism. Increased numbers of lymphoid aggregates and lymphocytic infiltrate in the mucosa with mild distortion of the surrounding glands were present without significant lymphocytic infiltrate in the epithelium. None of the children in our series had *Helicobacter pylori* infection, suggesting that the prevalence of *H. pylori* gastritis is probably not higher in autistic children than in nonautistic children undergoing endoscopy. Two

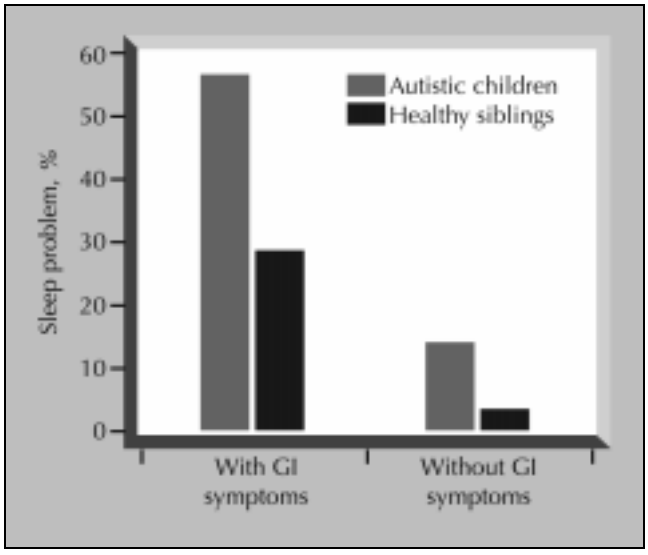

Figure 1. The prevalence of sleep disorders in children with and without gastrointestinal problems is shown. The presence of gastrointestinal symptoms was associated with a significantly higher prevalence of sleep disturbances in the autistic group (P=0.0001).

thirds of the children had various degrees of chronic, nonspecific duodenal inflammation. Only two children of the 36 had mild villous blunting, but the histologic features were inconsistent with celiac disease.

Wakefield *et al*. [8••] reported a detailed endoscopic and histologic analysis of ileocolonic biopsies from 60 children with developmental disorders, 50 of them with the diagnosis of autism. Reactive follicular hyperplasia was present in the ileum of 47 of 51 children with successful ileal biopsies. Histologic signs of chronic colitis were identified in 53 of 60 children (88%). Histologic analysis showed increased intraepithelial lymphocytes in 13% of the children with developmental disorders. None of these findings were compatible with inflammatory bowel disease. The authors concluded that a new variant of inflammatory bowel disease is present in children with autism and other developmental delays.

Immunohistochemistry and morphometric studies

Paneth cells are localized in the base of the crypts and produce many factors (*eg*, lysozyme, lactoferrin, and defensin) that may play a role in local immune defense. We performed a morphometric analysis and compared the number of Paneth cells seen in the crypts with the number seen in 22 non-PDD controls, finding an elevated number of Paneth cells per crypt (3.09 ± 0.46 vs 2.07 ± 0.32; P<0.05) [9••]. In addition to the cell number, the size of granules in the Paneth cells was larger, and discharge of granules into the crypt lumen was a frequent finding. Our recent immunohistochemical studies and enzyme-linked immunosorbent assay measurements of biopsy homogenates revealed that the lysozyme content was much higher in the Paneth cells of autistic subjects than in controls (322 ± 58 vs 150 ± 24 μg/g protein; P=0.017; Unpublished data).

Furlano *at al*. [10••] performed a histochemical analysis of transverse colonic biopsies of 21 children with autism and of four control groups: 1) normal controls (n=8), 2) patients with LNH (n=10), 3) patients with ulcerative colitis (n=14), and 4) patients with Crohn's disease (n=15). They reported significantly increased basement membrane thickness and mucosal gamma/delta cell density in autistic children compared with the other groups. They also described the disruption of epithelial glycosaminoglycans. The number of CD8+ suppressor cells and intraepithelial lymphocytes was higher in children with autism, compared with those with Crohn's disease or LNH and with normal controls. CD3+ cell, plasma cell density, and crypt proliferation ratio were higher than in normal controls. The epithelium in children with autism was negative for HLA-DR, which suggests a predominantly Th-2 response.

Collectively, these endoscopic, histologic, and immunohistochemical studies suggest the presence of chronic inflammation in the gastrointestinal tract of children with autism. It is tempting to conclude that the described gastrointestinal inflammation reflects a multiorgan inflammatory process, which may include specific brain regions. However, further rigorous studies are warranted to prove a brain–gut connection.

Gastrointestinal Dysfunction

In addition to the described gastrointestinal inflammation, functional changes have been reported in the small and large intestine in children with autism.

Intestinal permeability

In 1996, D'Eufemia *et al*. [11] reported that nine of 21 (43%) patients with autism and without evident gastrointestinal symptoms had increased intestinal permeability, compared with none of the 40 controls. We performed permeability studies by using lactulose–mannitol (LM) tests in 25 children with autistic behavior [12]. Seventy-six percent (19 of 25) of the children had an LM ratio above the cut-off value (P=0.03). We repeated the tests after secretin treatment and found that 13 of the 20 had a decrease (from 0.06 ± 0.031 to 0.02 ± 0.011) in LM ratio. No changes were observed in two children, and an increase in LM ratio was found in five children (range, 0.027 ± 0.011 to 0.043 ± 0.014).

Digestive enzymes

In contrast with endoscopy, measurement of breath hydrogen/methane for detection of carbohydrate malabsorption is difficult in autistic children because of the cooperation this test requires in patients. In lieu of this test, we routinely measured disaccharidase enzyme activity (lactase, sucrase, maltase, palatines, and glucoamylase) from endoscopic biopsies. We found that 44 of 90 (49%) autistic children had at least one deficient enzyme activity. Eighteen of the 44 children had decreased activity in two or more disaccharidase enzymes. Lactase and maltase deficiencies

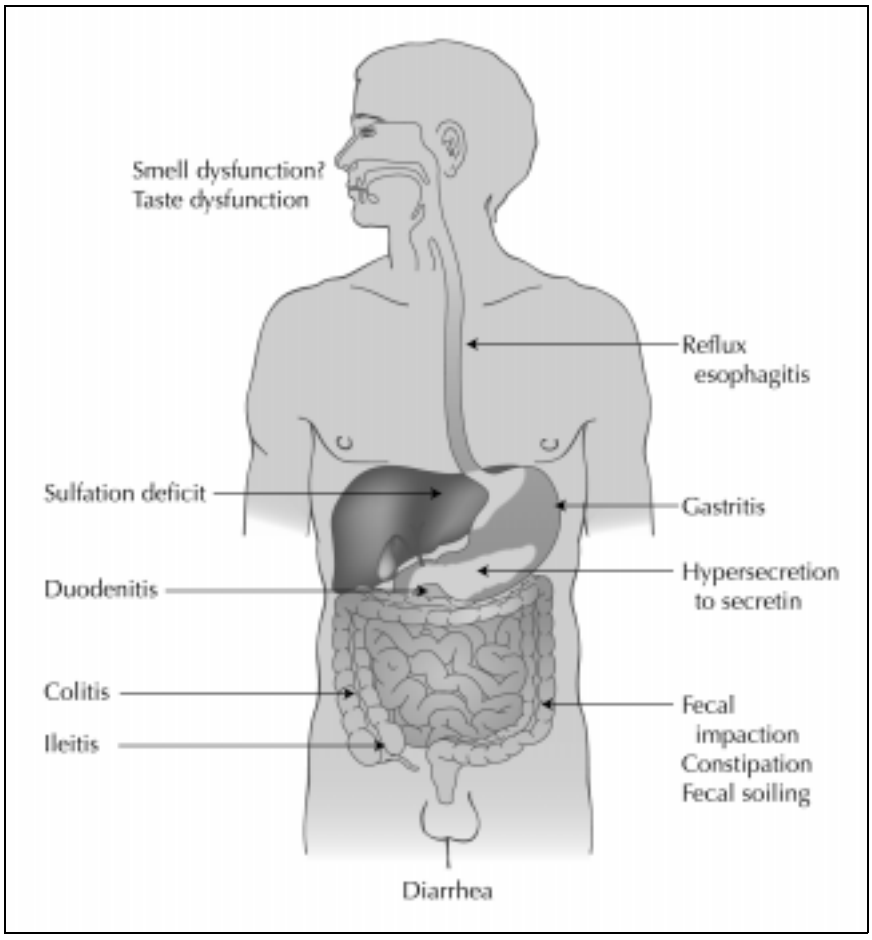

Figure 2. Schematic summary of the gastrointestinal abnormalities reported in children with autism.

were the most frequent, followed by low activity of sucrase, palatinase, and glucoamylase. All of the children with low enzyme activity had loose stools and/or gaseousness.

Parents have reported behavioral improvements in their children after the children are placed on a casein-free diet. One possible explanation for this beneficial effect is that the concomitant removal of lactose from the diet may resolve the symptoms related to lactose malabsorption.

Bacterial and yeast cultures of the duodenal fluid

Antibiotic therapy can result in dysbiosis and alteration of the gut microbial flora. A large proportion of children with autism receive several courses of antibiotics starting at the first year of life. A commercial laboratory (Great Plains, Lenexa, KS) has reported increased levels of urinary organic acids in children with autism. Their reports state that these organic acids come from intestinal bacteria and yeast. The performance characteristics of these tests have not been published or peer reviewed; however, this study has led to the general use of antifungal drugs in children with autism. Anecdotal reports have suggested that antifungal treatment can improve autistic behavior.

In the last 2 to 3 years, almost all of the children we evaluated had received low-dose, long-term antifungal therapy (Table 3). Consequently, we stopped the therapy 7 to 10 days prior to the endoscopic procedure and sent the fasting, unstimulated duodenal juice for fungal, anaerobic, and aerobic cultures. We found that 43.1% of these patients had positive fungal cultures. The prevalence of positive duodenal fungal culture was 23.1% in age-matched controls with various gastrointestinal problems. No significant difference was observed in the prevalence of positive aerobic and anaerobic cultures between the autistic and control subjects.

Based on the possibility of anaerobic bacterial overgrowth, Sandler *et al*. [13•] conducted a small study using oral vancomycin in 11 children with late-onset autism. They described short-term improvements based on evaluation before and after therapy, but the beneficial effect disappeared after the discontinuation of therapy. The authors concluded that a possible gut flora–brain connection warrants further investigation in a subset of children with autism.

Pancreatobiliary secretion

Secretin has a secretory effect in both the pancreatic duct cells and the biliary epithelium [14]. We used 2 IU/kg of IV secretin during endoscopy and observed increased volume of secreted fluid following secretin administration. The average stimulated pancreatobiliary fluid output was significantly higher (3.8 ± 2.2 mL/min) for the autistic group compared with the controls (1.46 ± 0.57 mL/min; $P<0.05$). In the majority of patients (75%), the volume of

Table 3. Unconventional gastrointestinal therapies used in autism

Therapy	Reason	Comment
Casein-free diet Gluten-free diet	"Opioid excess theory": exorphins (exogenous opioids: beta-casomorphins from casein and gliadorphins from gluten) enter the brain, causing dysfunctions	Only one small open pilot study examined the behavioral effects of these diets; elimination of lactose has beneficial effects in children with lactose malabsorption
Digestive enzyme supplements	Supposed digestive problems; it breaks down the exorphins	No evidence of pancreatic enzyme deficiency; approximately 50% have decreased activity in at least one of the disaccharidase enzymes
Probiotics	They may improve leaky gut and dysbiosis	No published research study in autism
Secretin	Behavioral improvement in a subgroup of young autistic patients after intravenous administration	Further research needed to explore clinical and biologic markers to identify responders
Vancomycin	Supposed anaerobic overgrowth	Temporary, no sustained behavioral benefits
Nystatin, fluconazole	For suspected fungal overgrowth based on urine organic acid tests	The organic acid test is not validated; microbiologic confirmation of the overgrowth is necessary

pancreatobiliary fluid output following secretin stimulation was 1 SD above the values of nonautistic patients. Children with autism and a history of chronic diarrhea had a statistically significantly higher fluid output compared with those without diarrhea (4.8 ± 2.3 vs 2.4 ± 1.3 mL/min; $P<0.05$).

This high response rate is suggestive of the upregulation of secretin receptors in the pancreatic duct and/or biliary tract. However, autistic children do release secretin. We performed a pilot study measuring the release of secretin into the blood after acidification of the duodenum during endoscopy and found no abnormality. Our data may therefore suggest a dysfunction in the cephalic phase of digestion in autism. Normal release of pancreatic enzymes after IV secretin administration was reported in children with autism. Only one child with autism out of the examined 89 was found to have pancreatic insufficiency.

Abnormal acetaminophen metabolism in the liver

Children with autism do not have any evident abnormalities in their liver function tests. The conjugation (sulfation and glucuronidation) process in the liver has been studied using acetaminophen as substrate [15•,16]. These studies showed that the ability of the liver to excrete the sulfate conjugate of acetaminophen was diminished, compared with the ability of age-matched children. There was no overall decrease in the conjugation capacity of the liver. The concentration of serum sulfate was significantly lower in children with autism than in controls (1.51 ± 2.75 vs 8.3 ± 5.4 pmol/mg protein), whereas cysteine (a sulfate precursor) was present in greater amounts (0.56 ± 0.4 vs 0.36 ± 0.359 mmol/mg protein), possibly because of inhibition of oxidative degradation pathways [17].

In our study, 22 of 26 children with late-onset autism (84.6%) had a low (<1) acetaminophen sulfate–glucuronide ratio even after two repeat measurements at 8- and 9-week intervals (Unpublished data). Urinary sulfite, sulfate, and thiosulfate excretion was elevated, whereas thiocyanate was reduced. These findings suggest a persistent defect in the sulfation capacity of the liver of children with autism.

Autism and Specific Diets

Solid scientific evidence is lacking on the benefit of gluten- or casein-free diets for children with autism. The main reason that many autistic children are placed on gluten-free diets is the anecdotal reports of behavioral improvement on such regimens (Table 3). To date, none of the 420 children with autism whose sera were tested in our laboratory had serologic evidence of celiac disease, nor were there histologic signs of celiac disease in 90 children on whom we performed upper gastrointestinal endoscopies. A small Italian study found no evidence of autistic behavior among 120 children diagnosed with celiac disease, and none of the 11 children with autism had histologic evidence of celiac disease [18]. In 1979, McCarthy and Coleman [19] examined eight autistic patients with steatorrhea and hypocalciuria, and alleged behavioral improvements on gluten restriction. They added 20 g of gluten per day into the diet of these patients for 4 weeks. No significant changes in body weight or bowel habits resulted from the gluten challenge, nor were any histologic abnormalities detected on intestinal biopsy. Large epidemiologic studies are warranted to clarify any association between autism and celiac disease.

Many indirect scientific data serve as the basis of the opioid excess theory. The starting point for this theory is the fact that some of the autistic behavioral symptoms are similar to those observed in morphine addicts. This observation was extended with the supposition that exogenous opioids from foods may contribute to the behavioral and communicative dysfunctions of children with autism. In vitro research revealed that gluten [20] and casein [21] have potentially opioid segments called gliadorphins [22] and beta-casomorphins [23], respectively. Intact transport of beta-casomorphins has been shown across intestinal

mucosa in the neonatal period in dogs [24]. Altered intestinal permeability has been described in children with autism. It is presumed that intact transport of opioid peptides from gluten and casein in the gut can occur in autistic children [25,26]

An increased amount of urinary peptide concentration (hyperpeptiduria) has been reported in subjects with autism, contributing more indirect support for the opioid excess theory [27]. However, the passage of these exogenous peptides through the intestinal lining, their entrance into the brain, and their appearance in the urine have not been documented in humans. Based on the report that endogenous opioids regulate the cell proliferation of the cerebellum in the postnatal period in rats, it was concluded that the gliadorphins and casomorphins could affect the neurotransmitter system in the central nervous system (CNS) and result in the social impairment seen in autism. [25–28]. Further indirect evidence for the opioid theory arises from therapeutic trials with an opioid antagonist (naltrexone), which demonstrated modest behavioral improvements in a subgroup of children with autism [29].

One uncontrolled study has addressed the opioid excess question. Knivsberg *et al*. [30] followed five patients with autistic spectrum disorders who had hyperpeptiduria in their 24-hour urine samples. All of these patients were placed on a gluten- and casein-free diet. The study assessed their social behavior and cognitive and communicative skills prior to the diet, and the patients were followed on the restricted diet for 4 years. Normalization of urine patterns and peptide levels was found after 1 year. A decrease in odd behaviors and an improvement in the use of social, cognitive, and communicative skills were observed. However, this was an open study that did not include a control group.

Autism and the Immune System

Autism and food allergies

A large proportion of children seen in our gastrointestinal clinic had undergone different blood tests for food allergies. In our survey, 24% of the 412 children with autism and 4.5% of their siblings were diagnosed with food allergies (Unpublished data). Many of them had IgG-type antibody tests, and only a minority had IgE-type tests performed. Parents attempted to eliminate the foods that tested positive from their children's diet. One child tested positive for 17 food antigens, and all of them were removed from his diet.

Despite the high proportion of reported food allergies, no large-scale study has been published regarding the relationship between autism and food allergy. An Italian study examined 36 autistic patients and found significantly higher levels of IgA antigen-specific antibodies for casein, lactalbumin, and beta-lactoglobulin, and IgG and IgM antibodies for casein, compared with levels of 20 healthy children [31]. A marked improvement in the behavioral symptoms of the autistic children was reported after 8 weeks on an elimination diet.

No study has examined the prevalence of eosinophilic esophagitis or gastroenteropathy in children with autism. In our practice, we did not find these entities to be more common in the autistic population.

Measles and autism

There is a controversy in the literature regarding two questions: first, whether the prevalence of autism has increased in the last 15 years, and second, whether this increase in the prevalence is related to the introduction of the combined measles-mumps-rubella (MMR) vaccination. From a gastrointestinal point of view, the question is, does the presence of measles virus genes in the lymph nodes prove that measles is the trigger of the gastrointestinal inflammation and is responsible for the behavioral problems? Participants in a recent meeting on this topic concluded that finding a portion of a virus in peripheral blood lymphocytes and intestinal tissue specimens using molecular techniques does not constitute evidence for a causal relationship, because some viruses persist in unaffected hosts [32]. Further research is clearly needed to prove the existence of an association between MMR immunization and autism.

Conclusions

In the last decade, a significant accumulation of data has come to our attention regarding biologic aspects of autism. However, the etiology and pathomechanism of this developmental disorder have remained a mystery. Many if these controversial epidemiologic and etiologic observations warrant further clarification. The different neuroanatomic, histologic, and functional observations have not yet been merged into one uniform hypothesis.

The gastrointestinal tract, recently referred to as the second brain, has many abnormalities in patients with autism [33]. Further research is necessary to clarify whether the digestive manifestations are a secondary consequence of the CNS dysfunctions or part of the same pathogenetic process involving both organs. From a clinical point of view, we are able to treat most of the gastrointestinal symptoms of children with autism, and these treatments often have beneficial effects on their behavior. Gastroenterologists evaluating these children should be aware of the fact that various gastrointestinal therapies are used in children with autism, but without scientific evidence of their efficacy.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

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.
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:**8830150884.
4. 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(suppl 2):**S31–S32.
5. Lightdale JR, Siegel B, Heyman MB: **Gastrointestinal symptoms in autistic children.** *Clin Perspect Gastroenterol* 2001, **31(suppl 2):**56–58.
6. Dalrymple NJ, Ruble LA: **Toilet training and behaviors of people with autism: parent views.** *J Autism Dev Disord* 1992, **22:**265–275.
7. 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.
8. •• Wakefield AJ, Anthony A, Murch SH, *et al.*: **Enterocolitis in children with developmental disorders.** *Am J Gastroenterol* 2000, **95:**2285–2295.

This study was comprised of 60 children with developmental delay including 50 children with autism. Ileal LNH was present in 93% and colonic LNH in 30% of the children. The histologic examination revealed reactive follicular hyperplasia in 88.5%, and chronic colitis was identified in 88% of the developmentally delayed children.

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 the gastrointestinal abnormalities found in 36 children with autism who underwent upper gastrointestinal endoscopy for the evaluation of chronic diarrhea, gaseousness, abdominal discomfort, and distention. Grade 1 or 2 reflux esophagitis was found in 25, chronic gastritis in 15, and chronic duodenitis in 24. An increase in the number of Paneth cells was observed. Low intestinal carbohydrate digestive enzyme activity was reported in 21 children, and 27 had increased pancreatobiliary fluid output after IV secretin administration.

10. •• 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.

These authors report the findings of immunohistochemical studies in 21 children with autism and four control groups. They describe lymphocytic colitis, basement membrane thickening, increased mucosal gamma delta cell and CD8+ density, and intraepithelial lymphocyte numbers. The epithelium was HLA-DR-negative, which is suggestive of a Th-2 response.

11. D'Eufemia P, Celli M, Finocchiaro R, *et al.*: **Abnormal intestinal permeability in children with autism.** *Acta Paediatr* 1996, **85:**1076–1079.
12. Horvath K, Zielke H, Collins J, *et al.*: **Secretin improves intestinal permeability in autistic children.** *J Pediatr Gastroenterol Nutr* 2000, **31(suppl 2):**S30–S31.
13. • Sandler RH, Finegold SM, Bolte ER, *et al.*: **Short-term benefit from oral vancomycin treatment of regressive-onset autism.** *J Child Neurol* 2000, **15:**429–435.

This report is from an open clinical trial with oral vancomycin in children with autistic behavior. Behavioral improvement was noted in eight of 10 children studied. The behavioral gains disappeared after the discontinuation of therapy. These results indicate that a possible gut flora–brain connection warrants further investigation.

14. Lenzen R, Alpini G, Tavoloni N: **Secretin stimulates bile ductular secretory activity through the cAMP system.** *Am J Physiol* 1992, **263:**G527–G532.
15. • Alberti A, Pirrone P, Elia M, *et al.*: **Sulphation deficit in 'low-functioning' autistic children: a pilot study.** *Biol Psychiatry* 1999, **46:**420–424.

This study examined the liver sulfation capacity in 20 "low-functioning" autistic children and in an age-matched control group by using paracetamol. The group of autistic subjects had significantly lower results than the control group ($P<0.00002$). The authors concluded that the inability to metabolize certain compounds effectively, particularly phenolic amines—which are toxic for the CNS—could exacerbate the wide spectrum of autistic behavior.

16. O'Reilly B, Waring R: **Enzyme and sulfur oxidation deficiencies in autistic children with known food/chemical intolerances.** *J Orthomolec Med* 1993, **4:**198–200.
17. Waring RH, Ngong JM, Klovrza L, *et al.*: **Biochemical parameters in autistic children.** *Dev Brain Dysfunction* 1997, **1:**40–43.
18. Pavone L, Fiumara E, Bottaro G, *et al.*: **Autism and celiac disease: failure to validate the hypothesis that a link might exist.** *Biol Psychiatry* 1997, **42:**72–75.
19. McCarthy DM, Coleman M: **Response of intestinal mucosa to gluten challenge in autistic subjects.** *Lancet* 1979, **2:**877–878.
20. Huebner FR, Lieberman KW, Rubino RP, Wall JS: **Demonstration of high opioid-like activity in isolated peptides from wheat gluten hydrolysates.** *Peptides* 1984, **5:**1139–1147.
21. Brantl V: **Novel opioid peptides derived from human beta-casein: human beta-casomorphins.** *Eur J Pharmacol* 1984, **106:**213–214.
22. 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.
23. Brantl V, Teschemacher H, Henschen A, Lottspeich F: **Novel opioid peptides derived from casein (beta-casomorphins). I. Isolation from bovine casein peptone.** *Hoppe-Seylers Zeitschrift Fur Physiologische Chemie* 1979, **360:**1211–1216.
24. Singh M, Rosen CL, Chang KJ, Haddad GG: **Plasma beta-casomorphin-7 immunoreactive peptide increases after milk intake in newborn but not in adult dogs.** *Pediatr Res* 1989, **26:**34–38.
25. Shattock P, Kennedy A, Rowell F, Berney T: **Role of neuropeptides in autism and their relationship with classical neurotransmitters.** *Brain Dysfunction* 1990, **3:**328–345.
26. Shattock P, Lowdon G: **Proteins, peptides and autism. Part 2: Implication for the education and care of people with autism.** *Brain Dysfunction* 1991, **4:**323–334.
27. Reichelt K, Ekrem J, Scott H: **Gluten, milk proteins and autism: dietary intervention effects on behavior and peptide secretion.** *J Appl Nutr* 1990, **42:**1–12.
28. Zagon I, McLaughlin P: **Endogenous opioid systems regulate cell proliferation in the developing rat brain.** *Brain Res* 1987, **412:**68–72.
29. Bouvard MP, Leboyer M, Launay JM, *et al.*: **Low-dose naltrexone effects on plasma chemistries and clinical symptoms in autism: a double-blind, placebo-controlled study.** *Psychiatry Res* 1995, **58:**191–201.
30. Knivsberg AM, Reichelt KL, Nodland M, Hoien T: **Autistic syndromes and diet: a follow-up study.** *Scand J Educ Res* 1995, **39:**223–236.
31. Lucarelli S, Frediani T, Zingoni AM, *et al.*: **Food allergy and infantile autism.** *Panminerva Med* 1995, **37:**137–141.
32. Halsey NA, Hyman SL: **Measles-mumps-rubella vaccine and autistic spectrum disorder: report from the New Challenges in Childhood Immunizations Conference convened in Oak Brook, Illinois, June 12-13, 2000.** *Pediatrics* 2001, **107:**E84.
33. Gershon MD: *The Second Brain: A Groundbreaking New Understanding of Nervous Disorders of the Stomach and Intestine.* New York: HarperPerennial; 1998.