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Incidence of Gastrointestinal Symptoms in Children With Autism: A Population-Based Study



WHAT'S KNOWN ON THIS SUBJECT: Recently, interest has focused on the potential association between autism and gastrointestinal pathology. This association has widespread popular acceptance, but epidemiologic studies investigating the relationship between autism and gastrointestinal symptoms have been limited.



WHAT THIS STUDY ADDS: This study provides data that compare the incidence of gastrointestinal symptoms between children with autism and age- and gender-matched control subjects using a population-based cohort.

abstract

OBJECTIVE: To determine whether children with autism have an increased incidence of gastrointestinal symptoms compared with matched control subjects in a population-based sample.

DESIGN/METHODS: In a previous study including all of the residents of Olmsted County, Minnesota, aged <21 years between 1976 and 1997, we identified 124 children who fulfilled criteria on the basis of *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*, for a research diagnosis of autism. Two matched control subjects were identified for each case subject. Through the Rochester Epidemiology Project, all medical diagnoses, are indexed for computerized retrieval. Gastrointestinal diagnoses before 21 years of age were grouped into 5 categories: (1) constipation; (2) diarrhea; (3) abdominal bloating, discomfort, or irritability; (4) gastroesophageal reflux or vomiting; and (5) feeding issues or food selectivity. The cumulative incidence of each category was calculated by using the Kaplan-Meier method. Cox proportional hazards models were fit to estimate the risk ratios (case subjects versus control subjects) and corresponding 95% confidence intervals.

RESULTS: Subjects were followed to median ages of 18.2 (case subjects) and 18.7 (control subjects) years. Significant differences between autism case and control subjects were identified in the cumulative incidence of constipation (33.9% vs 17.6%) and feeding issues/food selectivity (24.5% vs 16.1). No significant associations were found between autism case status and overall incidence of gastrointestinal symptoms or any other gastrointestinal symptom category.

CONCLUSIONS: As constipation and feeding issues/food selectivity often have a behavioral etiology, data suggest that a neurobehavioral rather than a primary organic gastrointestinal etiology may account for the higher incidence of these gastrointestinal symptoms in children with autism. *Pediatrics* 2009;124:680–686

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KEY WORDS

autism, constipation, food selectivity, gastrointestinal diseases

ABBREVIATIONS

CI—confidence interval

RR—risk ratio

MMR—measles mumps and rubella

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Autism is a neurodevelopmental disorder of unknown etiology with onset before 3 years of age and characterized by severe impairment in reciprocal social interaction and communication and a pattern of repetitive or stereotyped behavior.¹ Recently, interest has focused on the potential association between autism and gastrointestinal pathology. Case series from patients referred to pediatric gastroenterology clinics have suggested that children with autism may have an increased prevalence of gastrointestinal symptoms, including constipation, chronic loose stools, abdominal pain, and gaseousness/bloating.²⁻⁴ Some investigators have reported an association between autism and chronic inflammatory intestinal disease, reflux esophagitis, gastritis, and disaccharide malabsorption.⁵⁻⁸ These findings have led to a hypothesis that gastrointestinal dysfunction resulting from an autism-specific enterocolitis is the etiology of the neurobehavioral features observed in children with autism, via a "leaky gut" that results in an autoimmune or gut-mediated toxic encephalopathic process.^{2,9} Many families, searching for any biomedical intervention that may help their children with autism, have embraced this hypothesis. As a result, restrictive diets and other nutritional or gastrointestinal therapies, such as the gluten-free, casein-free diet¹⁰; intravenous secretin¹¹; prescription of antifungal medications to treat purported fungal overgrowth in the gut¹⁰; and dietary supplementation with vitamins, minerals,¹² or omega-3 fatty acids¹³ have become widely popular interventions for children with autism, despite a lack of evidence regarding their safety or efficacy.

Despite this widespread popular acceptance of a link between autism and gastrointestinal disease, epidemiologic studies investigating the relationship between autism and gastrointestinal

symptoms are limited. Population-based studies are required to determine whether the incidence of gastrointestinal symptoms in children with autism is truly increased compared with the general population. Thus, the goal of this study was to compare the incidence of gastrointestinal symptoms between children with autism and age- and gender-matched control subjects using a population-based cohort.

METHODS

Study Setting and Subjects

More than 95% of all medical care in Olmsted County, Minnesota, is provided locally by the Mayo Clinic and Olmsted Medical Center. Through the Rochester Epidemiology Project, all of the inpatient and outpatient diagnoses are indexed for computerized retrieval (medical index).¹⁴ The population is characterized by virtually universal access to high-quality health care; hence, medical charts are available for >95% of residents of the county. Medical charts contain complete, detailed information on all of the medical care provided to county residents, including developmental, psychiatric, neurologic, and psychological assessments. Medical charts also contain documentation from all of the well-child visits, including information on developmental progress and problems. All of the gastrointestinal diagnoses (and gastrointestinal symptoms) are also included in the medical index.

In a previous study among all of the residents of Olmsted County, aged <21 years, between 1976 and 1997, 124 children were identified who fulfilled criteria on the basis of the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*, for a research diagnosis of autism.¹⁵ Case identification was not based on the clinical diagnosis at the time of the medical visit but on information collected from review of the complete

medical and school records of each case subject. A detailed description of the case identification strategy has been published previously.¹⁵ Three of the autism incident case subjects have subsequently denied research authorization, leaving 121 case subject in the current study. Two control subject were selected for each autism case subject from Olmsted County residents seen at the Mayo Clinic and Olmsted Medical Center. Control subject were matched on gender, age, year of first registration as a patient, and duration of follow-up.

All of the gastrointestinal diagnoses or abnormal gastrointestinal symptoms reported in the medical charts of the autism incident case subjects and the matched control subjects before 21 years of age were identified using the resources of the Rochester Epidemiology Project. We first reviewed a list of all of the gastrointestinal diagnoses and gastrointestinal symptoms documented in the medical index for all of the autism case subjects and their matched control subjects. We then grouped these gastrointestinal diagnoses and symptoms into 5 categories: (1) constipation; (2) diarrhea; (3) abdominal bloating, discomfort, or irritability; (4) gastroesophageal reflux or vomiting; and (5) feeding issues or food selectivity. These categories were chosen after reviewing the literature related to gastrointestinal symptoms that have been reported to be common in patients with autism.¹⁶ The gastrointestinal symptoms described in the literature are nonspecific and have included chronic diarrhea, constipation, foul-smelling stools, gaseousness, abdominal bloating, and abdominal pain, vomiting, and belching.¹⁷ In our study, each specific gastrointestinal diagnosis/symptom was assigned to 1 of the 5 research categories described above. Examples of specific gastrointestinal diagnoses/symptoms corresponding

TABLE 1 Examples of Specific Gastrointestinal Symptoms/Diagnoses Relevant to Each Research Category

Research Category	Specific Gastrointestinal Diagnosis/Symptoms
Constipation	Encopresis, anal fissure, hemorrhoids, or obstipation
Diarrhea	Enteritis, colitis, gastroenteritis, or loose stool
Gastroesophageal reflux, vomiting	Emesis, nausea and vomiting, esophagitis, or Mallory-Weiss syndrome
Abdominal discomfort, irritability	Abdominal pain, dyspepsia, stomachache, or gastritis
Feeding issues and food selectivity	Feeding problem, lactose intolerance, loss of appetite, or loss of weight

with each of the 5 gastrointestinal research categories are given in Table 1. The protocol was approved by the institutional review boards of the Mayo Clinic and Olmsted Medical Center.

Statistical Analysis

Patients were followed from their date of birth to their date of last follow-up before 21 years of age. For each gastrointestinal symptom category, patients were followed until the date of their first diagnosis; otherwise, they were censored at the date of their last follow-up. The cumulative incidence of each gastrointestinal symptom category was calculated using the Kaplan-Meier method. Cox proportional hazards models were fit to estimate the risk ratios (RRs) (case subjects versus control subjects) and corresponding 95% confidence intervals (CIs).

RESULTS

Subjects were followed to median ages of 18.2 years (case subjects) and 18.7 years (control subjects). Subjects fulfilled research diagnostic criteria for autism at a mean age of 6.1 years, although subjects typically had their first documented autism symptom between ages 2 and 3 years.¹⁵ Seventy-six percent of both case and control subjects were boys, and 24% were girls (Table 2). There were significant differences between autism case and control subjects in the cumulative incidence of constipation by age 20 years (33.9% vs 17.6%; RR: 1.97 [95% CI: 1.25–3.10]; $P = .003$) and feeding issues/food selectivity (24.5% vs 16.1%; RR: 1.95 [95% CI: 1.18–3.24]; $P = .009$). There was no significant association between autism case status and

overall incidence of gastrointestinal symptoms (RR: 1.21), diarrhea (RR: 1.34), gastroesophageal reflux/vomiting (RR: 1.55), or abdominal bloating/discomfort/irritability (RR: 1.03; Table 3).

Few subjects had specific gastrointestinal diseases: 1 patient with autism had Crohn disease, 1 control subject had milk allergy, 2 control subjects had lactose intolerance, and 1 patient with autism had intestinal disaccharidase deficiency. We found 2 cases of pancreatitis, 1 among case subjects and the other among control subjects. No diagnoses of celiac disease were noted among either case or control subjects.

DISCUSSION

Our study is unique, because, to our knowledge, there are no published, long-term population-based studies of the incidence of gastrointestinal symptoms in children with autism compared with age- and gender-matched control subjects. We found no significant difference in the overall cumulative incidence of gastrointestinal symptoms between case and control subjects, although children with autism had a higher incidence of constipation and feeding issues/food selectivity. We found few subjects with specific diagnoses of gastrointestinal diseases, whereas the majority of both case and control subjects had nonspecific gastrointestinal symptoms.

Our findings are consistent with previous reports that have found that children with autism do not have an increased rate of either gastrointestinal disorders in general^{17,18} or celiac disease in particular.¹⁹ In our study, the frequency of gastrointestinal symptoms among both case and control subjects was high (77.2% vs 72.2%, respectively). Previous studies have reported a 9.0% to 70.0% frequency of gastrointestinal problems in children with autism.^{3,4,18} The highest previous estimates included a lifetime preva-

TABLE 2 Demographic Summary of Autism Case and Matched Control Subjects

Characteristic	Control Subjects (<i>N</i> = 242)	Case Subjects (<i>N</i> = 121)
Gender, <i>n</i> (%)		
Female	58 (24)	29 (24)
Male	184 (76)	92 (76)
Year of birth		
Median	1987	1987
IQR	1981–1991	1981–1991
Range	1963–1995	1963–1995
Age met autism research criteria, y		
Mean (SD)	NA	7.3 (4.8)
Median	NA	6.1
IQR	NA	3.4–9.7
Range	NA	1.9–20.9
Age at last follow-up before age <21, y		
Mean (SD)	17.4 (3.6)	16.0 (5.2)
Median	18.7	18.2
IQR	15.0–20.4	13.4–20.2
Range	3.8–21.0	2.7–21.0

IQR indicates interquartile range (25th–75th percentiles); NA, not applicable.

TABLE 3 Cumulative Incidence of Gastrointestinal Symptoms in Autism Case and Matched Control Subjects

Gastrointestinal Diagnosis Category	Autism Case Subjects (N = 121)						Matched (2:1) Control Subjects (N = 242)						RR (95% CI)	P
	No. of Patients With a Diagnosis	Cumulative Incidence, % ^a					No. of Patients With a Diagnosis	Cumulative Incidence, % ^a						
		By 1 y	By 5 y	By 10 y	By 15 y	By 20 y		By 1 y	By 5 y	By 10 y	By 15 y	By 20 y		
Any of the diagnoses of interest	87	20.7	46.5	58.4	67.2	77.2	167	15.7	36.8	49.9	62.0	72.2	1.21 (0.93–1.57)	.15
Constipation	35	1.7	6.7	17.7	26.6	33.9	40	0.4	7.0	10.9	15.8	17.6	1.97 (1.25–3.10)	.003
Diarrhea	57	10.7	34.0	40.3	46.5	50.3	93	12.4	24.8	31.2	36.1	41.1	1.34 (0.96–1.86)	.085
Gastroesophageal reflux and vomiting	26	4.1	7.5	14.9	21.3	25.3	38	2.1	4.5	8.3	13.1	16.9	1.55 (0.94–2.55)	.088
Abdominal discomfort and irritability	44	5.8	12.4	17.0	29.2	44.9	92	3.3	10.4	19.2	31.9	41.3	1.03 (0.72–1.47)	.87
Feeding issues and food selectivity	28	5.0	10.9	18.2	24.5	24.5	33	1.7	5.0	7.5	12.1	16.1	1.95 (1.18–3.24)	.009

^a The cumulative incidence estimates were calculated by using the Kaplan-Meier method to take into account the varying duration of follow-up across the subjects.

lence of gastrointestinal symptoms.⁴ Epidemiologic studies of the prevalence of gastrointestinal symptoms in individuals with typical development have also shown high rates.^{20,21} For example, a cross-sectional prevalence study showed that 28% of normal 8- to 10-year-old school children were constipated.²⁰ In addition, a population-based survey of children 10 to 11 years of age showed that 27% of subjects reported some gastrointestinal complaints during the previous 2 years.¹⁸ The higher prevalence of gastrointestinal symptoms in our study reflects the cumulative incidence during the period of follow-up to a median age of 18.2 years in case subjects and 18.7 years in control subjects.

Although we did not find an overall difference in the rate of gastrointestinal symptoms between children with and without autism, we did find that children with autism were more likely to manifest feeding issues/food selectivity and constipation. The ritualistic tendencies, need for routine, and insistence on sameness that are characteristic of children with autism may lead these children to choose and demand stereotyped diets that may result in an inadequate intake of fiber, fluids, and other food constituents.¹⁷ Thus, behaviorally related food selectivity may, in turn, lead to constipation.²² In a previ-

ous study, we reported that 52.4% of the children with autism in this population were treated with stimulant medications to control symptoms of hyperactivity, impulsivity, and inattention.²³ Because appetite suppression is a known adverse effect of these medications, this may represent another factor that contributes to changes in eating patterns experienced by children with autism. In addition, many children with autism are treated with risperidone, and this may result in increased appetite and weight gain.^{24,25} Thus, it is possible that the difference in the incidence of both food selectivity and constipation that we found in children with autism compared with age and gender matched control subjects without autism is attributable to the behavioral features that define autism or to adverse effects of treatment with psychotropic medications rather than to an underlying autism-specific organic gastrointestinal disease.

Although we did not find an increased rate of gastrointestinal diagnoses among individuals with autism on an epidemiologic basis, a number of gastrointestinal abnormalities have been reported previously in children with autism. For example, a chronic inflammatory process and increased intestinal permeability have been demonstrated by endoscopic and histologic examination of the gastrointestinal

tract in some children with autism.^{5–8,26} However, these findings have not been replicated in other studies.²⁷ In addition, there have also been concerns raised about the potential role of the measles, mumps, and rubella (MMR) vaccine in the causation of autism.⁹ This theory hypothesizes that the MMR vaccine produces the enterocolitis that causes a “leaky gut” that leads to increased absorption of peptides with neurotoxic or neuroactive properties that produce the symptoms of autism.²⁸ This hypothesis was disproven in a recent study.²⁹ In addition, introduction of the MMR vaccine has not been associated with an increase in complaints about gastrointestinal problems in children with autism.³⁰ In addition, a dramatically increased incidence of autism has been associated with the withdrawal of the MMR vaccine in Japan.³¹ We demonstrated previously that the introduction of mandatory MMR vaccination did not correlate with the apparent increase in the incidence of autism in Olmsted County.¹⁵ In the current study, we identified only 1 subject with autism and an inflammatory bowel disorder (Crohn disease) in our cohort, as well as 1 with pancreatitis. Autism is a chronic neurodevelopmental disability, and traditional medicine does not offer any cures. Thus, complementary and alternative treatments

are widely provided to children with autism by parents who are searching for any biomedical intervention that they believe may help their children. Autistic behaviors are coincidentally first recognized by many parents at the same time that infants are weaned from breast milk or infant formulas and begun on whole milk and table foods, including table foods containing gluten. Combining this temporal relationship with belief in a gastrointestinal-autism connection, where opioid-like peptides derived from casein and gluten are hypothesized to be absorbed through leaky guts to cause the symptoms of autism, many parents of children with autism are being advised to place their children on very restrictive gluten- and casein-free diets. However, evidence to support the safety and efficacy of gluten- and casein-free diets in the treatment of children with autism is lacking.^{32,33} Urinary chromatographic profiles have shown no consistent patterns indicating excessive amounts of opioid-like compounds among individuals with autism.^{34–36} In addition, given the already increased food selectivity among children with autism, as confirmed in our study, additional dietary restriction may place these children at risk for nutritional deficiencies.^{10,26} In our cohort, we identified only 1 child with autism who had intestinal disaccharidase deficiency, whereas several control children had lactose intolerance or milk allergy.

Although hypothesized as another potential cause of a leaky gut, fungal overgrowth in the intestines has not been documented by endoscopy in children with autism.⁵ However, many parents of children with autism are encouraged to send samples of their children's urine to laboratories that claim to find urinary organic acids of fungal origin. Despite

the lack of evidence to support their use or safety, many children with autism are then treated with systemic antifungal medications and/or other vitamin, mineral, or dietary supplements. Although there is no evidence that these interventions improve autistic behavior, it is important to note that systemic antifungal medications are associated with liver toxicity, anemia, diarrhea, and exfoliative dermatitis.¹⁰ No subjects in our study, either case or control subjects, had a history of intestinal fungal overgrowth.

Several potential limitations of our study should be noted. First our study was retrospective. Therefore, it is possible that we failed to detect all of the autism incidence cases or that some gastrointestinal symptoms were undetected or incompletely documented in the medical charts. However, given the increased medical scrutiny to which children with autism are subjected, it is unlikely that gastrointestinal symptoms would be missed and not documented more frequently among autism case subjects than among control subjects. Furthermore, the completeness of the data and the availability of records for virtually all of the residents of Olmsted County minimize the possibility that cases of autism or information on gastrointestinal symptoms were missed. In the current study we did not compare the incidence of gastrointestinal symptoms in children with cognitive impairment without autism to those with autism, but this will be interesting to explore in a future study. The population of Olmsted county was ~98% white between 1976 and 1997,³⁷ which may limit the generalizability of these results to other populations. We also did not attempt to assess duration, severity, and recurrence of the gastrointestinal symptoms in case or control

subjects in this study, because our main aim was to assess the prevalence of gastrointestinal symptoms. This will be a goal of the next phase of this project.

CONCLUSIONS

Although there may exist subgroups of children with gastrointestinal disorders that contribute to their autistic behaviors, in this population-based study of children with research-identified autism, we found that the overall incidence of gastrointestinal symptoms did not differ between children with autism and control subjects. Children with autism did have an increased incidence of feeding issues/food selectivity and constipation, problems that may result from behavioral characteristics of children with autism rather than from primary organic gastrointestinal pathology. We did not find that children with autism were more likely to manifest gastrointestinal disorders; specifically, there was no apparent increased risk for inflammatory or malabsorptive disorders. Many children with autism are treated with restrictive diets, vitamin, mineral, and other dietary supplements, as well as various medications aimed at putative gastrointestinal disorders. The findings from our study suggest that such treatments should not be provided indiscriminately to children with autism unless there is explicit evidence indicating the presence of a gastrointestinal disorder in a specific case.

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