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

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Abstract

Objective—To determine whether children with autism have an increased incidence of gastrointestinal (GI) symptoms compared to matched controls in a population-based sample.

Design/Methods—In a previous study including all residents of Olmsted County, MN age < 21 years between 1976 and 1997, we identified 124 children who fulfilled DSM-IV based criteria for a research diagnosis of autism. Two controls were identified for each autism case, matched on gender, age, year of first registration, and duration of follow-up. Through the Rochester Epidemiology Project, all inpatient and outpatient diagnoses, including GI diagnoses, are indexed for computerized retrieval. GI diagnoses prior to 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 using the Kaplan-Meier method. Cox proportional hazards models were fit to estimate the risk ratios (RR: cases versus controls) and corresponding ninety-five percent confidence intervals (95% CI).

Results—Subjects were followed to median ages of 18.2 (cases) and 18.7 (control) years. There were significant differences between autism cases and controls in the cumulative incidence by age 20 of constipation (33.9% versus 17.6%; RR=1.97; 95% CI: 1.25–3.10; p = 0.003) and feeding issues/food selectivity (24.5 % versus 16.1%; RR=1.95; 95% CI: 1.18–3.24; p = 0.009). There was no significant association between autism case status and overall incidence of GI symptoms (RR=1.21), diarrhea (RR=1.34), gastroesophageal reflux/vomiting (RR=1.55), or abdominal bloating/discomfort/irritability (RR=1.03).

Conclusions—We found that children with autism had an increased incidence of constipation and feeding issues/food selectivity. Since these symptoms often have a behavioral etiology, our population-based data suggest a neurobehavioral rather than a primary organic gastrointestinal etiology, may account for the higher incidence of these GI symptoms in children with autism.

Keywords

autism; constipation; food selectivity; gastrointestinal diseases

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Introduction

Autism is a neurodevelopmental disorder of unknown etiology with onset before 3 years of age, 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 (GI) pathology. Case series from patients referred to pediatric gastroenterology clinics have suggested that children with autism may have an increased prevalence of GI 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 GI therapies, such as the gluten-free, casein-free diet,[10] intravenous secretin,[11] prescription of antifungal medications to treat purported fungal overgrowth in the gut,[10] and dietary supplementation with vitamins, minerals,[12] or omega-three fatty acids[13] 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 GI disease, epidemiologic studies investigating the relationship between autism and GI symptoms are limited. Population-based studies are required to determine whether the incidence of GI symptoms in children with autism is truly increased compared to the general population. Thus, the goal of this study is to compare the incidence of gastrointestinal symptoms between children with autism and age- and gender-matched controls, 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 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 records are available for more than 95% of residents of the county. Medical records contain complete, detailed information on all medical care provided to county residents, including developmental, psychiatric, neurologic, and psychological assessments. Medical records also contain documentation from all well-child visits, including information on developmental progress and problems. All GI diagnoses (and GI symptoms) are also included in the Medical Index.

In a previous study among all residents of Olmsted County, age < 21 years, between 1976 and 1997, 124 children were identified who fulfilled DSM-IV based criteria 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. A detailed description of the case identification strategy has been published previously.[15] Three of the autism incident cases have subsequently denied research authorization, leaving 121 cases in the current study. Two controls were selected for each autism case from Olmsted County residents seen at the Mayo Clinic and Olmsted Medical Center. Controls were matched on gender, age, year of first registration as patients, and duration of follow-up.

All the GI diagnoses, or abnormal GI symptoms reported in the medical records of the autism incident cases and the matched controls prior to 21 years of age were identified using the resources of the Rochester Epidemiology Project. We first reviewed a list of all GI diagnoses and GI symptoms documented in the Medical Index for all autism cases and their matched controls. We then grouped these GI 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 GI symptoms that have been reported to be common in patients with autism.[16] The GI 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 GI diagnosis/ symptom was assigned to one of the five research categories described above. Examples of specific GI diagnoses/symptoms corresponding to each of the five GI research categories are given in Table 1.

The protocol was approved by the institutional review boards of Mayo Clinic and Olmsted Medical Center.

STATISTICAL ANALYSIS

Patients were followed from their date of birth to their date of last follow-up prior to 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 (cases versus controls) and corresponding ninety-five percent confidence intervals (95% CI).

Results

Subjects were followed to median ages of 18.2 (cases) and 18.7 (control) years. 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 (12). Seventy-six percent of both cases and controls were male and 24% were female (Table 2). There were significant differences between autism cases and controls in the cumulative incidence by age 20 of constipation (33.9% versus 17.6%; RR=1.97; 95% CI: 1.25–3.10; p = 0.003) and feeding issues/food selectivity (24.5 % versus 16.1%; RR=1.95; 95% CI: 1.18–3.24; p = 0.009). There was no significant association between autism case status and overall incidence of GI 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 GI diseases: 1 patient with autism had Crohn's disease, 1 control subject had milk allergy, 2 controls had lactose intolerance, and 1 patient with autism had intestinal disaccharidase deficiency. We found two cases of pancreatitis, one among cases and the other among controls. No diagnoses of celiac disease were noted among either cases or controls.

Discussion

Our study is unique, since to our knowledge there are no published, long term population-based studies of the incidence of GI symptoms in children with autism compared to age- and gender-matched controls. We found no significant difference in the overall cumulative incidence of GI symptoms between cases and controls, although children with autism had a higher incidence of constipation and feeding issues/ food selectivity. We found few subjects with specific

diagnoses of GI diseases, while the majority of both cases and controls had nonspecific GI 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 GI symptoms among both cases and controls was high (77.2% versus 72.2%, respectively). Prior studies have reported a 9% to 70% frequency of GI problems in children with autism.[3, 4, 18] The highest previous estimates included lifetime prevalence of GI symptoms.[4] Epidemiologic studies of the prevalence of GI 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 years aged school children were constipated.[20] Further, a population-based survey of children 10 to 11 years of age showed that 27% of subjects reported some GI complaints during the last 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 in cases and 18.7 years in controls.

While we did not find an overall difference in the rate of GI 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 previous 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] As appetite suppression is a known side effect of these medications, this may represent another factor that contributes to changes in eating patterns experienced by children with autism. Further, 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 to age and gender matched controls without autism is attributable to the behavioral features that define autism or to side 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 GI diagnoses among individuals with autism on an epidemiologic basis, a number of gastrointestinal abnormalities have been previously reported in children with autism. For example, a chronic inflammatory process and increased intestinal permeability have been demonstrated by endoscopic and histological examination of the GI tract in some children with autism. [5–8, 26] However, these finding have not been replicated in other studies.[27] Further, there have also been concerns raised about the potential role of the MMR (Measles, Mumps, Rubella) 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] Further, a dramatically increased incidence of autism has been associated with the withdrawal of the MMR vaccine in Japan.[31] We previously demonstrated that the introduction of mandatory MMR vaccination did not correlate with the apparent increase in the incidence of autism in Olmsted County, Minnesota.[15] In the current study, we identified only one subject with autism and an inflammatory bowel disorder (Crohn's 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 GI-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, further 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, while 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. While 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 cases or controls, 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 autism incidence cases or that some GI symptoms were undetected or incompletely documented in the medical records. However, given the increased medical scrutiny to which children with autism are subjected, it is unlikely that GI symptoms would be missed and not documented more frequently among autism cases than among controls. Furthermore, the completeness of the data and the availability of records for virtually all 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 GI 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 approximately 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 GI symptoms in cases or controls in this study, as our main aim was to assess the prevalence of GI symptoms. This will be a goal of the next phase of this project

Conclusions

Although, there may exist subgroups of children with GI 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 GI symptoms did not differ between children with autism and controls. 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 GI pathology. We did not find that

children with autism were more likely to manifest GI 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, and various medications aimed at putative GI 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 GI disorder in a specific case.

Acknowledgments

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Abbreviations

GI, gastrointestinal; RR, risk ratios; CI, confidence intervals; MMR, measles, mumps, and rubella; No, number; Pts, patients; Dx, diagnosis.

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Table 1

Examples of specific GI symptoms /diagnoses relevant to each Research category

GI Diagnoses/Symptoms	
Research Category	**Specific GI Diagnosis/Symptoms**
1)- Constipation	Encopresis, anal fissure, hemorrhoids, obstipation.
2)- Diarrhea	Enteritis, colitis, gastroenteritis, loose stool.
3)- Gastroesophageal reflux, vomiting	Emesis, nausea and vomiting, esophagitis, Mallory-Weiss syndrome
4)- Abdominal discomfort, irritability	Abdominal pain, dyspepsia, stomach ache, gastritis.
5)- Feeding issues & food selectivity	Feeding problem, lactose intolerance, loss of appetite, loss of weight.

Table 2

Demographic summary of autism cases and matched controls

	Controls (N=242)	Cases (N=121)
Gender		
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 (years)		
Mean (SD)		7.3 (4.8)
Median		6.1
IQR*		3.4, 9.7
Range		(1.9–20.9)
Age at last follow-up prior to age <21 (years)		
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 = interquartile range, 25th and 75th percentiles.

Table 3

Cumulative incidence* of GI symptoms in autism cases and matched controls

Gastrointestinal diagnosis category	Autism Cases (N=121)						Matched (2:1) Controls (N=242)						RR (95% CI)	P value
	No. pts with a dx	Cumulative Incidence *					No. pts with a dx	Cumulative Incidence *						
		By age 1	By age 5	By age 10	By age 15	By age 20		By age 1	By age 5	By age 10	By age 15	By age 20		
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)	0.15
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)	0.003
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)	0.085
Gastroesophageal reflux & 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)	0.088
Abdominal discomfort & 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)	0.87
Feeding issues & 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)	0.009

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