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Gastrointestinal Symptoms in a Sample of Children with Pervasive Developmental Disorders

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Abstract *Objective* To evaluate gastrointestinal (GI) problems in a large, well-characterized sample of children with pervasive developmental disorders (PDDs). *Methods* One hundred seventy two children entering one of two trials conducted by the Research Units on Pediatric Psychopharmacology (RUPP) Autism Network were assessed comprehensively prior to starting treatment and classified with regard to GI symptoms. *Results* Thirty nine (22.7%) were positive for GI problems, primarily constipation and diarrhea. Those with GI problems were no different from subjects without GI problems in demographic characteristics, measures of adaptive functioning, or autism symptom severity. Compared to children without GI problems, those with GI problems showed greater symptom severity on measures of irritability, anxiety, and social withdrawal. Those with GI problems were also less likely to respond to treatment.

Keywords Autism · Chronic gastrointestinal problems · Pervasive developmental disorders

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Introduction

Autistic disorder (autism) is a neurodevelopmental disorder of early childhood onset characterized by delays in socialization and language, as well as repetitive behavior or unusual preoccupations. In the Diagnostic and Statistical Manual—Fourth Edition (DSM-IV), autism is categorized as a pervasive developmental disorder (PDD) in addition to Asperger's Disorder, Pervasive Developmental Disorder—Not Otherwise Specified (PDD-NOS), Rett's Disorder, and Childhood Disintegrative Disorder (American Psychiatric Association 2000). Differential diagnosis is based on the combination and degree of impairment across these domains. Children with autism show impairment across all three domains: social, communication and repetitive behavior. By contrast, children with Asperger's disorder do not have a history of language delay, but do show social delays and intense preoccupation with specific topics. In PDD-NOS, children have a degree of social delay, but the language delay, or repetitive behavior may be not sufficiently prominent to warrant a more specific diagnosis of autism or Asperger's disorder (Scahill 2005). In addition to these qualitative developmental delays, children with PDDs are more likely to have intellectual disability ranging from 25% to 75% depending on the source of sample or the specific PDD diagnosis (Scahill 2005).

The etiology of autism is unknown. It is likely heterogeneous. (Autism Genome Project Consortium 2007). Although there is considerable evidence that genetic factors play a prominent role in the etiology of autism, (Gupta and State 2007), environmental exposures may also be important (Lawler et al. 2004). Gene-environment interactions have also been proposed to explain the etiological and biological heterogeneity of the disorder (Herbert et al. 2006).

Historically, the prevalence of autism was estimated to fall between 2 and 5 children per 10,000 (Fombonne 2005). Due to incremental broadening in the diagnostic criteria, improved sampling and better assessment methods, the prevalence is now placed in a range from 15 to 20 per 10,000 (Fombonne 2005). Taken together, the prevalence of Autistic Disorder, Asperger's Disorder, and PDD-NOS is 6 children per 1,000 (Fombonne 2005). Based on observations in samples ascertained from specialty clinics, some investigators have focused on a potential association between PDD and gastrointestinal (GI) problems (Horvath et al. 1999). In an attempt to integrate the seeming rise in prevalence of PDD and the occurrence of GI problems, it has been proposed that the MMR vaccine in vulnerable children increases the risk of PDD through the GI mechanism (Wakefield et al. 2000). Findings from epidemiological studies have not supported the proposed link between vaccination and autism and estimates of the prevalence of GI symptoms in children with PDD (Fombonne and Chakrabarti 2001; Black et al. 2002; Taylor et al. 2002; Fombonne et al. 2006) are not far from the prevalence of GI problems in normally developing children (Saps et al. 2006).

GI problems described in children with PDD encompass a wide range of symptoms including heartburn, gastritis, abdominal pain, bloating, food intolerance, chronic constipation, and diarrhea (Erickson et al. 2005). Upper GI tract endoscopic findings include reflux esophagitis, chronic gastritis, and chronic doudenitis (Horvath et al. 1999); lower GI tract pathology includes chronic ileocolonic lymphoid nodular hyperplasia and inflammation, referred to as "autistic enterocolitis" (Wakefield et al. 2000). The pathological findings in the GI tracts of individuals with autism have generated the hypothesis that inflammatory and immune changes lead to increased intestinal permeability with associated adverse central nervous system consequences that may affect development and behavior D'Eufemia et al. (1996).

Support for observations of GI problems in autism is inconsistent and some of the published data are contradictory. Case reports describe improvements in behavior and cognition following dietary exclusion of gluten, casein or both (Lucarelli et al. 1995; Knivsberg et al. 1995). Analysis of dietary intake of well-characterized cohort of children diagnosed with ASD does not suggest an association between diet and GI symptoms (Levy et al. 2007). The presence of GI symptoms has also been associated with the presence of developmental regression (Afzal et al. 2003). Among children diagnosed with ASD attending a specialized care program, however, regression was not found to be associated with GI symptoms (Molloy and Manning-Courtney 2003). The frequently observed behavioral difficulties in children diagnosed with autism have also been described as related to GI abnormalities (Horvath and Perman 2002b). Moreover, reports suggest that treatment of the GI problem may be associated with improvements in behavior (Balzola et al. 2005). Systematic comparisons of clinical characteristics in children with GI symptoms and GI asymptomatic children with PDD are few in number and replication all but nonexistent. If there is an association between GI problems and dysfunctional behavior, it would be important to identify this association and characterize affected patients. The purpose of this study is to evaluate the prevalence and impact of GI problems in a large sample of children with PDD who were enrolled in one of two multisite clinical trials. These subjects were ascertained without reference to the presence or absence of GI problems. Using all available information collected in the context of two multisite medication trials, we compared children with PDD plus GI problems to those without GI problems to look for differences on measures of autism core symptom severity, IQ, adaptive functioning, and maladaptive behavior.

Methods

Setting and Subjects

The sample of 172 medication-free children (145 males and 27 females) had a mean age of 8.3 ± 2.6 years (range 5–17 years). Of the 172 subjects, 152 (88.4%) were diagnosed with autistic disorder, 6 (3.5%) were diagnosed with Asperger's disorder and 14 (8.1%) with PDD-NOS. Subjects were enrolled in one of two randomized clinical trials conducted by the Research Units on Pediatric Psychopharmacology (RUPP) Autism Network. The first study was a double-blind, placebo-controlled trial of risperidone in children with autism accompanied by aggression, tantrums and self-injury ($n = 100$) (Research Units on Pediatric Psychopharmacology, RUPP Autism Network (2002). The second trial was a double-blind, placebo-controlled trial of methylphenidate in children with PDD and hyperactivity ($n = 72$) (Research Units on Pediatric Psychopharmacology, RUPP Autism Network 2005a). The characteristics of the combined sample have been described in previous reports (Scahill et al. 2006; Sukhodolsky et al. 2007). These projects were approved by the

Institutional Review Boards at each participating medical center and written informed consent was provided by a parent or guardian before individual study data were collected.

Procedures

Prior to randomization in either trial, each child received a comprehensive assessment to establish the PDD diagnosis and characterize them across several domains including IQ, adaptive functioning, and the severity of maladaptive behavior (Arnold et al. 2000; Research Units on Pediatric Psychopharmacology, RUPP Autism Network 2002, 2005a). Subjects also received a health assessment that included complete medical history, review of systems, and a physical examination by a pediatric nurse practitioner, child psychiatrist or pediatrician. In addition, the primary caretaker was systematically interviewed with a structured questionnaire called the *Side Effects Review Form*. This instrument, which was developed by the RUPP Autism Network for our multisite studies, is a 32-item checklist containing specific items across the major body systems, as well as sleep and appetite. Sample GI questions from the form are presented in Fig. 1.

The purpose of the *Side Effects Review Form* was to establish the presence or absence of specific problems prior to drug exposure and to track changes in these same domains during the trial. There were slight differences in the *Side Effects Review Form* across the two studies; however, the interview method was virtually identical. The interview with the primary care taker was conducted by a child psychiatrist, a child psychiatric nurse practitioner, or a pediatrician. Positive answers were followed up with additional inquiries about severity and then rated *mild, moderate or severe*. Cross-site training established the following conventions: a rating of mild was given when the problem was present, but not a source of impairment and there was no need of intervention; a rating of *moderate* was used when the problem caused some impairment or required intervention to prevent likely impairment; the rating of *severe* was used when the problem caused impairment and required intervention. Throughout both studies, problems rated as *severe* were discussed on weekly case review panels, which reinforced the anchor points for these ratings.

Does your child have any current health complaints? □ Yes □ No

Has your child had any recent injuries or illnesses? □ Yes □ No

Has your child seen doctor for any reason? □ Yes □ No

Is your child taking any new medications (over the counter or prescription)?

Side Effect	Absent	Mild	Moderate	Severe
Constipation	0	1	2	3
Diarrhea/loose stools	0	1	2	3
Dyspepsia (acid stomach)	0	1	2	3
Nausea or vomiting	0	1	2	3

Fig. 1 Sample questions from the Side Effects Review Form*. (*The full form can be made available for review upon request)

For this study, presence of a GI problem was determined by a report in the medical history of a past, current, or chronic GI problem. A GI problem was defined as one that caused impairment in function, had been brought to the attention of a medical professional and had been or was currently under treatment. In addition, a pre-treatment rating of *moderate* or *severe* on the *Side Effects Review Form* in response to one or more GI questions (Fig. 1), led to a classification of GI positive.

Study participants were medication-free for at least 2 weeks for all psychotropic medications (4 weeks for fluoxetine or depot neuroleptics) prior to their baseline visit.

Measures

Autism Diagnostic Interview-Revised (ADI-R) (Lord et al. 1997)

Training on the ADI-R was rigorous, involving didactic sessions, supervised administration of a live interview, reliable rating of a taped interview, and demonstrated competence in at least three taped interviews by the new rater.

Intellectual Functioning

Children were assessed on one of several intelligence tests: Wechsler Intelligence Scales for Children-III (Wechsler 1991) (29% of the sample); Leiter International Performance Scale-Revised (Roid and Miller 1997) (28% of the sample); Mullen Scales of Early Learning (Mullen 1995) (23% of the sample); Slosson Intelligence Test (Jensen and Armstrong 1985) (14% of the sample); or Wechsler Preschool and Primary Scale of Intelligence-Revised (Wechsler 1989) (2% of the sample). Eighteen subjects (10%) could not be tested due to lack of cooperation. Because several different tests were employed, children were classified categorically (e.g., average intelligence, borderline, mild, moderate, or severe mental retardation).

Vineland Adaptive Behavior Scales

The Vineland is a semi-structured, parent interview that measures the child's competence in communication, daily living skills, and socialization. The scale is a standard assessment in children with developmental disabilities with excellent reliability and validity for each domain (Sparrow et al. 1984).

Aberrant Behavior Checklist (ABC)

The ABC has normative data in developmentally disabled populations (Aman et al. 1985; Brown et al. 2002) and is sensitive to change (Research Units on Pediatric Psychopharmacology, RUPP Autism Network 2002, 2005a, b).

Children's Yale-Brown Obsessive Compulsive Scale for Pervasive Developmental Disorder (CYBOCS-PDD)

This interview (Scahill et al. 2006) was administered to primary caretakers at baseline when subjects were medication-free and at regular intervals throughout the medication trials. In most instances, the child was present during the assessments which allowed direct participation in the interview and first-hand observation of behavior.

Child and Adolescent Symptom Inventory (CASI) Anxiety Scale

This 20-item parent-rating provides a dimensional measure of anxiety symptoms. The reliability and validity of this 20-item scale was demonstrated in this same combined sample of study subjects (Sukhodolsky et al. 2007).

Analytic Strategy

First, we analyzed the percentage of GI positive subjects across the five sites and found no significant differences. In the absence of a significant difference across sites, data were combined. Continuous variables were evaluated by independent sample *t*-tests; categorical variables were evaluated by chi square tests. All analyses were two tailed tests. We set the p value for statistical significance at 0.01 to reduce the likelihood of chance findings on the ADI-R, IQ, Vineland domains, ABC subscales, and CYBOCS-PDD. Exploratory analysis compared the 20-item CASI Anxiety scale across GI positive and GI negative groups in the combined sample and the rate of positive response to treatment in GI positive and GI negative subjects within each study.

Results

Of the 172 patients surveyed, 39 (22.7%) were positive for GI symptoms; 26 by medical history, and 6 by the Side Effects Review Form at baseline. Seven subjects were identified by both both methods; four children had more than one GI problem. Of those with more than one GI problem, two had a history of constipation and diarrhea, one with nausea and GI reflux, and one with enterocolitis and vomiting. The GI complaints reported in the medical history were: constipation ($n = 14$), diarrhea ($n = 5$), gastroesophageal reflux ($n = 4$), vomiting ($n = 3$), pyloric stenosis ($n = 2$), enterocolitis ($n = 1$), lactose intolerance ($n = 2$), bowel malrotation ($n = 1$), colon polyps ($n = 1$), stomach cramps ($n = 1$). The GI problems identified by the Side Effects Review Form at baseline were: diarrhea ($n = 4$ moderate, $n = 3$ severe), constipation ($n = 6$ moderate) and stomachaches ($n = 2$ moderate).

Of the subjects participating in the risperidone study, 29% were identified positive for GI symptoms, whereas 13.9% of the subjects in the methylphenidate study were identified positive for GI symptoms ($\chi^2 = 5.45$; $p = 0.02$). We viewed this heterogeneity as an advantage for this study.

Subjects in the risperidone trial were more impaired on measures of behavioral problems, lower in IQ and lower on measures of adaptive behavior than those in the methylphenidate trial (Table 1).

Not surprisingly, given the differences in entry criteria, the risperidone sample had a mean ABC Irritability score at baseline of 25.72 ± 7.54 compared with 17.29 ± 10.47 in the methylphenidate study ($p < 0.01$).

As shown in Table 2, there were no differences between the GI positive and GI negative groups on demographic variables such as age, sex, ethnicity, weight, rate of placement in special education classes, or percentage of subjects living in a two parent family in the combined sample.

When examining the core symptoms of autism, there were no differences between the GI positive and GI negative groups in relation to impairments in communication, social development or stereotypic behavior as measured on the ADI-R. Using standard scores, there were no differences on any Vineland domains across GI positive and GI negative groups. Using an IQ cutoff of below 70 for mental retardation, there was no difference in the rate of intellectual disability in the GI positive and GI negative subjects. As shown in Table 2, the GI positive group had significantly higher scores on the Irritability and Social Withdrawal subscales of the ABC. The two groups were not significantly different on the Stereotypy, Hyperactivity, or Inappropriate Speech subscales. There was no difference between groups in the severity of compulsive behaviors as measured by the CYBOCS-PDD. On the 20-item CASI Anxiety scale, the GI positive group was rated significantly higher than the GI negative group.

The GI negative subjects were two times more likely to show a positive response to treatment than those who were GI positive ($\chi^2 = 3.86$; $p = 0.05$). Given this difference, we examined whether this association was true in both studies. In the methylphenidate trial 43 of 62 GI negative subjects showed a positive response to treatment compared to 6 of 10 GI positive subjects ($\chi^2 = 0.35$; $p = 0.56$) (see

Table 1 Sample Comparison between MPH and risperidone studies

Variable	Risperidone[a] ($N = 100$)		MPH ($N = 72$)		
	X	*SD*	*X*	*SD*	*p*
Age	8.75	2.73	7.55	2.21	0.01
Weight	34.65	18.22	30.32	13.72	0.10
ABC					
Irritability	25.72	7.54	17.29	10.47	0.01
Social Withdrawal	16.56	8.51	12.22	9.08	0.02
Stereotypy	9.78	4.74	7.79	6.01	0.02
Hyperactivity	32.20	9.09	33.22	8.77	0.46
Inappropriate speech	5.67	3.92	6.01	3.94	0.57
Vineland					
Communication	43.54	15.54	61.09	22.05	0.01
Daily living	37.48	18.67	52.41	20.45	0.01
Socialization	48.25	13.67	60.64	16.63	0.01
Adaptive composite	40.19	14.92	52.16	19.32	0.01
ADI					
Communication	17.36	4.21	14.29	4.62	0.01
Social	26.18	3.37	20.72	5.31	0.01
Stereotypy	7.82	2.67	7.36	2.63	0.27
CASI anxiety	13.75	8.31	13.13	8.86	0.64
	n	%	*n*	%	X^2 *p*
GI positive	29	29.0	10	13.9	0.02
GI negative	71	71.0	62	86.1	
Treatment responder	70	70.0	49	68.1	0.79
Treatment nonresponder	30	30.0	23	31.9	
IQ < 70[b]	73	81.1	32	50.0	0.01
IQ ≥ 70	17	18.9	32	50.0	
Male	81	81.0	64	88.9	0.16
Female	19	19.0	8	11.1	
Age ≥ 8.3 years[c]	48	48.0	23	31.9	0.04
Age < 8.3 years	52	52.0	49	68.1	

[a] one subject in risperidone trial had missing data at baseline; [b] missing IQ data for 18 subjects; [c] mean age for sample. ABC = Aberrant Behavior Checklist; ADI = Autism Diagnostic Inventory; CASI Anxiety = Child and Adolescent Symptom Inventory Anxiety scale

Research Units on Pediatric Psychopharmacology, RUPP Autism Network 2005a for a definition of positive reference). In the risperidone study 54 of 71 GI negative subjects showed a positive response to treatment compared to 16 of 29 in the GI positive group ($\chi^2 = 4.28$; $p = 0.04$) (positive response defined Research Units on Pediatric Psychopharmacology, RUPP Autism Network 2002, 2005b). Thus the association between treatment response and GI status was true for the risperidone sample only.

Twenty-five of the 133 GI negative subjects endorsed mild GI symptoms (GI symptoms present without impairment and not requiring intervention). Data analyses were repeated with these mildly affected subjects removed and the findings were virtually identical. There were no differences between the GI positive and GI negative groups in adaptive behavior, symptoms of autism, or intellectual functioning. Higher scores on the ABC Irritability and

Table 2 Comparison of clinical characteristics GI positive and GI negative children

Variable	GI Positive ($n = 39$)		GI Negative ($n = 133$)		
	X	*SD*	*X*	*SD*	*p*
Age	8.64	2.24	8.13	2.68	0.28
Weight	33.85	13.22	32.43	17.31	0.65
ABC					
Irritability	25.55	7.95	21.14	10.10	0.01
Social withdrawal	18.74	7.60	13.54	9.05	0.01
Stereotypy	10.21	5.44	8.57	5.33	0.10
Hyperactivity	34.84	7.37	31.99	9.28	0.05
Inappropriate speech	6.42	4.28	5.64	3.81	0.28
Vineland					
Communication	54.82	23.56	49.56	19.26	0.16
Daily living	42.69	22.46	43.91	20.25	0.75
Socialization	56.13	17.21	52.53	15.75	0.22
Adaptive composite	46.37	19.35	44.79	17.43	0.63
CYBOCS Total	14.97	3.44	14.21	3.97	0.28
ADI					
Communication	16.08	5.00	16.08	4.54	0.99
Social	24.28	5.04	23.78	5.07	0.59
Stereotypy	7.56	2.69	7.64	2.66	0.87
CASI anxiety	16.56	10.13	12.58	7.79	0.01
	n	%	*n*	%	X^2 *p*
Female	4	10.3	23	17.3	0.29
Male	35	89.7	110	82.7	
Two Parent	31	79.5	107	80.5	0.89
Other[a]	8	20.5	26	19.5	
Regular Ed	11	28.2	48	37.2	0.18
Special Ed Classes	24	61.5	58	45.0	
Special Ed School	4	10.3	23	17.8	
Caucasian[b]	33	84.6	87	65.4	0.02
African American	2	5.1	18	13.5	
Asian/Pacific Islander	2	5.1	12	9.0	
Hispanic/Latino	1	2.6	10	7.5	
Other	1	2.6	6	4.5	
IQ < 70	27	69.2	96	72.2	0.72
IQ ≥ 70	12	30.8	37	27.8	

[a] Single Parent, Adoptive Parent, Foster Parent, Relative Care; [b] Caucasian versus all other. ABC = Aberrant Behavior Checklist; CYBOCS = Children's Yale-Brown Obsessive-Compulsive Scales for Pervasive Developmental Disorders; ADI = Autism Diagnostic Inventory; CASI Anxiety = Child and Adolescent Symptom Inventory Anxiety scale

social withdrawal subscales, and the CASI Anxiety scale remained.

Additional analyses in the subgroup of children with autism (i.e., with the six children with Asperger's Disorder and 14 children with PDD-NOS removed) also showed similar findings. Once again, children in the GI positive group showed higher scores on the ABC Irritability and Social Withdrawal subscales, as well as the CASI Anxiety scale, but no differences on ratings of adaptive behavior on the Vineland, severity of autism on the ADI, or intellectual functioning.

Discussion

We examined the prevalence and impact of GI problems in a well-characterized sample of 172 children with PDDs entering two large-scale multisite medication trials. Assessments were conducted prior to starting treatment. Using information from a systematic Side Effects Review Form, medical history and physical examination, we classified 39 (22.7%) subjects with moderate or greater GI problems. This number is higher than the 9% estimate from the largest available case control sample surveyed in the UK (Black et al. 2002). The difference can be attributed to ascertainment methods (record review for the UK sample vs. concurrent data collection for our sample) and to sample differences (mean age around 4 years in the UK sample compared to 8 years in our sample). Our rate of children with PDD and GI problems is, however, substantially lower than the 85.3% reported in retrospective reviews of GI specialty clinic samples (Horvath and Perman 2002a) and the 70% lifetime prevalence of GI symptoms in a convenience sample of 50 children with PDD ascertained through interview and record review of cases followed by pediatric neurology and developmental pediatrics programs (Valicenti-McDermott et al. 2006). Our results are comparable to the prevalence of GI problems observed in the population-based UK studies with $n = 262$ (18.8%) (Fombonne and Chakrabarti 2001), and $n = 473$ (17%) (Taylor et al. 2002). The rate we found is close to the 24.1% prevalence of GI symptoms reported in a sample of 137 children attending a medical clinic specializing in the care of children with autism and ASD in a large pediatric medical center (Molloy and Manning-Courtney 2003). Gastrointestinal problems are fairly common in otherwise healthy children as well. In a prospective cohort study by weekly surveys of 48 children age 9 to 11, 60% of the children reported at least one GI symptom weekly during 16 weeks, without missing school because of the symptom (Saps et al. 2006). Further research is needed to provide a credible answer whether GI problems are more common among children with than without autism (Kuddo and Nelson 2003).

In our sample of children with PDD, we were not able to detect any differences between children with and without GI symptoms, including sex, race, special education placement, and family background. Similarly, children with greater intellectual disability and lower adaptive function were not more likely to have a history of GI problems. Furthermore, on measures reflecting the core symptoms of autism—communication, social development and repetitive behavior—there were no differences between those with or without GI problems as determined with the ADI-R or CYBOCS-PDD. The observation of no differences in adaptive functioning or core features of autism may be due to an inadequate sample size, subject ascertainment or both. These observations are not consistent with reports of association between the severity of autism and GI problems. It may be, however, that the observed association in previous reports is due to an ascertainment bias.

The higher scores on the ABC Irritability subscale in the GI positive group suggest an association between GI problems and severe behavioral difficulties. We considered the possibility that the GI symptoms are causing the irritability/aggressive behavior captured by the ABC. However, when we examined the ABC Irritability scores within the GI positive group, subjects with "current GI+" problems ("current" as identified by the Side Effects Review Form) had lower ABC Irritability scores than those with a "History of GI+" symptoms (subjects identified by medical history). Therefore, "active" GI symptoms did not seem to correspond to more explosive and aggressive behavior as measured by the ABC. Another possibility is that the irritability causes GI symptoms. If this were the case, however, we would have found much higher prevalence of GI complaints in the risperidone sample, in which explosive and aggressive behaviors were overrepresented. Finally, an independent yet unidentified factor (for example anxiety), could be mediating both irritability and GI problems. In that case, the irritability and the somatic symptoms would be less likely to resolve unless the intervention treated the mediating factor. Our data do not permit a full examination of this question, but it is of note that GI positive subjects were less likely to show a positive response to risperidone.

We found children with autism and GI problems had significantly higher scores on the Social Withdrawal subscale on the ABC. The items of this subscale include descriptions of behaviors such as: "Listless; seeking isolation; staring into space; emotional unresponsiveness." By contrast, we did not find higher scores for social problems domain on the ADI-R. Given previous findings that behaviors measured by the ABC subscales are not highly correlated with ADI-R symptom composites, this seeming discrepancy is not surprising (Lecavalier et al. 2006; Brinkley et al. 2007).

Our data show that children with autism and GI problems score significantly higher than children with autism without GI problems on a measure of anxiety (the 20-item CASI Anxiety scale). We examined our data to test if increased vagal tone may be a common biological pathway to explain our findings. There were no group differences between the GI positive and the GI negative group on measures of blood pressure and heart rate, leading us to conclude that higher vagal tone is not a distinctive characteristic of the GI positive group. We also looked at the entire sample to look for significant relationship between blood pressure readings and CASI Anxiety scores. We found a correlation between CASI scores and systolic blood pressure ($r = .27$; $p < 0.01$), suggesting that a weak association between anxiety and higher blood pressure may exist in children with autism in general without regard to GI status.

Symptoms of anxiety have been reported to be relatively common in children with PDD, with higher levels of anxiety associated with higher IQ, the presence of functional language use, and with higher levels of stereotypy (Sukhodolsky et al. 2007). GI symptoms of patients in primary care are associated with anxiety and depression (Mussel et al. 2008). It could be hypothesized that anxiety may be contributing to the frequency and intensity of GI problems in children with autism in ways similar to normally developing children. Based on our data, it may be that anxiety, irritability with aggression and GI problems are interconnected in children with autism, but more study is needed to support this speculation.

Limitations

This study used a convenience sample of children with PDD to examine the prevalence and associations between the presence of GI problems and specific indices of PDD severity, intellectual functioning and behavior problems. Given that this was a convenience sample, the results warrant caution. The sample is over-represented with children with PDD accompanied by hyperactivity and serious behavioral problems (tantrums, aggression, and self-injury). These children may have different GI problem profiles from the children with PDD who do not have these characteristics. In addition, children in the risperidone trial were generally more impaired on measures of behavior problems, IQ and adaptive function, than children in the methylphenidate trial. However, given the different entry criteria for these two trials, this heterogeneity was expected and considered desirable for the purpose of this study.

Another limitation is that the documentation of GI problems in these children is based on a relatively brief screening questionnaire and medical history. This method did not fully characterize the nature of the GI problems, nor did it confirm the time frames for the reported GI problems. It relied on parent recall and did not include medical record review. However, our methods of medical screening are close to real world practice. Moreover, we consider it strength of this study that children were ascertained without specific focus on GI tract symptoms, avoiding selection bias. Finally, the exclusion of children classified with mild GI problems showed virtually identical findings across the GI positive and GI negative groups, suggesting that children in the GI negative group were not misclassified.

The findings of this study illustrate the characteristics of children with PDD and GI symptoms in comparison to children without GI symptoms. To the best of our knowledge, this is the first study to examine the association between GI complaints and specific characteristics of the PDD population. Further studies should look at large well-characterized samples of children with autism and appropriate controls. GI problems of concern should be defined and classified using universally accepted criteria. Although no discrete subtype of autism emerged from our data, the associations between Irritability and Social Withdrawal subscales on the ABC and anxiety on the CASI Anxiety scale with GI problems are of interest and may warrant further examination.

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