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Gastrointestinal Symptoms in Autism Spectrum Disorder: A literature review.

Arlene Mannion

Geraldine Leader

National University of Ireland, Galway.

Corresponding author: Geraldine Leader, Ph.D., Irish Centre for Autism and Neurodevelopmental Research, School of Psychology, National University of Ireland, Galway, Ireland. Tel: 0035391 493434, Fax: 00353 91 521355

Abstract

The purpose of this literature review was to provide an overview of the research on Gastrointestinal (GI) symptoms in Autism Spectrum Disorder. Topics explored include the prevalence of GI symptoms, the importance of studying GI symptoms, the difficulties in diagnosis as well as the questionnaire measures used to assess gastrointestinal symptoms. Research on the relationships between gastrointestinal symptoms and developmental regression, language and communication, autism severity, challenging behavior, comorbid psychopathology, sleep problems and sensory issues is also discussed. The use of special diets is discussed also. Finally, recommendations for treatment are given as well as areas where future research is needed.

Key words: Autism spectrum disorders, Gastrointestinal symptoms, Comorbidity,

Gastrointestinal Symptoms in Autism Spectrum Disorder: A Literature Review

1.1. Introduction

The most common gastrointestinal (GI) symptoms reported in individuals with autism spectrum disorder (ASD) are chronic constipation, abdominal pain with or without diarrhea and encopresis as a consequence of constipation (Buie, Campbell, Fuchs, Furuta, Levy & VandeWater, 2010a). Buie et al. (2010a) also commented that other gastrointestinal abnormalities include gastroesophageal reflux disease (GERD), abdominal bloating, disaccharidase deficiencies, inflammation of the gastrointestinal tract and abnormalities of the enteric nervous system.

2. Gastrointestinal Symptoms and ASD Comorbidity

2.1. Prevalence

The reported prevalence of gastrointestinal problems in children with ASD has ranged from 9% to 91% (Coury, Ashwood, Fasano, Fuchs, Geraghty, Kaul et al., 2012; Ming, Brimacombe, Chaaban, Zimmerman-Bier & Wagner, 2008; Black, Kaye & Jick, 2002; Fombonne & Chakrabarti, 2001; Ibrahim, Voigt, Katusic, Weaver & Barbaresi, 2009; Molloy & Manning-Courtney, 2003; Mouridsen, Rich & Isager, 2010; Nikolov, Bearss, Lettinga, Erickson, Rodowski, Aman et al., 2009; Taylor, Miller, Lingam, Andrews, Simmons & Stowe, 2002; Valicenti-McDermott et al., 2008; Horvath & Perman, 2002; Wang, Tancredi & Thomas, 2011; Parracho, Bingham, Gibson & McCartney, 2005; Smith, Farnworth, Wright & Allgar, 2009). Wang et al. (2011) commented on the factors that lead to differing rates of GI symptoms across studies. First, there are differences in the target population being studied. Some participants may have different diagnoses on the autism spectrum. Some studies use control groups, while others do not. Second, there are differences in how data is gathered, whether it is by medical records, physicians or questionnaire-based research. Finally, there

are different definitions used for what are considered gastrointestinal symptoms (Wang et al., 2011).

2.2. Importance of studying gastrointestinal symptoms

There are many reasons gastrointestinal symptoms in autism need to be researched. First, given that a high prevalence of GI symptoms have been found in the literature, it is possible that GI symptoms affect a large proportion of those with autism. Second, these symptoms may cause pain and discomfort. Individuals that are non-verbal or have little communication skills may not be able to tell parents or caregivers that they are in pain. Third, it is important to recognise that abdominal pain or discomfort may act as a setting event for challenging behavior (Buie et al., 2010a). This discomfort and in turn, challenging behavior can get in the way of the individual acquiring new academic or self-help skills. Mulloy, Lang, O' Reilly, Sigafoos, Lancioni and Rispoli (2010) commented on these biological motivating operations, whereby an upset stomach may act as a motivating operation affecting social consequences. Mulloy et al. (2010) gave the example that a child with an upset stomach may find academic work more demanding than if they did not have an illness. Therefore they may engage in increasing levels of challenging behavior to escape the demand. Finally, an individual's quality of life can be affected in they present with GI symptoms. Williams, Fuchs, Furuta, Marcon and Coury (2010) found that children with ASD with GI symptoms had lower quality of life compared to children without GI symptoms. GI complaints are therefore associated with overall decreased health-related quality of life.

2.3. Difficulty of diagnosis

GI symptoms are difficult to diagnose in individuals with ASD for several reasons. First, clinical practice guidelines in place for the diagnosis of ASD do not include routine consideration of potential gastrointestinal or other medical conditions (Buie et al., 2010a). Second, many individuals with ASD are non-verbal or have communication difficulties.

Because of this, they may not be able to express pain or discomfort in a typical manner. They may not be able to communicate their symptoms as clearly as those who are typically developing. Those who can verbally communicate may have difficulty describing subjective experiences or symptoms (Buie et al., 2010a). Third, those with ASD may present with GI symptoms in atypical ways. One may assume that if an individual has abdominal or other discomfort that they would touch their abdomen. However, this is not necessarily the case for those with ASD. Gastrointestinal disorders can present as non-gastrointestinal problems (Buie et al., 2010a). For example, individuals may present with sleep problems or challenging behavior. Where they present with vocal stereotypy or repetitive behavior, it could be incorrectly attributed to being symptoms of autism. Fourth, diet may play a role in GI symptoms. Kuddo and Nelson (2003) commented that the insistence on sameness in autism may lead children to demand stereotyped diets which are lacking in fibres, fluids or other constituents. Finally, if children are on medication, this can have side-effects. Kuddo and Nelson (2003) comment that most medication administered to children with autism can influence gut function.

2.4. Measures used to assess gastrointestinal symptoms

While some studies used medical history to assess gastrointestinal symptoms (Molloy & Manning-Courtney, 2003; Nikolov et al., 2009; Maenner, Arneson, Levy, Kirby, Nicholas & Durkin, 2012), a variety of questionnaires have also been used. As well as past medical history, Nikolov et al. (2009) used the Side Effects Review Form (Research Units on Pediatric Psychopharmacology). The form was designed to establish whether certain problems are present prior to drug exposure and to track changes. In Nikolov et al.'s 2009 study, a pre-treatment rating of moderate or severe on the Side Effects Review Form in response to one or more GI questions was classified as the presence of a GI symptom. Hansen, Ozonoff, Krakowiak, Angkustsiri, Jones, Deprey et al. (2008) used the CHARGE

(Childhood Autism Risks from Genetics and the Environment) gastrointestinal history form, which includes 10 items describing current gastrointestinal symptoms as well as questions relating to food allergies and diet restrictions.

Valicenti-McDermott et al. (2008) developed The Gastrointestinal Questionnaire, derived from the Clinical Diagnostic Questionnaire for Pediatric Functional Gastrointestinal Disorders, as developed by the Committee on Childhood Functional Gastrointestinal Disorders Multinational Working Teams to Develop Criteria for Functional Disorders (Rome II). The Gastrointestinal Questionnaire includes questions on current GI symptoms, as well as lifetime gastrointestinal or feeding problems. Gorrindo, Williams, Lee, Walker, McGrew, and Levitt (2012) used the Questionnaire on Pediatric Gastrointestinal Symptoms-Rome III Version (QPGS) which is a 71 item parent report instrument that assesses GI symptoms and classifies functional GI disorders (FGID) according to Rome III criteria. It is available online at <http://romecriteria.org/>. Gorrindo et al. (2012) also included clinical evaluation in their study. The authors found that parent report of any gastrointestinal dysfunction in those with ASD was highly concurrent (92.1%) with a clinical diagnosis of any gastrointestinal dysfunction.

Chandler, Carciani-Rathwell, Charman, Pickles, Lucas, Meldrum et al. (2013) constructed a 20 item GI symptom questionnaire. Questions were asked by current (last 3 months) and past (prior to the last 3 months symptoms). The GI symptoms included persistent vomiting; stool consistency; abdominal pain; abdominal pain associated with food, bowel movement or sleep; constipation; subjective difficulties with bowel movements, stool withholding and soiling; diarrhea, weight loss, mouth ulcers and presence of mucus or blood in the stools.

The Gastrointestinal Symptom Inventory (Autism Treatment Network, 2005) is a 35-item questionnaire that was developed by the Autism Treatment Network (ATN). The ATN is the first network of hospitals and physicians dedicated to developing a model of comprehensive medical care for children and adolescents with autism through seventeen participating institutions in the U.S. and Canada. In the inventory, there are additional items should a participant exhibit certain symptomatology, and therefore includes 77 items in total. This tool has not been validated. It was based on previous questionnaires and on clinical symptom assessment for children with autism and identified gastrointestinal disorders. It measures questions about the presence and duration of GI symptoms. The inventory is scored initially dichotomously i.e. whether or not the child has any of the gastrointestinal symptoms. The GI symptoms it measures are abdominal pain, nausea, bloating, diarrhea or other GI symptom. The inventory also allows branching into specific areas of symptomatology: abdominal pain, abnormal bowel movements, reflux, and food insensitivity. These branches will allow determination of rates of these categories as well.

Mazurek, Vasa, Kalb, Kanne, Rosenberg, Keefer et al. (2013b) used the GI Symptom Inventory in their research. It was also used in Williams et al. (2010); Williams, Christofi, Clemons, Rosenberg and Fuchs (2012a); Williams, Christofi, Clemons, Rosenberg and Fuchs (2012b) and Mannion, Leader and Healy (2013). The GI Symptom Inventory is no longer used by the ATN as part of its registry battery. Instead, questions are included about gastrointestinal symptoms in the ATN Parent Baseline Assessment. The following symptoms are assessed: nausea/vomiting, reflux, diarrhea, constipation, stomach/abdominal pain. Mazurek, Kanne and Wodka (2013a) used the Parent Baseline Assessment in their research.

2.5. Regression

Valicenti-McDermott, McVicar, Cohen, Wershil and Shinnar (2008) found that children with autism spectrum disorder who presented with language regression had more

gastrointestinal problems (84%) than those without language regression (61%). The authors also found that abnormal stool patterns were reported more frequently in the group with language regression (42% vs. 12%). Niehus and Lord (2006) found that the medical records of children with ASD and regression indicated significantly more parental reports of bloody stools than those with ASD and no regression. Though non-significant, those with ASD and regression had more chronic diarrhea and stool complaints than those with ASD and no regression or those that were typically developing.

Baird, Charman, Pickles, Chandler, Loucas, Meldrum et al. (2008) investigated factors associated with regression in children with autism. Current gastrointestinal symptoms varied across the three groups in the study; those with no regression, lower level regression and definite language regression. Current gastrointestinal symptoms varied across regression groups, but the rate was higher in the no regression group than the lower or definite regression groups. In terms of past gastrointestinal symptoms, there was no group difference found between those with no regression, lower or definite regression. This is supported by Chandler et al. (2013) who found that there were no differences between ASD children with and without a history of regression for current and past GI symptoms. Similarly, Molloy and Manning-Courtney (2003) found that developmental regression was not significantly associated with gastrointestinal symptoms. Hansen et al. (2008) found no significant differences between the children with ASD with or without regression in terms of gastrointestinal symptoms.

2.6. Language and Communication

Gorrindo et al. (2012) examined expressive language and social responsiveness as communication variables in their study. They found that children with ASD and GI symptoms showed higher levels of social impairment than those with ASD only. However,

social impairment was not associated with impaired language. In the ASD and GI symptoms group, there was no difference in social impairment in those that were verbal and non-verbal. Gorrindo et al. (2012) also investigated the risk factors for constipation as constipation was found to be the most common GI symptom in their study. The authors found that younger, more socially impaired and non-verbal children had increased odds for constipation. In contrast, Chandler et al. (2013) did not find a difference between verbal ability in children with and without reported pain abdominal pain or constipation. This is supported by Williams et al. (2012b) who found that rates of GI complaints did not differ between four verbal ability groups; Non-verbal, some words, phrase speech and verbal.

2.7. Autism Severity

Wang et al. (2011) classified autism severity into three groups; full autism, almost autism and not quite autism. Increased autism symptom severity was associated with increased odds of having significantly more GI problems being reported. Specifically, having full autism or almost autism was most highly associated with experiencing GI problems (Wang et al., 2011). However, Molloy & Manning-Courtney (2003) found that frequency of gastrointestinal symptoms did not vary by age, gender, race or severity of autism. In support of this finding, Nikolov et al. (2009) also found that those with gastrointestinal problems were no different from those without gastrointestinal problems in autism symptom severity, demographic characteristics or measures of adaptive functioning. Chandler et al. (2013) found that there was no significant association between autism severity and current and past GI symptoms in the ASD group. Williams et al. (2010) found that presence of GI problems did not differ by gender, ASD subtype, race or IQ. However, Williams et al. (2012b) found that chronic GI symptoms were more likely in children with Asperger's than Autism.

2.8. Challenging behavior

Horvath, Papadimitriou, Rabsztyn, Drachenberg and Tyson Tildon (1999) commented that unrecognised gastrointestinal symptoms and disorders may contribute to the behavioral problems of non-verbal children with autism, such as sudden irritability and aggressive behavior. Mazurek et al. (2013a) investigated the relationship between aggression and other variables, including gastrointestinal symptoms in children with ASD. Children with aggression had significantly greater difficulties with GI problems than those without aggression. However, GI problems did not emerge as significant predictors of aggression.

Children with GI problems were more likely to present with argumentative, oppositional or destructive behaviors than those without GI problems (Maenner, et al., 2012). Tantrum behaviors were more common in those with GI problems than those without, but the association did not reach statistical significance. No association was found between presence of GI problems and stereotypic/repetitive behaviors or self-injurious behaviors (Maenner et al., 2012).

2.9. Comorbid Psychopathology

Williams et al. (2010) found that children aged 1 to 5 years with GI symptoms had higher total scores on the Child Behavior Checklist (CBCL) (Achenbach & Roscorla, 2000) and for the emotionally reactive, anxious/depressed, somatic complaints, internalising problems, affective problems, anxiety problems subscales. The authors also found that children aged 6 to 18 years had higher total scores on the Child Behavior Checklist (CBCL) (Achenbach & Roscorla, 2001) and on all subscales. Maenner et al. (2012) found that mood disturbances were more common in children with GI problems than those without but this association did not reach statistical significance. In terms of other comorbid disorders, children with ASD and GI problems were significantly more likely than those without GI problems to have co-occurring cerebral palsy and seizure-like activity (Maenner et al., 2012).

Mannion and Leader (under submission) investigated predictors of GI symptoms in children with ASD. In the study, total number of GI symptoms predicted total scores on the Autism Spectrum Disorder-Comorbid for Children (ASD-CC) (Matson & González, 2007). The ASD-CC is a questionnaire used to assess comorbid psychopathology in those with autism. Specifically, abdominal pain and constipation also predicted conduct behavior. Diarrhea predicted tantrum behavior. Nausea predicted worry/depressed behavior, avoidant behavior and conduct behavior. The worry/depressed subscale and the avoidant behavior subscale of the ASD-CC form a measure of anxiety (Davis, Moree, Dempsey, Reuther, Fodstad, Hess et al. 2011).

Other authors have also investigated the relationship between GI problems and anxiety. Nikolov et al. (2009) found that when compared to children without gastrointestinal problems, those with gastrointestinal problems showed greater symptom severity on measures of irritability, anxiety and social withdrawal. Williams et al. (2012b) found that clinical anxiety is associated with chronic GI symptoms in children with autism. Chronic GI complaints were greater in children with clinical anxiety compared to those with no anxiety. Mazurek et al. (2013b) found that children with chronic constipation, chronic diarrhea, chronic bloating, chronic nausea and chronic abdominal pain had higher anxiety than those without these symptoms. Those with more chronic GI problems had higher anxiety scores than those with no chronic GI problems. Anxiety contributed to the prediction of chronic constipation, chronic bloating, chronic nausea and chronic abdominal pain, but not to the prediction of chronic diarrhea.

2.10. Sleep Problems

Horvath et al. (1999) commented that unrecognised gastrointestinal symptoms may lead to night time awakenings in non-verbal children with autism. Maenner et al. (2012) found that children with sleep abnormalities were more likely to have a medically

documented history of GI problems, than those without. Williams et al. (2010) found that sleep problems occurred most frequently in those with gastrointestinal problems (50%) than those without (37%). Williams et al. (2012a) found that 24.5% of children with autism had sleep problems and chronic GI symptoms, while 25.2% had neither sleep nor GI problems. It was found that 42.5% had sleep problems only, while 7.8% had a chronic GI complaint only. Sleep problems occurred in 84% of children with chronic nausea, 82% of children with chronic diarrhea, 81% of children with chronic bloating, 79% of children with chronic constipation and 78% of children with chronic abdominal pain.

Mannion et al. (2013) investigated predictors of sleep problems in children with ASD. The total number of GI symptoms predicted higher rates of sleep problems. Under-eating, avoidant behavior and gastrointestinal symptoms predicted sleep problems. Specifically, abdominal pain predicted sleep anxiety. Under-eating, avoidant behavior and the five GI symptoms (Constipation, Diarrhea, Nausea, Abdominal Pain and Bloating) predicted parasomnias and daytime sleepiness. Mannion and Leader (under submission) found that sleep problems predicted gastrointestinal symptoms. Specifically, sleep disordered breathing and daytime sleepiness predicted both abdominal pain and bloating. Sleep anxiety predicted abdominal pain. It was found that 67.8% of individuals had both sleep problems and gastrointestinal symptoms, while only 8% had neither sleep problems nor gastrointestinal symptoms. Sleep problems occurred in 92.3% of those with nausea and in 91.1% of those with abdominal pain. Sleep problems occurred in 90.9% of those with bloating. Sleep problems occurred in 90% of those with diarrhea, and in 83.7% of those with constipation. It was found that 11.5% had gastrointestinal symptoms only, while 12.6% had sleep problems only.

2.11. Sensory Issues

Mazurek et al. (2013b) investigated the relationship between sensory over-responsivity and GI problems. They found that those with chronic GI problems had higher levels of sensory over-responsivity. Increasing numbers of GI problems were associated with higher levels of sensory over-responsivity. Sensory over-responsivity also predicted chronic GI problems.

3. Special Diets

Perrin, Coury, Hyman, Cole, Reynolds and Clemons (2012) investigated complementary and alternative medicine (CAM) use in children with autism. Parents of children with autism were asked if their children use any of the following treatments: acupuncture, chelation, chiropractic, or hyperbaric oxygen therapy; dietary supplements (vitamin supplements, probiotics, antifungal agents, digestive enzymes, glutathione, sulfation, amino acids, or essential fatty acids); and special diets(classified as gluten free, casein free, Feingold, no processed sugars, no salicylates, or other). Special diets usage versus no CAM usage was investigated in the study also. Parents reported higher rates of CAM usage in general and for special diets when they also reported GI problems. The authors commented that families seek to address problematic behaviors or symptoms using CAM and that parents whose children have GI symptoms may try both dietary changes and other CAM treatments to improve their child's nutrition and symptoms.

Pennesi and Klein (2012) investigated the effectiveness of the gluten-free, casein-free (GFCF) diet in children with ASD. The authors found the diet to be effective in improving ASD behaviors, physiological behaviors and social behaviors for children with GI symptoms (specifically, constipation and diarrhea) compared to children with no GI symptoms. The authors suggested that children predisposed to GI abnormalities might particularly benefit more from a GFCF dietary intervention. However, the authors also commented that the findings reported may be highly sensitive to parental perceptions and that the high

effectiveness ratings may be explained by a placebo effect. In terms of future research, the authors stated that the priority of future research should be to define the immunological and GI diagnoses and symptoms that best predict those individuals who will be most responsive to the gluten-free, casein-free diet.

Mulloy et al., (2010) conducted a systematic review on gluten-free and casein-free diets in the treatment of autism spectrum disorder. The authors concluded that the published studies they located do not support the use of GFCF diets in the treatment of ASD. The authors commented on negative consequences for the use of the GFCF diet, such as use of treatment resources, stigmatization and reduced cortical bone thickness. The authors recommended that should a child with ASD experience behavioral changes seemingly associated with change in diet, practitioners should consider testing the child for allergies and food intolerances and eliminate identified allergens or irritants from their environment.

4. Recommendations for treatment

Buie, Fuchs III, Furuta, Kooros, Levy, Lewis et al. (2010b) commented that children with ASD can benefit from the adaptation of general pediatric guidelines for diagnosing GI symptoms. The authors provided a review of guidelines to diagnose and treat GI symptoms using current general pediatric guidelines, until specific guidelines are designed for those with ASD. Information on differential diagnosis, evaluation and treatment considerations are provided for chronic abdominal pain, constipation, chronic diarrhea and gastroesophageal reflux disease (GERD) in children with ASD.

Furuta, Williams, Kooros, Kaul, Panzer, Coury et al. (2012) developed an algorithm to help health care providers identify, evaluate and manage constipation in children with ASD. The consensus among the authors is that 1) subtle or atypical symptoms might indicate the presence of constipation; 2) screening, identification and treatment through a deliberate approach for underlying causes of constipation is appropriate; 3) diagnostic-therapeutic

intervention can be provided when constipation is documented and 4) careful follow-up after any intervention be performed to evaluate effectiveness and tolerance of the therapy (Furuta et al., 2012). According to the algorithm any child with atypical behaviors should be evaluated for constipation. Examples of these behaviors include self-injurious behavior, posturing, grimacing, holding the abdomen, squeezing the legs together or walking around with a narrow gait to hold the stool in (Furuta et al., 2012).

Buie et al. (2010a) commented that integrating behavioral and biomedical roles can be advantageous. Firstly, functional behavioral assessments can be used in order to interpret the function of challenging behavior. Second, it is important to be aware of pain and discomfort can function as a setting event for challenging behavior. Third, functional communication skills may be taught. Buie et al. (2010a) commented that it would be useful for diagnosis to teach a child to identify the location and type of pain they are experiencing. Finally, the individual could be taught skills for coping with a task demand appropriately during moments of pain or discomfort (Buie et al., 2010a).

5. Future research

Coury et al. (2012) developed a research agenda for gastrointestinal conditions. They defined four priority areas for research: epidemiology of GI conditions in ASD; underlying pathology; treatment and outcome; and nutrition. There is a need for rigorously designed prevalence studies in order to identify risk factors including clinical and behavioral indicators of GI problems; identify atypical presentations of GI disorders in ASD and identify subpopulations within ASD that have GI symptoms (Coury et al., 2012).

As evidenced by the lack of papers on adults with autism in the current review, there is a real need for more research to be conducted with adults with autism to investigate the relationship between GI problems and autism in adults. Edwards, Watkins, Lotfizadeh and

Poling (2012) found that in intervention research on autism, only 1.7% of participants were 20 years or more. In autism research, in general, there is a need for adult research and this is especially so in relation to gastrointestinal symptoms.

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