ORIGINAL ARTICLE

WILEY | AMERICAN JOURNAL OF medical genetics A

Prevalence of gastrointestinal symptoms in Angelman syndrome

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Angelman syndrome (AS) is a neurogenetic disorder characterized by intellectual disability, expressive speech impairment, movement disorder, epilepsy, and a happy demeanor. Children with AS are frequently reported to be poor feeders during infancy and as having gastrointestinal issues such as constipation, reflux, and abnormal food related behaviors throughout their lifetime. To assess the prevalence of gastrointestinal disorders in individuals with AS, we retrospectively analyzed medical records of 120 individuals seen at the Angelman Syndrome Clinic at Massachusetts General Hospital and 43 individuals seen at the University of North Carolina Comprehensive Angelman Clinic. The majority of patients' medical records indicated at least one symptom of gastrointestinal dysfunction, with constipation and gastroesophageal reflux disease (GERD) the most common. Other gastrointestinal issues reported were cyclic vomiting episodes, difficulty swallowing, excessive swallowing, and eosinophilic esophagitis. Upper gastrointestinal symptoms such as GERD, swallowing difficulties, cyclic vomiting, and eosinophilic esophagitis were more common in those with deletions and uniparental disomy, likely related to the involvement of multiple genes and subsequent hypotonia. The frequency of constipation is consistent among all genetic subtypes while early feeding issues appear to mainly affect those with deletions. Caregivers and healthcare providers should be aware of the high prevalence of these issues, as proper treatment may improve not only gastrointestinal dysfunction but also sleep and behavioral issues.

KEYWORDS
Angelman syndrome, constipation, gastroenterology, GERD, reflux

1 | INTRODUCTION

Angelman Syndrome (AS) is a neurogenetic disorder attributed to an abnormality in the 15q11.2-q13.1 region of the maternal chromosome, which contains the UBE3A gene (Kishino, Lalande, & Wagstaff, 1997). This gene codes for the E6-Associated Protein-3A (E6AP-3A) ubiquitin protein ligase, which is critical for normal brain development (Jiang, Lev-Lehman, Bressler, Tsai, & Beaudet, 1999; Kishino et al., 1997). AS is present in 1/12,000–20,000 of the US population and common features include global developmental delay, expressive speech

deficits, seizures, and a happy disposition (Williams et al., 2006; Williams, Driscoll, & Dagli, 2010).

There are multiple molecular subtypes of AS, with the majority of individuals having a deletion of the maternal 15q11.2-q13.1 region (68–70%) (Kishino et al., 1997). Other genetic etiologies include a UBE3A gene mutation (UBE3A, 5–10%), paternal uniparental disomy (UPD, 3–5%), or abnormal imprinting of the maternal chromosome (IC, 2%) (Clayton-Smith & Laan, 2003). The severity of the clinical features of AS is variable and has been found to correlate with genotype. The deletion subtype correlates with a more severe phenotype, with more

frequent and severe seizures, more significant developmental issues and a higher incidence of autistic-like features (Williams et al., 2006; Williams, Driscoll, and Dagli, 2010).

Children with AS are frequently reported as poor feeders during infancy and as having mild gastrointestinal issues such as constipation or reflux during their lifetime (Thibert, Larson, Hsieh, Raby, & Thiele, 2013; Williams, 2010). These gastrointestinal issues were categorized as associated clinical features of AS in the 2005 updated diagnostic consensus, which included gastroesophageal reflux disease (GERD), constipation and other abnormal food related behaviors (Thibert et al., 2013; Williams et al., 2006). The frequency and scope of these illnesses, however, have never been studied and the diagnostic consensus estimates that the prevalence of these illnesses may affect between 20% and 80% of individuals with AS (Williams et al., 2006; Williams, Driscoll, & Dagli, 2010).

Gastrointestinal disorders are not unique to Angelman syndrome and are commonly reported in individuals with neurodevelopmental disabilities. It has been reported that individuals with neurodevelopmental disabilities, autism, and ID have a higher prevalence of gastrointestinal disorders than the general population (Horvath & Perman, 2002; Schieve et al., 2012; Sullivan, 2008). Individuals with ASD or ID can experience an increased prevalence of poor feeding, GERD, and constipation (Böhmer, Taminiau, Klinkenberg-Knol, & Meuwissen, 2001; Charlot et al., 2011; Fodstad and Mantson, 2008; Ibrahim, Voigt, Slavica, Weaver, & Barbaresi, 2009; Pang and Croaker, 2011; Schreck, Williams, & Smith, 2004; Wang, Tancredi, & Thomas, 2011).

Recent studies have also described individuals adhering to a low glycemic index diet experiencing a reduction in seizure frequency along with improvements in neurocognitive function (Grocott, Herrington, Pfeifer, Thiele, & Thibert, 2017; Thibert et al., 2012). With over 80% of individuals with AS experiencing seizures, this emphasizes the importance of the gastrointestinal system to the overall clinical phenotype of those with AS (Williams et al., 2006; Williams, Driscoll, and Dagli, 2010).

Treatment of these gastrointestinal issues is critical for those with AS, as physical illness and discomfort has been found to exacerbate sleep issues, irritability, seizures, or other behavioral problems in individuals with developmental disorders with limited communication skills (Buie et al., 2010; Carr & Owen-DeSchryver, 2007). This study aims to assess the prevalence of gastrointestinal disorders in individuals with AS in order to increase awareness and early diagnosis of these issues by healthcare providers.

2 | MATERIALS AND METHODS

We retrospectively analyzed the medical records of 120 patients who had visited the Angelman Syndrome Clinic at Massachusetts General Hospital (MGH), all with a genetic diagnosis of AS. The medical records were evaluated through a retrospective medical record review of clinic notes from initial clinic visits and routine follow-ups. Data were collected on patient age, sex and genetic subtype as well as feeding behaviors, the presence of gastrointestinal symptoms and treatments

trialed. Questions regarding gastrointestinal function were addressed by the MGH provider [R.T.] at the initial visit and each follow-up visit, regardless of having a history of gastrointestinal dysfunction. Data were collected by two research assistants [A.P. and O.G.] at Massachusetts General Hospital who reviewed charts from the opening of the clinic in 2006 through 2015. If parents reported a prior history of gastrointestinal dysfunction during their initial visit that dated back prior to that date, it was still included in the data set. Every clinic note written by the provider [R.T.] for each patient in that time frame was reviewed for mention of gastrointestinal dysfunction which was recorded with start and stop dates in order to avoid duplication of results.

Information for an additional 43 patients was obtained from the University of North Carolina Comprehensive Angelman Clinic (UNC), all with a genetic diagnosis of AS. Information reported from these patients included age at evaluation, genetic subtype, early feeding issues, history of gastrointestinal symptoms, and their treatments. Questions regarding gastrointestinal function were addressed by the Carolina Institute of Developmental Disabilities neuropsychologists as part of a standardized intake assessment at initial clinic visits that occurred from 2011 through 2015. Data on GI function was not collected at follow-up visits. If parents reported a history of gastrointestinal dysfunction during their initial visit that dated back prior to that visit, it was still included in the data set.

3 | RESULTS

3.1 | Cohort demographics

The MGH cohort was comprised of 81 patients with a maternal deletion (68%), 16 with UPD (13%), 17 with UBE3A (14%), and 6 with IC (5%). The average age of this cohort, calculated at of the date of initial data collection on 5/27/14, was 12.8 years (range 1–42 years), and was comprised of 54 females (45%) and 66 males (55%).

The UNC cohort was comprised of 30 patients with a maternal deletion (70%), four with UPD (9%), five with UBE3A (12%), and two with IC (5%). The genotype of two patients from this cohort was unknown, and they were excluded from the analysis-stratified by-genotype. The average age of this cohort, calculated as of the date of initial data collection on 5/27/14, was 9.41 years (range 1–33 years) and the cohort was comprised of 25 females (58%) and 18 males (42%).

These group data were combined for similar measurements whenever possible. Genotype analysis for the combined data included 111 subjects with deletions (69%), twenty subjects with UPD (12%), twenty-two subjects with UBE3A (14%), and eight subjects with IC (5%).

3.2 | Gastrointestinal issues

Results are summarized in Table 1. For all results, subjects were excluded from analysis in each GI category if there was insufficient information in the medical record. For example, poor feeding or poor suck/swallow was reported in 74/151 patients (49%). Twelve subject

TABLE 1 Frequency of gastrointestinal conditions and procedures in AS patient records

GI issues	Total (163)	Deletion (111)	UPD (20)	UBE3A (22)	IC (8)
Condition					
Constipation	116/163 (71%)	78/111 (70%)	14/20 (70%)	16/22 (73%)	6/8 (75%)
Poor feeding- infant	74/151 (49%)	59/103 (57%)	5/19 (26%)	7/20 (35%)	3/8 (38%)
GERD	72/163 (44%)	54/111 (49%)	9/20 (45%)	7/22 (32%)	2/8 (25%)
Decreased appetite[a]	13/120 (11%)	11/81 (14%)	1/16 (6%)	1/17 (6%)	0/6 (0%)
Vomiting	16/163 (10%)	12/111 (11%)	3/20 (15%)	1/22 (5%)	0/8 (0%)
Difficulty swallowing	9/163 (6%)	8/111 (7%)	1/20 (5%)	0/22 (0%)	0/8 (0%)
Eosinophilic esophagitis[a]	4/120 (3 %)	3/81 (4%)	1/16 (6%)	0/17 (0%)	0/6 (0%)
Excessive swallowing[a]	2/120 (2%)	2/81 (2%)	0/16 (0%)	0/17 (0%)	0/6 (0%)
Other	21/163 (13%)	14/111 (13%)	2/20 (10%)	3/22 (14%)	2/8 (25%)
Procedure					
Swallow study[a]	10/120 (8%)	9/81 (11%)	1/16 (6%)	0/17 (0%)	0/6 (0%)
NG-tube	9/163 (6%)	9/111 (8 %)	0/20 (0%)	0/22 (0%)	0/8 (0%)
Endoscopy[a]	7/120 (6%)	5/81 (6%)	1/16 (6%)	1/17 (6%)	0/6 (0%)

UPD, uniparental disomy; UBE3A, UBE3A mutation; IC, imprinting center defect; GERD, gastrointestinal reflux disease; NGtube, nasogastric feeding tube.
[a]Data only available for MGH cohort (n = 120).

records had no mention of early feeding behaviors and were excluded from the analysis.

Gastrointestinal issues were reported in 141/163 (87%) subjects, while 116/163 (71%) experienced symptoms of constipation and 72/163 (44%) experienced symptoms of GERD. Thirteen subjects with GERD presented with typical symptoms such as excessive biting, drooling, and/or increase in appetite, but had yet to be seen by a gastroenterologist.

Nine (6%) subjects had a nasogastric tube placed outside of brief hospital stays, typically due to poor oral intake. Sixteen subjects (10%) reported multiple, cyclic vomiting episodes without any concurrent illness or food allergy and nine (6%) subjects reported difficulty swallowing. None underwent a colonoscopy.

From just the MGH cohort, two (2%) reported excess swallowing and ten (8%) had a swallow study performed. A total of 7 (6%) had endoscopies performed, 4 (3%) were diagnosed with eosinophilic esophagitis (EoE), and 13 (11%) experienced a period of decreased appetite.

3.3 | Gastrointestinal issues by genetic subtype

There was no significant difference in the rates of constipation between genetic subtypes, with 78/111 (70%) with deletions, 14 out of 20 (70%) with UPD, sixteen out of 22 (73%) with UBE3A, and 6 out of 8 (75%) with IC reporting symptoms.

GERD symptoms were also common among all genetic subtypes but more common in those with deletions and UPD. A total of 54 (49%) subjects with deletions and 9 (45%) with UPD reported GERD symptoms, while 7 (32%) with UBE3A and only 2 (13%) with IC reported symptoms of GERD. There was no clear difference between the deletion, UPD, and UBE3A subtypes as to who underwent an endoscopy with five (6%), one (6%), and one (6%), respectively reporting the procedure.

There were some other notable differences in gastrointestinal issues between the various subtypes, with some issues being much more common or only present in those with deletions. Poor feeding and suck/swallow in infancy were present in 59/111 (57%) subjects with deletions, as compared to 5 (26%), 7 (35%), and 3 (38%) subjects in the UPD, UBE3A, and IC subtypes, respectively. Eleven subjects with a known genetic subtype had no mention of early feeding behaviors in their record and were excluded from analysis. Additionally, only 2 (2%) subjects reported excessive swallowing, both having deletions, and all 9 (8%) of the subjects who required a nasogastric tube had deletions.

Other GI symptoms were more common or present only in those with deletions or UPD. Difficulty swallowing was present in 8 (7%) subject with deletions and 1 (5%) subject with UPD, as compared to zero in the UBE3A and imprinted subtypes. Similarly, vomiting (unrelated to any illness), was more common in those with deletions and UPD, with 3 (15%) subjects with UPD and 12 (11%) subjects with deletions reporting cyclic vomiting, as compared to 1 (5%) with UBE3A and zero with IC. A total of 9 (11%) subjects with deletions and 1 (6%) subject with UPD underwent a swallow study, compared to zero subjects with UBE3A or IC subtypes.

Records of EoE, endoscopy, excessive swallowing and decreased appetite were only available for the MGH cohort. A diagnosis of EoE was reported by 3 of 81 (4%) subjects with deletions, 1 of 16 (6%) subjects with UPD, and zero subjects with UBE3A or imprinting subtypes. A total of 11 (14%) subjects with deletions reported a decreased appetite, compared to one of 16 (6%) subjects with UPD, one out of 17 (6%) subjects with UBE3A and zero subjects with IC.

3.4 | Treatment

Almost half of subjects with constipation (46%) were started on polyethylene glycol. Other common treatments included other

laxatives like senna and bisacodyl (12%), dietary changes (14%) such as increased fiber or fruit consumption, and stool softeners (4%) such as docusate sodium. Less common treatments for constipation included enemas (1%) and suppositories (2%).

Subjects with GERD were commonly treated with proton pump inhibitors (65%), such as lansoprazole (26%) and omeprazole (21%). Some subjects used ranitidine (10%) as a treatment for GERD and 3 (4%) were fed with Neocate or Nutramigen during infancy to reduce GERD symptoms due to milk protein allergy or delayed gastric emptying. One subject additionally had a Nissen fundoplication and used sucralfate.

Sixteen subjects were on the low glycemic index treatment or ketogenic diet for treatment of epilepsy. One subject was treated with simethicone for gas pain and two were treated with cyproheptadine to increase appetite. A summary of common treatments for constipation and GERD can be found in Table 2.

4 | DISCUSSION

Individuals with AS commonly experience a broad range of gastrointestinal symptoms. Medical records for the majority of subjects (87%) indicated at least one GI symptom, with constipation and reflux being most commonly reported. A review of the prevalence of constipation estimates that 2–28 percent of the general population in North America suffers from constipation (Higgins & Johanson, 2004) and a United States-based population study of GERD reported that 20–30% of individuals experience GERD weekly (El-Serag et al., 2004; Locke, Talley, Fett, Zinsmeister, & Melton, 1997). Compared to the general population, individuals with intellectual disability (ID) and neurodevelopmental disorders may experience an increased frequency of these issues (Motil et al., 2012; Schieve et al., 2012; Sullivan, 2008). Several review articles addressing the prevalence of GI symptoms in autism spectrum disorder (ASD) or in children with neurodevelopmental disabilities, have reported the prevalence of GI issues across a wide range (9–76%) (Buie et al., 2010; Horvath & Perman, 2002; Sullivan, 2008). Some specific

etiologies of ID are associated with a higher frequency of GI issues, such as Rett Syndrome (92%) (Motil et al., 2012). The lack of consensus on the prevalence of GI issues in ASD and neurogenetic disorders makes it difficult to speculate the true incidence of GI issues in these populations (Buie et al., 2010). Additionally, the review articles analyzed papers of varying methodologies of data collection, most of which differed from our own retrospective review, and could explain some of the differences in the reported incidences.

Other neurodevelopmental disorders associated with the same chromosomal region as AS also show an increased prevalence of GI symptoms. Prader–Willi syndrome is caused by a similar loss of chromosome 15q to Angelman syndrome, but the paternal chromosome is affected rather than the maternal chromosome, which is affected in AS (Cassidy & Driscoll, 2009). This syndrome is marked by early onset hyperphagia, with over 90% of individuals displaying sucking/feeding issues as an infant, often requiring feeding via a nasogastric tube or dropper (Bray et al., 1983). Additionally, individuals with 15q Duplication syndrome, which results from a copy number gain of the same chromosomal region that is deleted in AS, have a similar prevalence of GI dysfunction, with 77% of those with isodicentric chromosome 15 having GI symptoms and 88% of those with interstitial duplications of 15q having GI dysfunction (Shaaya et al., 2015).

Constipation was common in all subtypes with similar prevalence (70–75%). Feeding and swallowing difficulties in the first few months were most common in those with maternal deletions (57%) as compared to those with non-deletions (26–38%), and every subject that required a nasogastric feeding tube had a deletion. Several other symptoms were most frequently or only present in those with deletions and UPD. GERD was present more frequently in those with deletion (48%) and UPD (45%) as compared to UBE3A (31%) and IC (13%), while only those with deletions and UPD reported difficulty swallowing and/or underwent swallow studies. Also, all but one subject with cyclic vomiting had either deletions or UPD. Maternal deletions are associated with the most severe phenotype, likely due to multiple genes lost on the maternal

TABLE 2 Treatments for constipation and GERD

Indication	Treatment type	Number used
Constipation (n = 141)	Laxatives	
	Polyethylene glycol	65 (46%)
	Senna	11 (8%)
	Other laxatives	5(4%)
	Dietary changes[a]	20 (14%)
	Stool softeners	5(4%)
GERD (n = 72)	Proton pump inhibitors (PPI)	
	Lansoprazole	19(26%)
	Omeprazole	15(21%)
	Other PPI's	13(18%)
	Ranitidine	7 (10%)

[a]Not including individuals who made dietary changes for epilepsy therapy with the low-glycemic index treatment or the ketogenic diet.

chromosome and the haploinsufficiency of the remaining paternal genes (Lossie et al., 2001). It may be that the more significantly decreased muscle tone in children with maternal deletion is associated with poor lower esophageal sphincter and oromotor tone, increasing the risk of GERD, and feeding and swallowing difficulties in this population. This haploinsufficiency may also explain why those with UPD may experience more GI dysfunction than those with UBE3A, as multiple maternal genes are inactive in UPD as opposed to a single gene in UBE3A, but this is not well understood. Some studies have noted that individuals with AS caused by UPD share some behavioral food related similarities to individuals with Prader–Willi Syndrome (PWS) such as hyperphagia (Poyatos et al., 2002; Smith, Marks, Haan, Dixon, & Trent, 1997 Smith, Robson, & Buchholz, 1998). Although this was not specifically noted in our cohort, it is worth noting that individuals with UPD who display these eating behaviors can have issues with cyclic vomiting and GERD caused by overeating or eating inedible items. The prevalence of these issues in UPD compared to the other genetic subtypes of AS could be due to genetic differences in expression of imprinted genes on the paternal chromosome that are shared by those with PWS and AS caused by UPD.

There may be a behavioral component to the constipation issues found among all subtypes of AS. Like those with ASD, anxiety, and sensory issues surrounding bathroom routines may contribute to avoidance of stooling (Buie et al., 2010; Peters, 2017). They may also be inattentive or busy leading to a lack of attention to toileting cues or impatience during stooling. It is also possible that they withhold stool due to increased anxiety following a traumatic stooling experience (Buie et al., 2010). Treatment of constipation in our cohort was usually through three particular methods: laxatives, dietary changes, and stool softeners. The most commonly used treatment among those was laxatives with polyethylene glycol being used by nearly half of individuals with constipation. Although the efficacy of these treatments was not determined in this study, the popularity of this option suggests that this may be a favorable method of combating constipation in this population. Along with laxatives, stool softeners and dietary changes were used by some individuals but were not widely used overall (Table 2).

Treatment of GERD in our cohort was most frequently treated with PPI's, of which lansoprazole and omeprazole were the most popular. A small portion of individuals used other PPI's as well as ranitidine. Efficacy was not determined for any of these treatment options but they show a trend in treatment among this cohort in favor of PPI use for treatment of GERD (Table 2).

Dietary therapy of epilepsy, including the low-glycemic index treatment and the ketogenic diet, was used by 16 individuals in our cohort for seizure management. The side effect profile of low carbohydrate, high fat diets can impact GI function and has been shown to worsen or trigger constipation in some individuals with AS (Grocott et al., 2017). Due to this, close monitoring of GI function while on the diet is recommended and dietary changes, supplements such as MCT oil, and additional treatments for constipation could be considered.

It is important for caregivers and medical professionals to be aware of the high prevalence of GI issues in the AS population, as pain and discomfort in these individuals may have atypical presentations (Foley & McCutcheon, 2004). Based on the analysis of caregiver's reports, children with severe cognitive impairments are more likely to suffer pain from medical illness and ongoing medical issues than typically developing children (Breau, Camfield, McGrath, & Finley, 2003). In addition to progressing to more serious health issues, unresolved pain/discomfort may manifest as behavioral issues, which may prevent effective integration and socialization for those with AS (Horner, Carr, Strain, Todd, & Reed, 2002). In both children and adults with developmental disabilities, caregivers report a greater occurrence of problem behaviors on days with increased or aggravated physical discomfort (Carr & Owen-DeSchryver, 2007). Common GI issues that remain undiagnosed in AS may cause this discomfort and subsequently worsening behavioral issues.

Additionally, individuals with AS have been found to frequently display abnormal sleep-wake cycles, frequent episodes of nocturnal waking, and seemingly diminished sleep requirements (Bruni et al., 2004; Williams Driscoll & Dagli, 2010). In children with ASD, concurrent GI disorders were found to worsen and increase the frequency of sleep problems (Horvath & Perman, 2002; Mannion & Leader, 2013). Children with ID and sleep disorders were found to have a rise in disruptive behaviors when compared to either children with ID and no sleep disorder or typically developing children with sleep disorders. This increase in sleep disturbance may further impair their daily functioning and integration into educational or social environments, while also lowering seizure threshold (Conant, Thibert, & Thiele, 2009; Richdale, Francis, Gavidia-Payne, & Cotton, 2000).

There have been many studies on the source of the increased prevalence of GI disorders in neurodevelopmental disorders like AS and ASD, but little consensus has been reached, likely due to the high variability of GI disorders and contributing factors. Abnormal food preferences may play a major role as individuals with AS may consume a less varied diet and reduced fluids, increasing the likelihood of constipation and other GI issues (Ahearn, Castine, Nault, & Green, 2001; Williams et al., 2006; Williams, Driscoll, & Dagli, 2010). The majority of individuals with AS have epilepsy and require antiepileptic drug therapy (Conant et al., 2009; Shaaya, Grocott, Laing, & Thibert, 2016). This prolonged antiepileptic drug therapy may also be an additional factor leading to gastrointestinal issues (Böhmer et al., 2001; McCarron, O'Dwyer, Burke, McGlinchey, & McCallion, 2014). It has also been suggested that the pro-inflammatory conditions found in many individuals with ASD may contribute to GI dysfunction (Horvath & Perman, 2002). Multiple studies have found that individuals with ASD and GI dysfunction may have abnormal IgG deposits in the intestine, altered cytokine production, and increased Paneth cell secretions, suggesting a possible altered local immune defense in patients with ASD (Ashwood & Wakefield, 2006; Erickson et al., 2005; Horvath & Perman, 2002) . Huge variations, however, in these study outcomes make it difficult to determine the exact cause of GI disorders. Other studies have suggested that individuals with ASD and other forms of ID may have abnormal gut flora, which could contribute to neural and GI dysfunction

through the formation of toxic metabolites (Finegold et al., 2002; Parracho, Bingham, Gibson, & McCartney, 2005). It has yet to be determined, however, if this abnormal gut flora is congenital or caused by antibiotics and other environmental factors. The gut flora of individuals with AS has not yet been described in the literature.

This study indicates that the majority of individuals with AS suffer from constipation and other GI issues, such as GERD, feeding and swallowing difficulties, and less commonly cyclic vomiting and EoE. The prevalence of GI issues reported in our study may be confounded by a few factors such as relying on parental reporting and not accounting for age as many younger patients may go on to experience some of these GI issues later in life but have not yet experienced them. Constipation is equally common in all genetic subtypes, where disorders of the upper GI tract are more common in those with deletions and UPD. This may indicate that constipation has a more functional component where upper GI issues are more related to decreased tone. Caregivers and medical professionals should be aware of the high prevalence of these disorders, as individuals with AS may be unable to effectively communicate discomfort and pain. Untreated, GI issues can exacerbate disruptive behaviors, which may limit the amount of educational and social integration that individuals may experience. Additionally, GI discomfort can lead to decreased sleep and, therefore, increased seizure frequency. Further research into the causes of GI dysfunction in AS is necessary with a hope that better understanding of these mechanisms will lead to earlier diagnosis, more effective treatment, and improved quality of life in those affected by AS.

ACKNOWLEDGMENTS

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