Association between early and current gastrointestinal symptoms and comorbidities in children and adolescents with Angelman syndrome

Association between Early and Current Gastro-Intestinal Symptoms and Comorbidities in Children and Adolescents with Angelman Syndrome.

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Abstract

Background: Angelman Syndrome (AS) is a neurogenetic disorder that causes severe intellectual disability, expressive language deficits, motor impairment, ataxia, sleep problems, epileptic seizures, and a happy disposition. People with AS frequently experience gastrointestinal (GI) symptoms.

Method: This study used data from the Global Angelman Syndrome Registry to explore the relationship between early and current GI symptoms and comorbidity in children and adolescents with AS (n = 173). Two groups that experienced a high (n = 91) and a low (n = 82) frequency of GI symptoms were examined in relation to feeding and GI history in infancy, sleep and toileting problems, levels of language and communication, and challenging behaviours. Predictors of GI symptoms were then investigated using a series of logistic regressions.

Results: This analysis found that constipation and gastroesophageal reflux affected 84% and 64%, of the sample, respectively. The high frequency of GI symptoms were significantly associated with: 'refusal to nurse', 'vomiting', 'arching', 'difficulty gaining weight', gastroesophageal reflux, 'solid food transition', frequency of night-time urinary continence, and sleep hyperhidrosis during infancy. GI symptoms were not significantly associated with sleep, toileting, language or challenging behaviours. Significant predictors of high frequency GI symptoms were gastroesophageal reflux, and sleep hyperhidrosis.

Conclusions: Future research needs to investigate the association between AS and GI comorbidity in adults with AS.

Keywords: Angelman Syndrome, Comorbidity, Gastrointestinal Symptoms, Global Angelman Syndrome Registry.

Introduction

Angelman Syndrome

Angelman Syndrome (AS) is a rare neurogenetic disorder determined by an abnormality in the expression of the maternal chromosome that contains the ubiquitin-protein ligase E3A (UBE3A) gene in the brain (Margolis et al., 2015). The abnormality in the genetic expression of UBE3A is caused by four genetic mechanisms: (1) a deletion of the chromosome 15q11-q13; (2) paternal uniparental disomy (UPD); (3) an imprinting defect; (4) a mutation in the UBE3A (Bindels-de Heus et al., 2020). Angelman syndrome is distinguished by its phenotype that consists of severe intellectual disability, expressive language deficits, motor impairment, ataxia, sleep problems, epileptic seizures, and a uniquely happy disposition (Dagli et al., 2017). The most severe phenotype is related to the 15q11.2-q13 deletions subtype (Bindels-de Heus et al., 2020). AS occurs in 1 in every 15,000 to 24,000 individuals (Tones et al., 2018). However, there is a shortage of large population studies, and many individuals are undiagnosed, misdiagnosed, or lack a genetic confirmation of AS (Wheeler et al., 2017). There have also been to date relatively few studies that have investigated comorbidities that occur in the AS population.

Comorbidity has been defined as two or more disorders that occur concurrently in an individual (Matson & Nebel-Schwalm, 2007). Comorbid conditions that co-occur with AS include gastrointestinal (GI) symptoms, epilepsy, sleep problems, toileting problems, and behavioural problems (Arron et al., 2011; Bevinetto & Kaye, 2014; Bonati et al., 2007; Glassman et al., 2017; Pelc et al., 2008; Radstaake et al., 2013; Wang et al., 2020). AS has genetic, clinical features, and

symptoms, that overlap with autism spectrum disorder (ASD) (Richards et al., 2015; Walz, 2007), and a comorbid diagnosis of ASD with AS is prevalent, occurring in between 50% and 81% of people with ASD (Bonati et al., 2007; Peters et al., 2004).

GI symptoms are diagnostic criteria for AS, and a clinical feature of the disorder (Williams et al., 2006). The GI symptoms that can be experienced by people with AS include constipation, diarrhoea, gastroesophageal reflux, and cyclic vomiting (Thibert et al., 2013). Estimates of the prevalence of GI symptoms in AS vary between 20% and 87% (Glassman et al., 2017; Williams et al., 2006), which is higher than the 13.5% prevalence in typically developing children (Korterink et al., 2015). Determining the cause and severity of GI symptoms in people with AS is complex (Glassman et al., 2017; Buiting et al., 2016). One study that investigated the prevalence of GI symptoms in individuals with AS (n = 120), reported that constipation and gastroesophageal reflux occurred most commonly, impacting 71% and 44% respectively, of children and adults with AS (Glassman et al., 2017). It is known that GI symptoms cause discomfort which may aggravate sleep problems, disruptive behaviours, and hinder social development (Bird, 2014).

The weight gain of infants with AS may be impeded (Mertz et al., 2014), and individuals may present with sucking and swallowing difficulties, gastroesophageal reflux, and a reduced ability to breast and bottle feed (Dagli et al., 2017). Feeding difficulties continue into childhood, with oral motor problems, and tongue thrusting, sucking, drooling, and mouthing behaviours (Thibert et al., 2013). Feeding difficulties in infancy may be associated with the GI symptoms of people with AS and GI symptoms that occur during the first year of life may be associated with GI symptoms experienced in childhood and adolescents. However, little is currently known about the relationship between the history of people with AS in their infancy and GI symptoms as they age.

Few studies to date have focused on toileting issues in AS (Buntinx et al., 1995; Radstaake et al., 2013) and yet toileting problems and incontinence considerably negatively impact the quality of life of people with AS and caregivers (Kirli et al., 2021). Higher rates of incontinence in children are generally associated with developmental disorders such as AS (Matson & LoVullo, 2009) and 85.6% of children and adults with AS have at least one subtype of incontinence (Wagner et al., 2017).

Wagner et al. (2017) conducted the largest study to date on incontinence in children (n = 90) and adults (n = 54) with AS. This study analysed rates of constipation but it did not assess the relationship between GI symptoms and incontinence. It can be hypothesised that a relationship may exist between GI symptoms and incontinence in AS, because the former may be aggravated by the latter.

People with AS, of all age groups, have severe communication impairment (Larson et al., 2015; Williams et al., 2009), and frequently individuals have deficient expressive language skills and little or no functional speech (Gentile et al., 2010). Natural nonverbal gestures are the most commonly used method of expressive communication by children with AS (Calculator 2013; Quinn & Rowland, 2017). However, the gesturing used by children with AS to communicate with caregivers can lack any deliberate intention (Grieco et al., 2019). Due to communication deficiencies, GI symptoms may be undiagnosed in people with AS but this possibility has been little explored amongst AS populations (Dagli et al., 2017).

Challenging behaviours observed in people with AS include but are not limited to, tantrums, excessive laughter, self-injury, restlessness, stereotypical behaviour, hyperactivity, and a strong fascination with water (Clarke & Marston, 2000; Horsler & Oliver, 2006). Although people with AS present with a happy demeanour, they often exhibit challenging behaviours that inhibit their interactions in social environments (Sadhwani et al., 2019). Aggression, irritability and hyperactivity significantly increase with age (Sadhwani et al., 2019) and aggression is exhibited by from 59% to 73%, of adolescents (Arron et al., 2011; Larson et al., 2015; Sadhwani et al., 2019) and 83.3% of children with AS (Strachan et al., 2009). Challenging behaviours are likely to be exacerbated by an underlying illness or pain (Didden et al., 2009). Prasad et al. (2018) characterised the changes over time in the history of AS, examining the frequency of GI symptoms, and aggressive behaviour in adolescents and adults with AS. However, no study to date has investigated the relationship between GI symptoms and aggression in people with AS.

It is known that GI symptoms and discomfort can exacerbate sleep problems in people with AS (Tan & Bird, 2017) and that the history of gastroesophageal reflux in children with AS is associated with higher levels of sleep-disordered breathing (Tones et al., 2019). However, these

studies did not examine the relationship between GI symptoms and sleep problems in relationship with other co-occurring conditions, and they did not examine adolescents and adults with AS. It is important to further investigate the relationship between GI symptoms and sleep in people with AS due to their impact on the quality of life for people with AS and their caregivers (Richdale et al., 2000). Indeed, a recent meta-analysis that investigated sleep problems in children and adults with AS found that reduced sleep time was present in 71.4% of studies, and reduced sleep quality was established in 64.3% of studies (Spruyt et al., 2018).

In order to increase knowledge about the aetiology of gastrointestinal symptoms in the context of children and adolescents with AS, the current study examined the GI symptoms that are experienced by people with AS. It aimed to compare people with AS who have a high frequency of GI symptoms with those who have a low frequency of GI symptoms regarding the following variables: infancy history, toileting, challenging behaviour, language and communication, and sleep problems. It also aimed to investigate possible predictors of GI symptoms in people with AS.

Method

Procedure

This study used a cross-sectional design and secondary analysis of data collected from participants who were recruited by the Global Angelman Syndrome Registry (https://angelmanregistry.info/), before this study. The Registry assembles data using parent or caregiver-reported surveys that are completed online, in English, by primary caregiver informants who participate in the Registry on behalf of people who have a parent-reported diagnosis of AS. Consent and participant information forms are provided to informants by the registry and the registry collects data regarding the developmental, behavioural, and clinical status of people with AS, categorizing data into eleven different modules (Napier et al., 2017; Tones et al., 2018). The data sets contained in these modules are informed through research (Gentile et al., 2010; Tan et al., 2011) and research priorities that are identified by stakeholders, including the families of children with AS.

Researchers accessed the anonymised module data sets that were relevant to the study aims, by applying to the Registry curator, using the online data request forms. The modules requested were

the: Newborn and Infancy History, History of Diagnoses and Results, Illnesses or Medical problems, Medical History, Communication, Behaviour and Development, and the Sleep Disturbance Scale for Children (Tones et al., 2018). Ethical approval for this study was granted by the Research Ethics Committee in the National University of Galway, Ireland.

Participants

The study sample comprised n = 173 people with AS who were enrolled in the Global Angelman Syndrome Registry. The sample size was calculated using 'G*Power' Version 3.1.9.2.

Measures

Gastrointestinal Symptoms

Data about GI symptoms were obtained from the data set module 'Illnesses and Medical Problems'. This questioned informants about the occurrence and severity of gastroesophageal reflux, strep throat, constipation, and vomiting during feeding. Questions used a Likert scale with values that ranged from 1 to 6. For example, informants were asked: Has the individual suffered from constipation? Informants selected answers from the options: All the time; Most of the time; Some of the time; Rarely; Never, Unknown.

Infancy History

Data concerning infancy history was collected through the 'Newborn and Infancy History' module. This module involved 20 questions that used a Likert 1 to 6 scale. Questions focused on feeding history, reported difficulties feeding as a newborn and during infancy, swallowing difficulties, history of GI difficulties, and any other health difficulties. For example, regarding difficulty feeding, informants were asked: Does/did he/she appear irritable in association with feeding?

Challenging Behaviour

Data on challenging behaviour was obtained through the 'Behaviour and Development' module. The module had seven subscales that focused on specific types of challenging behaviour: repetitive behaviours, aggression, spontaneous affect, appropriate affect, anxiety, inattention/hyperactivity, and behaviour dysregulation including self-injury. A total of 29 questions

were answered using a Likert 1 to 5 scale. The Informant could also reply with the answer 'unknown'. For example, does he/she exhibit any of the following behaviours? Aggressive behaviours: biting.

Toileting

Toileting was examined through the 'Behaviour and Development' module. Data on toileting behaviours concerning the timing of toileting, the amount of bowel and urinary continence, and night-time continence were collected. Questions were again answered with a 1 to 5 Likert scale or 'unknown'. For example, how often is he/she continent of urine?

Language and Communication

Caregivers answered questions in the 'Communication' module regarding expressive speech, ability to engage in different communication methods including assisted and augmented communication, and participants' preferred method of communicating. This module involved 20 questions that were answered using a Likert scale that ranged from 1 to 5 or 'unknown'. For example, if the informant answered that the participant was verbal, they were asked to indicate his/her best verbal language communication. The answer choices were: Moans, Babbles; Uses an intentional sound to attract attention; Single words; 2-3 word phrases; Longer phrase speech.

Sleep Disturbance Scale for Children (SDSC)

The Sleep Disturbance Scale for Children *(SDSC)* (Bruni et al., 1996) examines disorders of sleep initiation, sleep maintenance, sleep-disordered breathing, disordered arousal, sleep-wake transition disorders, and excessive somnolence disorders (Romeo et al., 2013). The scale was originally validated using a sample of 1,157 healthy children from the general population ranging from six to 16 years of age (Bruni et al., 1996). The scale shows good internal consistency (α = .83) among the 26 items (Romeo et al., 2013). An analysis of reliability was also good showing Cronbach's alpha values greater than 0.55 on each of the subscales (Ferreira et al., 2009). The scale consists of 26 items scored on a Likert type 5-point scale were; 0 = least severe, and 5 = most severe (Bruni et al., 1996). The scale is categorised into 6 sleeping disturbance subscales: 1) onset of sleep and sleep maintenance, 2) disorders of sleep-related breathing, 3) arousal disorders, 4) sleep-wake transition disorders, 5) disorders of excessive somnolence, and 6) sleep hyperhidrosis. The sum of raw

scores provides a total sleep score that ranges from 26 to 130. A total sleep score of > 39 was the cut-off for abnormal sleep (Bruni et al., 1996).

Analyses

The overall purpose of the analysis was to determine the association between infant and current GI symptoms and whether a history of GI symptoms in infancy can statistically predict GI symptoms later on. To achieve this purpose, the frequency of each GI symptom for the total sample and the number of GI symptoms present in individuals was calculated. Participants were then divided into two groups according to the frequency of their GI symptoms which involved constipation, gastroesophageal reflux, and vomiting. The high frequency GI symptom group was defined as having two or more of these symptoms. The low frequency group contained participants with only one of these symptoms or less.

A series of Pearson's χ^2 cross-tabulations were conducted on nominal variables including infancy history, language and communication, and toileting to assess frequencies and associations with low frequency and high frequency GI symptoms groups. Mann-Whitney *U* tests were conducted on sleep problems and challenging behaviour variables that were not normally distributed, to detect differences between the two groups. Then, a series of logistic regressions were conducted to investigate possible predictors of the GI symptoms.

Results

Sample Description

Participants ranged in age from 3 to 17 years, with a mean age of 8.38 years (*SD* = 4.08). The sample included 50.29% males (*n* = 87). Diagnoses of AS were made independent of the study and, 93.06% (*n* = 161) of informants reported that they had received genetic confirmation of the diagnosis. The genetic confirmations received included: UBE3A mutation confirmation (21%, *n* = 35), UPD confirmation (8.7%, *n* = 14); imprinting centre defect confirmation (4.97%, *n* = 8), a chromosome deletion confirmation (61.49%, *n* = 99), and 'other' (3.11%, *n* = 5).

GI Symptoms

Constipation was the most common GI symptom. This was experienced by 84% (n = 147) of participants. Gastroesophageal reflux was second most common, present in 64% (n = 111) participants, and vomiting with feeds occurred in 58% (n = 101) of participants. One GI symptom was present in 34.7% (n = 60) of participants. A further 34.7% (n = 60) experienced two GI symptoms, whilst 17.9% (n = 31) experienced all three GI symptoms. No GI symptoms were experienced by 12.7% (n = 22) of participants. The low frequency GI group (n = 82) comprised of 46% males (n = 38) and 53% females (n = 44). The high frequency GI group (n = 91) included 53% males (n = 49) and 46% females (n = 42). There were no statistical differences between the GI groups regarding gender, $\chi 2$ (df = 1, n = 173) = .97, p = .32. A Mann-Whitney U test was conducted to determine if the GI groups differed regarding age of participants. The results suggested there was no difference according to age, z = -1.155, p = .248.

GI Symptoms & Infancy History

Pearson's χ^2 analysis was conducted to investigate the relationship between GI groups and infancy history variables. Table 1 presents the results of this analysis. Significant associations with the high frequency GI group were observed on numerous variables including 'refusal to nurse', 'vomiting', and 'arching', 'weight gain difficulty', 'gastroesophageal reflux', and 'solid food transition'. History of 'strep throat', 'tube feeding', 'other health problems', and 'diagnosed intolerances' were also significantly associated with high frequency GI symptoms.

A binary logistic regression was conducted to examine predictors for the frequency of GI symptoms. The criterion variable was binary with a high frequency GI level and a low frequency GI level. The predictor variables were refusal to nurse, vomiting, arching, weight gain difficulty, gastroesophageal reflux, transition to solid food, any other health problems, history of strep throat, and history of tube feeding, and diagnosed intolerances. The analysis found the full model was significant, χ^2 (df = 10, n = 127) = 47.60, p < .001, implying these predictor variables significantly predict high frequency GI symptoms. The model correctly classified 74.8% of participants. Wald statistics indicated that gastroesophageal reflux (Wald = 12.99, p < .001) and history of strep throat

(Wald = 6.72, $p < .05$) significantly predicted GI symptoms. Table 2 below presents the results of the logistic regression.

GI Symptoms & Toileting

Chi-square statistics and frequencies were conducted to examine associations between toileting variables and the GI groups. The results of this analysis are presented in Table 3 below. A significant association was observed between night-time urinary continence frequency and high frequency GI symptoms. The remainder of the toileting variables did not have any statistically significant associations between GI frequency groups.

GI Symptoms & Language and Communication

No significant associations were observed between GI frequency groups and language and communication using Pearson's chi-square analyses. Table 4 presents the results of the frequencies and associations between the language and communication variables and GI groups.

GI Symptoms & Challenging Behaviour

Descriptive statistics of the means and standard deviations of the challenging behaviour variables are presented in Table 5 below. The Mann-Whitney *U* tests revealed that none of the challenging behaviour variables significantly differed between GI groups. Low frequency GI symptoms, however ($M = 60.53$), scored higher than high frequency GI symptoms ($M = 52.33$) on mean ranks inappropriate affect but without reaching statistical significance, $U = 1338$, $p = .17$. High frequency GI symptoms ($M = 60.69$) and low frequency GI symptoms ($M = 52.46$) also differed largely on inattention-hyperactivity ($U = 1337$, $p = .17$), without being statistically significant.

GI Symptoms & Sleep Problems

Participants were categorised into presence or non-presence of sleep disturbance categories based on a total sleep cut-off score of > 39. Scores above 39 were considered disturbed sleep (Bruni et al., 1996). Within the high frequency GI symptoms group, 42.47% ($n = 31$) experienced sleep disturbance, whereas 46.48% ($n = 34$) of the low frequency GI symptoms group experienced sleep disturbance. Of the high frequency GI symptoms group, 4.12% ($n = 3$) did not experience any sleep

disturbance, while 6.85% (n = 5) of the Low frequency GI symptoms group did not experience any sleep disturbance. Pearson's χ^2 found there was no statistically significant association between sleep disturbance groups and the high frequency or low frequency GI groups, χ^2 (df = 1, n = 73) = .30, p = .59. Means and standard deviations of sleep subscales are presented in Table 6 below.

A series of Mann-Whitney U tests were conducted to investigate differences in sleep disturbance subscales between GI frequency groups. A statistically significant difference was observed in sleep hyperhidrosis between GI groups (U = 835, p < .05), where high frequency GI symptoms had a higher mean rank (M = 53.52) than low frequency GI symptoms (M = 42.20). The high frequency GI symptoms group scored higher in mean rank (M = 50.05) than the low frequency GI symptoms group (M = 42.21), on sleep-breathing disorders but did not reach statistical significance (U = 856, p = .15). A difference was also observed in excessive somnolence mean ranks, with high frequency GI symptoms (M = 52) scoring higher than low frequency GI symptoms (M = 42.11) without being statistically significant (U = 851, p = .08).

A binary logistic regression was conducted to examine predictors of GI frequency. The six subscales of the sleep disturbance scale were entered into the model. A test of the full model revealed it was not statistically significant, $\chi 2$ (df = 6, n = 76) = 8.41, p = .21. The model correctly classified 60.5% of individuals. An examination of Wald statistics revealed sleep hyperhidrosis as a significant predictor of GI symptoms (Wald = 5.02, p < .05). The results of the logistic regression are presented in Table 7.

Discussion

The results indicate that GI symptoms are common in people with AS. In this study, GI symptoms occurred in 87.3% of the participants. Constipation was the most common symptom occurring in 84% of the current study sample. This prevalence was similar to that found by Glassman et al. (2017) who identified GI symptoms in 87% of their AS sample, of whom, 71% experienced constipation. The findings also revealed it is relatively common for people with AS to have more than one GI symptom, as 34.7% of participants had two GI symptoms and 17.9% experienced all three symptoms.

Gastroesophageal reflux presented in 64% of the participants in the current study, whereas Glassman et al. (2017) reported a prevalence of 44%. The current study also reported a higher incidence of vomiting with feeds (58%) than Glassman et al. (2017) where it occurred in 10% of the sample. This discrepancy may arise because the two studies included participants of different age ranges and because the current study did not evaluate GI symptoms in AS adults. However, the finding suggests that GI symptomology in AS populations may change with age and this possibility should be examined in future research.

The current study is the first research to date to have focused on the association of comorbidity in infancy history with GI symptoms within the AS population. The current study found that GI symptom frequency was significantly associated with several variables in infancy history. Significant associations between GI frequency groups were found in refusal to nurse, vomiting in infancy, and difficulty in gaining weight. Mertz et al. (2014) reported that children with AS had difficulty gaining weight in their first three years of life, but they did not investigate its association with GI symptoms.

Further significant associations were found between high frequency GI symptoms and other health problems, diagnosed intolerances, and history of tube feeding. And, further analysis found that gastroesophageal reflux in infancy significantly predicted the frequency of GI symptoms.

Indeed, it has been stated in a clinical report that medical and behavioural history in infancy may play a role in generating gastroesophageal reflux in children with AS (Dagli et al., 2017). The current study findings support this statement and they suggest that behaviours in the postnatal period of infancy may be associated with an increased likelihood of developing GI symptoms. However, further studies are needed to replicate and consolidate these findings.

The study findings suggest that people with AS and with more GI symptoms are more likely to experience difficulty with night-time urinary continence than those with low frequency GI symptoms. Therefore physical discomfort may be associated with greater difficulties successfully toileting and maintaining continence. Frequent GI symptoms causing discomfort may distract the individual from toileting cues. A similar association has been found among people with ASD whereby

GI symptoms predicted toileting difficulties (Leader et al., 2018). However, because the current study is the first to examine the association between GI symptoms and toileting in people with AS, further studies need to replicate these findings. Future studies might explore which specific GI symptoms are related to night-time urinary continence. It would also be important to examine these in the adult population to ascertain whether this association changes over time.

Sleep disturbance was common in the current study and affected 89.04% of the total sample. The study identified that 42.47% of participants in the high frequency GI group and 46.48% of individuals in the low frequency GI group had sleep disturbance. However, a significant difference was found between GI frequency groups only on the sleep hyperhidrosis subscale, suggesting that people with more GI symptoms experienced more excessive night-time sweating. Sleep hyperhidrosis was also a significant predictor of high frequency GI symptoms. These findings concur with and expand the findings of other studies that also found sleep hyperhidrosis is associated with GI symptoms in AS populations (Tones et al., 2019; Tan and Bird, 2017). Sweating can result from problems in temperature regulation, that are common in AS, and it can be a sign of discomfort, perhaps caused by gastroesophageal reflux (Agar et al., 2021; Berdnikov et al., 2020). The current study also found a higher incidence of sleep-disordered breathing in the GI group. Although this finding was of borderline significance, it concurs with Tones et al., (2019) who found a significant association between a history of gastroesophageal reflux and sleep-disordered breathing in children and adolescents with AS. In addition, previous research has highlighted that children with AS and sleep disturbance and gastro-osophageal reflux had significantly higher sleep-disordered breathing scores ($p < .01$) (Trickett et al., 2018). These are important findings that may be used to guide clinicians to investigate, treat, or out rule, GI symptoms, when an individual with AS presents with sleep and/or behavioural problems, given that lack of sleep significantly contributes to the stress of caregivers of children with AS (Wheeler et al., 2017).

This study has several limitations. AS research is a new field of research and the measures used, apart from the SDSFC, have not been psychometrically validated. Also, data collection relied on

parental-report surveys, which may have impacted its reliability. However, parental reports of child development can be reliable and consistent with clinical reports (Gorrindo et al., 2012).

Another possible bias may arise because informants who upload data to the Angelman Registry are encouraged, to supply verification of the clinical AS diagnosis of participants, but they are not required to do so (Tones et al., 2018). However, the accuracy of self-reported diagnoses of rare diseases in registries has been reported to be 99% (Sharkey et al., 2015). This study, and all Registry-based research, may also have been impacted by recall bias, as parents of older participants may inaccurately remember GI symptoms that occurred during their child's infancy.

To conclude, this study has extended knowledge on AS and it has provided novel findings on GI symptom comorbidity in children and adolescents with AS. GI symptoms were found to be very common in people with AS and significant associations were identified between high frequency GI symptoms and infancy history, toileting, and sleep hyperhidrosis. Furthermore, gastroesophageal reflux, and sleep hyperhidrosis significantly predicted current GI symptoms. The study findings may inform clinical professionals about the co-occurring symptoms of GI in people with AS, particularly those that might exacerbate night-time continence problems and sleep problems. Future research should further investigate GI comorbidity in AS, particularly in the adult AS population. It should also include examination of the genotype of individuals, and focus on oral motor problems and gastrointestinal motility problems.

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Data Availability: The data on which this study is based is available on request through the Global Angelman Syndrome Registry (https://angelmanregistry.info/).

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