Association between early and current gastro-intestinal symptoms and co-morbidities 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 co-morbidity 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 co-morbidity in adults with AS.

Keywords   Angelman syndrome, co-morbidity, 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

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chromosome 15q11-q13; (2) paternal uniparental disomy (UPD); (3) an imprinting defect and (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 co-morbidities that occur in the AS population.

Co-morbidity has been defined as two or more disorders that occur concurrently in an individual (Matson and Nebel-Schwalm 2007). Co-morbid conditions that co-occur with AS include gastrointestinal (GI) symptoms, epilepsy, sleep problems, toileting problems and behavioural problems (Bonati *et al.* 2007; Pelc *et al.* 2008; Arron *et al.* 2011; Radstaake *et al.* 2013; Bevinetto and Kaye 2014; Glassman *et al.* 2017; Wang *et al.* 2020). AS has genetic, clinical features and symptoms that overlap with autism spectrum disorder (ASD) (Walz 2007; Richards *et al.* 2015), and a co-morbid diagnosis of ASD with AS is prevalent, occurring in between 50% and 81% of people with ASD (Peters *et al.* 2004; Bonati *et al.* 2007).

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% (Williams *et al.* 2006; Glassman *et al.* 2017), 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 (Buiting *et al.* 2016; Glassman *et al.* 2017). 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 that 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 and 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 (Williams *et al.* 2009; Larson *et al.* 2015), 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 and 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 among 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 and Marston 2000; Horsler and 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 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 and 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, categorising data into 11 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 were 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 were 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 as follows: moans, babbles; uses an intentional sound to attract attention; single words; 2–3 word phrases; longer phrase speech.

Sleep Disturbance Scale for Children

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 1157 healthy children from the general population ranging from 6 to 16 years of age (Bruni *et al.* 1996). The scale shows good internal consistency ($\alpha = 0.83$) 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 six 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).

Gastrointestinal 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) composed 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, χ^2 (df = 1, n = 173) = 0.97, P = 0.32. 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 = 0.248.

Gastrointestinal symptoms and 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 < 0.001, implying that 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 < 0.001) and history of strep throat (Wald = 6.72, P < 0.05) significantly predicted GI symptoms. Table 2 presents the results of the logistic regression.

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Table 1 Infancy history frequencies and Pearson's chi-square analyses between GI groups

Infancy history		Low frequency GI symptoms (N = 82)	High frequency GI symptoms (N = 91)	Pearson χ^2
Type of feeding	Bottle fed	42	42	1.01
	Breast fed	33	33	
	Other	3	6	
Infancy feeding difficulties	Yes	56	70	3.32
	No	20	17	
	Missing	2	0	
Infancy feeding assistance	Yes	37	49	0.61
	No	28	33	
	Missing	3	2	
Infancy: Refusal to nurse	Yes	22	39	7.53*
	No	45	39	
	Missing	5	1	
Infancy: Latching difficulty	Yes	34	49	2.92
	No	30	24	
	Missing	5	7	
Infancy: Ineffective Suck	Yes	41	58	2.87
	No	26	21	
	Missing	3	2	
Infancy: Biting	Yes	20	21	0.54
	No	45	56	
	Missing	5	4	
Infancy: Vomiting	Yes	43	75	15.97**
	No	28	11	
	Missing	1	0	
Infancy: Arching	Yes	28	49	5.95*
	No	29	21	
	Missing	13	13	
Infancy: Excessive moving	Yes	34	50	2.41
	No	32	28	
	Missing	6	6	
Infancy: Irritable feeding	Yes	39	50	1.67
	No	34	32	
	Missing	1	3	
Suck/swallow difficulties	Yes	52	71	4.52
	No	23	14	
	Missing	1	1	
Weight gain difficulty	Yes	34	56	7.28*
	No	42	29	
	Missing	1	1	
Gastroesophageal reflux	Yes	43	81	35.13**
	No	29	3	
	Missing	5	1	
Solid food transition	Yes	35	55	8.87*
	No	42	28	
	Missing	0	2	
Other health problems	Yes	21	37	9.36*
	No	55	42	
	Missing	1	6	
Strep throat history	Yes	27	53	11.58**
	No	49	32	

Table I. *(Continued)*

Infancy history		Low frequency GI symptoms (*N* = 82)	High frequency GI symptoms (*N* = 91)	Pearson χ^2
	Missing	6	6	
Tube feeding history	Yes	3	13	6.16*
	No	72	75	
	Missing	0	1	
Diagnosed allergies	Yes	21	31	2.74
	No	51	49	
	Missing	3	1	
Diagnosed intolerances	Yes	23	22	6.79*
	No	48	47	
	Missing	2	12	

$^{**}P < 0.001$.
$^{*}P < 0.05$.

Table 2 Binary logistic regression odds ratios (OR), confidence intervals (CI) and significance value for infancy history predictors

Predictors	OR	95% CI	P-value
Refusal to nurse	1.19	0.45–3.01	0.76
Vomiting in infancy	0.57	0.18–1.79	0.34
Arching in infancy	1.10	0.43–2.84	0.83
Weight gain difficulty	0.79	0.32–1.93	0.60
Gastroesophageal reflux	0.08	0.02–0.31	0.001**
Solid food transition	0.84	0.32–2.18	0.72
Other health problems	0.49	0.19–1.23	0.13
History of strep throat	0.3	0.12–0.74	0.01*
History of tube feeding	0.38	0.06–2.29	0.29
Diagnosed intolerances	1.23	0.48–3.11	0.67

$^{*}P < 0.05$.
$^{**}P < 0.001$.

Gastrointestinal symptoms and 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. 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.

Gastrointestinal symptoms & language and communication

No significant associations were observed between GI frequency groups and language and communication using Pearson's χ^2 analyses. Table 4 presents the results of the frequencies and associations between the language and communication variables and GI groups.

Gastrointestinal symptoms & challenging behaviour

Descriptive statistics of the means and standard deviations of the challenging behaviour variables are presented in Table 5. 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* = 0.17. High frequency GI symptoms (*M* = 60.69) and low frequency GI symptoms (*M* = 52.46) also differed largely on inattention-hyperactivity (*U* = 1337, *P* = 0.17), without being statistically significant.

Gastrointestinal symptoms & sleep problems

Participants were categorised into presence or non-presence of sleep disturbance categories based

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Table 3 Toileting frequencies and Pearson's χ^2 analyses between GI groups

Toileting		Low frequency GI symptoms (*N* = 82)	High frequency GI symptoms (*N* = 91)	Pearson χ^2
Continence frequency	Yes	33	35	0.07
	No, Never	24	23	
	Missing			
Continence ability	Able	33	38	0.03
	Unable	16	18	
	Missing			
Toilet behaviour frequency	Yes	36	39	0.04
	No, Never	20	20	
	Missing			
Toilet behaviour ability	Able	37	40	1.28
	Unable	11	16	
	Missing	0	1	
Timed toileting frequency	Yes	32	36	1.25
	No, Never	24	22	
	Missing	0	1	
Timed toileting ability	Able	31	35	1.8
	Unable	14	13	
	Missing	2	6	
Signal need to go, frequency	Yes	30	34	0.42
	No, Never	27	24	
	Missing			
Signal need to go, ability	Able	30	35	1.71
	Unable	16	18	
	Missing	0	2	
Stool continence frequency	Yes	27	33	3.23
	No, never	30	24	
	Missing	0	2	
Stool continence ability	Able	31	35	0.88
	Unable	15	18	
	Missing	0	1	
Day-time continence frequency	Yes	26	32	5.77
	No, never	31	23	
	Missing	0	4	
Day-time continence ability	Able	30	31	0.64
	Unable	13	18	
	Missing	1	2	
Night-time continence frequency	Yes	15	27	8.41*
	No, never	41	29	
	Missing	0	3	
Night-time continence, ability	Able	19	25	2.28
	Unable	19	24	
	Missing	0	3	

**P < 0.001.
*P < 0.05.

Table 4 Language and communication frequencies and Pearson's χ^2 analyses between GI groups

		Low frequency GI symptoms (*N* = 82)	High frequency GI symptoms (*N* = 91)	Pearson χ^2
Expressive language	Yes	52	54	2.34
	No	16	13	
	Missing	0	2	
Best verbal communication	Babbles	6	15	6.9
	Moans	15	13	
	Single Words	15	10	
	Intentional sound	20	22	
	2–3 phrases	1	3	
	Longer phrase speech	1	0	
Use of babble	Yes	28	43	3.06
	No	54	48	
Use of moan	Yes	46	50	0.02
	No	36	41	
Use of single word	Yes	27	31	0.03
	No	55	60	
Use of intentional sound	Yes	48	56	0.16
	No	34	35	
Use 2–3 phrases	Yes	2	3	0.11
	No	80	88	
Use of longer phrase	Yes	1	0	1.12
	No	81	91	
Response to request	Single Word	14	13	1.93
	Simple command	10	16	
	1 step command	10	8	
	2 step command	17	16	
	3 step command	1	2	
Ability spoken word	Uses	31	35	0.27
	Does not use	36	34	
Use of gestures	Uses	63	62	0.40
	Does not use	4	6	
Use of signing	Uses	36	33	0.37
	Does not use	30	34	
Use visual pictures	Uses	47	44	0.01
	Does not use	20	19	
Use of formal PODD book	Uses	28	19	2.1
	Does not use	37	43	
Use of iPad apps	Uses	35	39	0.63
	Does not use	32	27	
Use of eye-tracking device	Uses	4	6	0.54
	Does not use	61	56	
Use of low tech AAC	Uses	33	32	0.08
	Does not use	32	32	
Use of mid tech AAC	Uses	20	16	0.46
	Does not use	45	47	
Use of high tech AAC	Uses	29	34	0.75
	Does not use	38	33	
Caregiver and child's preferred communication				6.47

Table 4. *(Continued)*

	Low frequency GI symptoms (N = 82)	High frequency GI symptoms (N = 91)	Pearson χ^2
Spoken words	4	4	
Gestures	46	43	
Signing	8	6	
Visual pictures	1	0	
Formal PODD books	1	0	
Ipad apps	0	3	
Low tech AAC	2	3	
Mid tech AAC	1	0	
High tech AAC	4	4	

[**]$P < 0.001$.
[*]$P < 0.01$.

Table 5 Means and standard deviations on challenging behaviour variables between GI groups

	Low frequency GI symptoms		High frequency GI symptoms	
	M	**SD**	**M**	**SD**
Appropriate affect	3.95	0.71	4.06	0.88
Self-injury	1.46	0.63	1.53	0.89
Spontaneous affect	2.2	1.06	2.3	1.16
Anxiety	2.41	0.86	2.33	0.73
Behaviour dysregulation	2.71	0.73	2.67	0.76
Repetitive behaviours	2.14	1.05	2.29	0.94
Inattention hyperactivity	3.36	0.86	3.17	0.89

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, $\chi^2(df = 1, n = 73) = 0.30$, $P = 0.59$. Means and standard deviations of sleep subscales are presented in Table 6.

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 ($U = 835$, $P < 0.05$), 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 ($U = 856$, $P = 0.15$). A difference was also observed in excessive somnolence mean ranks, with high frequency GI symptoms ($M = 52$) scoring higher than low frequency GI symptoms ($M = 42.11$)

Table 6 Means and standard deviations on the SDSFC subscales between GI groups

	Low frequency GI symptoms		High frequency GI symptoms	
	M	*SD*	*M*	*SD*
Sleep initiation and maintenance	2.78	0.52	2.83	0.53
Sleep breathing disorders	1.49	0.59	1.77	0.85
Arousal disorders	1.17	0.34	1.13	0.28
Sleep–wake transition	2.1	0.68	2.19	0.70
Excessive somnolence	1.77	0.58	1.98	0.65
Sleep hyperhidrosis	1.41	0.82	1.93	1.24

Table 7 Binary logistic regression odds ratios (OR), confidence intervals (CI) and significance value for Sleep Disturbance Scale for Children subscales

Predictors	OR	95% CI	*P*-value
Sleep initiation and maintenance	1.66	0.52–5.26	0.39
Sleep breathing disorders	1.57	0.69–3.58	0.29
Arousal disorders	0.73	0.14–3.79	0.71
Sleep–wake transition	0.49	0.17–1.43	0.19
Excessive somnolence	1.21	0.5–2.95	0.67
Sleep hyperhidrosis	2.07	1.1–3.9	0.03*

[*]$P < 0.05$,
[**]$P < 0.001$.

without being statistically significant ($U = 851$, $P = 0.08$).

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, $\chi^2(df = 6, n = 76) = 8.41$, $P = 0.21$. 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, $P < 0.05$). 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 that 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 co-morbidity 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 3 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 (Tan and Bird 2017; Tones *et al.* 2019). 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 (Berdnikov *et al.* 2020; Agar *et al.* 2021). 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 ($P < 0.01$) (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 co-morbidity 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 co-morbidity 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.

Acknowledgements

Source of funding

Conflict of interest

The authors declare they have no conflicts of interest.

Data availability statement

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

References

Agar G., Brown C., Sutherland D., Coulborn S., Oliver C. & Richards C. (2021) Sleep disorders in rare genetic syndromes: a meta-analysis of prevalence and profile. *Molecular Autism* **12**, 1–17.

Arron K., Oliver C., Moss J., Berg K. & Burbidge C. (2011) The prevalence and phenomenology of self-injurious and aggressive behaviour in genetic syndromes. *Journal of Intellectual Disability Research* **55**, 109–20.

Berdnikov A., McPhee S., LaBine L. & Fatoye T. (2020) Night sweats as a manifestation of gastroesophageal reflux disease. *Canadian Family Physician* **66**, 901–3.

Bevinetto C. & Kaye A. (2014) Perioperative considerations in the patient with Angelman syndrome. *Journal of Clinical Anesthesia* **26**, 75–9.

Bindels-de Heus K., Mous S., Hooven-Radstaake M., Iperen-Kolk B., Navis C., Rietman A. *et al.* (2020) An overview of health issues and development in a large clinical cohort of children with Angelman syndrome. *American Journal of Medical Genetics Part A* **182**, 53–63.

Bird L. M. (2014) Angelman syndrome: Review of clinical and molecular aspects. *Application of Clinical Genetics* **7**, 93–104.

Bonati M., Russo T., Finelli S., Valsecchi P., Cogliati R., Cavalleri F. *et al.* (2007) Evaluation of autism traits in Angelman syndrome: A resource to unfold autism genes. *Neurogenetics* **8**, 169–78.

Bruni O., Ottaviano S., Guidetti V., Romoli M., Innocenzi M., Cortesi F. *et al.* (1996) The Sleep Disturbance Scale for Children (SDSC) Construction and validation of an instrument to evaluate sleep disturbances in childhood and adolescence. *Journal of Sleep Research* **5**, 251–61.

Buiting K., Williams C. & Horsthemke M. (2016) Angelman Syndrome - insights into a rare neurogenetic disorder. *Nature Reviews Neurology* **12**, 584–93.

Buntinx I. M., Hennekam R. C. & Brouwer O. F. (1995) Clinical profile of Angelman syndrome at different ages. *American Journal of Medical Genetics* **56**, 176–83.

Calculator S. (2013) Parents' reports of patterns of use and exposure to practices associated with AAC acceptance by people with Angelman syndrome. *Augmentative and Alternative Communication* **29**, 146–58.

Clarke D. J. & Marston G. (2000) Problem behaviours associated with15q-Angelman syndrome. *American Journal on Mental Retardation* **105**, 25–31.

Dagli, A.I., Mueller, J., & Williams, C.A. (2017) Angelman Syndrome. *Gene Reviews*. Available at: http://www.genereviews.org/ and copyright (© 1993–2020 University of Washington).

Didden R., Sigafoos J., Korzilius H., Baas A., Lancioni G. E., O'Reilly M. F. *et al.* (2009) Form and function of communicative behaviours in people with Angelman syndrome. *Journal of Applied Research in Intellectual Disability* **22**, 526–37.

Ferreira V. R., Carvalho L. B. C., Ruotolo F., Fausto De Morais J., Prado L. B. F. & Prado G. F. (2009) Sleep disturbance scale for children: Translation, cultural adaptation, and validation. *Sleep Medicine* **10**, 457–63.

Gentile J., Tan W., Horowitz L., Bacino C., Skinner S., Barbieri-Welge R. *et al.* (2010) A neurodevelopmental survey of Angelman syndrome with genotype-phenotype correlations. *Journal of Developmental and Behavioural Pediatrics* **31**, 592–601.

Glassman L., Grocott O., Kunz P., Larson A., Zella G., Ganguli K. *et al.* (2017) Prevalence of gastrointestinal symptoms in Angelman syndrome. *American Journal of Medical Genetics Part A* **173**, 2703–9.

Gorrindo P., Williams K., Lee E., Walker L., McGrew S. & Levitt P. (2012) Gastrointestinal dysfunction in autism: Parental report, clinical evaluation, and associated factors. *Autism Research* **5**, 101–8.

Grieco J. C., Bahr R. H., Schoenberg M. R., Conover L., Mackie L. N. & Weeber E. J. (2019) Quantitative measurement of communication ability in children with Angelman syndrome. *Journal of Applied Research in Intellectual Disabilities* **31**, 49–58.

Horsler K. & Oliver C. (2006) The behavioural phenotype of Angelman syndrome. *Journal of Intellectual Disability Research* **50**, 33–53.

Kirli E. A., Türk Ş. & Kırlı S. (2021) The Burden of Urinary Incontinence on Caregivers and Evaluation of Its Impact on Their Emotional Status. *Anatolian Journal of Psychiatry/Anadolu Psikiyatri Dergisi* **22**, 43–8.

Korterink J. J., Diederen K., Benninga M. A. & Tabbers M. M. (2015) Epidemiology of pediatric functional abdominal pain disorders: A meta-analysis. *Paediatric Gastroenterology* **10**, 1932–6203.

Larson A. M., Shinnick J. E., Shaaya E. A., Thiele E. A. & Thibert R. L. (2015) Angelman syndrome in adulthood. *American Journal of Medical Genetics A* **167**, 331–44.

Leader G., Francis K., Mannion A. & Chen J. (2018) Toileting problems in people with parent-reported diagnoses of Autism Spectrum Disorder. *Journal of Developmental and Physical Disabilities* **30**, 307–27.

Margolis S. S., Sell G. L., Zbinden M. A. & Bird L. M. (2015) Angelman syndrome. *Neurotherapeutics* **12**, 641–50.

Matson J. & Nebel-Schwalm M. (2007) Comorbid psychopathology with autism spectrum disorder in children: An overview. *Research in Developmental Disabilities* **28**, 341–52.

Matson J. L. & LoVullo S. V. (2009) Encopresis, soiling and constipation in children and adults with developmental disability. *Research in Developmental Disabilities* **30**, 799–807.

Mertz L., Christensen R., Vogel I., Hertz J. & Østergaard J. (2014) Eating behaviour, prenatal and postnatal growth in Angelman syndrome. *Research in Developmental Disabilities* **35**, 2681–90.

Napier K. R., Tones M., Simons C., Heussler H., Hunter A. A., Cross M. *et al.* (2017) A web-based, patient driven registry for Angelman syndrome: The Global Angelman Syndrome Registry. *Orphanet Journal of Rare Diseases* **12**, 134.

Pelc K., Cheron G., Boyd S. & Dan B. (2008) Are there distinctive sleep problems in Angelman syndrome? *Sleep Medicine* **9**, 434–41.

Peters S. U., Beaudet A. L., Madduri N. & Bacino C. A. (2004) Autism in Angelman syndrome: Implications for autism research. *Clinical Genetics* **66**, 530–6.

Prasad A., Grocott O., Parkin K., Larson A. & Thibert R. (2018) Angelman syndrome in adolescence and adulthood: A retrospective chart review of 53 cases. *American Journal of Medical Genetics Part A* **176**, 1327–34.

Quinn E. D. & Rowland C. (2017) Exploring expressive communication skills in a cross-sectional sample of children and young adults with Angelman syndrome. *American Journal of Speech-Language Pathology* **26**, 369–82.

Radstaake M., Didden R., Peters-Scheffers N., Moore D., Anderson A. & Curfs L. (2013) Toilet training in people with Angelman syndrome: A case series. *Developmental Neurorehabilitation* **17**, 243–50.

Richards C., Jones C., Groves L., Moss J. & Olivers C. (2015) Prevalence of autism spectrum disorder phenomenology in genetic disorders: a systematic review and meta-analysis. *The Lancet Psychiatry* **2**, 909–16.

Richdale A., Francis A., Gavidia-Payne S. & Cotton S. (2000) Stress, behaviour and sleep problems in children with an intellectual disability. *Journal of Intellectual and Developmental Disability* **25**, 147–61.

Romeo D., Bruni O., Brogna C., Ferri R., Galluccio C., De Clemente V. *et al.* (2013) Application of the sleep disturbance scale for children (SDSC) in preschool age. *European Journal of Paediatric Neurology* **17**, 374–82.

Sadhwani A., Willen J., LaVallee N., Stepanians M., Miller H., Peters S. *et al.* (2019) Maladaptive behaviours in people with Angelman syndrome. *American Journal of Medical Genetics Part A* **179**, 983–92.

Sharkey E. K., Zoellner N. L., Abadin S., Gutmann D. H. & Johnson K. J. (2015) Validity of participant-reported diagnoses in an online patient registry: a report from the NF1 Patient Registry Initiative. *Contemporary Clinical Trials* **40**, 212–7.

Spruyt K., Braam W. & Curfs L. (2018) Sleep in Angelman syndrome: A review of evidence. *Sleep Medicine Reviews* **37**, 9–84.

Strachan R., Shaw R., Burrow C., Horsler K., Allen D. & Oliver C. (2009) Experimental functional analysis of aggression in children with Angelman syndrome. *Research in Developmental Disabilities* **30**, 1095–106.

Tan W. H., Bacino C. A., Skinner S. L., Anselm I. J., Barbieri-Welge R. K., Bauer-Carlin A. G. *et al.* (2011) Angelman syndrome: Mutations influence features in early childhood. *American Journal of Medical Genetics, Part A* **155**, 81–90.

Tan W. H. & Bird L. M. (2017) Pharmacological therapies for Angelman syndrome. *Wien Med Wochescher* **167**, 205–18.

Thibert R., Larson A., Hsieh D., Raby A. & Thiele E. (2013) Neurologic manifestations of Angelman syndrome. *Pediatric Neurology* **48**, 271–9.

Tones M., Cross M., Simons C., Napier K., Hunter A., Render L., et al. (2019) The impact of seizure and gastrophageal reflux history on sleep and behaviour in Angelman syndrome. Paper presented at the 22nd Society for the Study of Behavioural Phenotypes (SSBP) International Conference, Birmingham, UK.

Available at: https://researchrepository.murdoch.edu.au/id/eprint/50859/

Tones M., Cross M., Simons C., Napier K. R., Hunter A., Bellgard M. I. *et al.* (2018) Research protocol: The initiation, design, and establishment of the Global Angelman Syndrome Registry. *Journal of Intellectual Disability Research* **62**, 431–43.

Trickett J., Heald M., Oliver C. & Richards C. (2018) A cross-syndrome cohort comparison of sleep disturbance in children with Smith-Magenis syndrome, Angelman syndrome, autism spectrum disorder and tuberous sclerosis complex. *Journal of Neurodevelopmental Disorders* **10**, 1–14.

Wagner C., Niemczyk J., Equit M., Curfs L. & Gontard A. (2017) Incontinence in persons with Angelman syndrome. *European Journal of Pediatrics* **176**, 225–32.

Walz N. C. (2007) Parent report of stereotyped behaviours, social interaction, and developmental disturbances in people with Angelman syndrome. *Journal of Autism and Developmental Disorders* **37**, 940–7.

Wang T. S., Tsai W., Tsai L. & Wong S. (2020) Clinical characteristics and epilepsy in genomic imprinting disorders: Angelman Syndrome and Prader-Willi syndrome. *Tzu Chi Medical Journal* **32**, 137–44.

Wheeler A. C., Sacco P. & Cabo R. (2017) Unmet clinical needs and burden in Angelman syndrome: A review of the literature. *Orphanet Journal of Rare Diseases* **12**, 1–17.

Williams, C., Peters, S., & Calculator, S. (2009). Angelman syndrome foundation: Facts about Angelman syndrome. Available at: https://www.angelman.org/what-is-as/facts-about-angelmansyndrome/

Williams C. A., Beaudet A. L., Clayton-Smith J., Knoll J. H., Kyllerman M., Laan L. A. *et al.* (2006) Angelman syndrome 2005: Updated consensus for diagnostic criteria. *American Journal of Medical Genetics* **140**, 413–8.