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Relationships between challenging behavior and gastrointestinal symptoms, sleep problems, and internalizing and externalizing symptoms in children and adolescents with Angelman syndrome

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ABSTRACT

Background: Angelman syndrome (AS), is a rare genetic disorder. This study investigated the relationship between parent-reported comorbid symptoms including gastrointestinal symptoms, sleep problems, internalizing symptoms, and behavior problems in children and adolescents with AS.

Method: Parents of 98 children and adolescents with AS completed the Gastrointestinal Symptom Inventory, Children's Sleep Habits Questionnaire, Child Behavior Checklist, Social Communication Questionnaire, and the Behavior Problem Inventory-Short Form. Data were analyzed using descriptive statistics, Pearson's correlation coefficients, and hierarchical multiple regressions.

Results: There was a high frequency of GI symptoms (99%), sleep problems (95.9%), challenging behavior (98%), internalizing symptoms (38%), and 72.4% of children and adolescents presented with ASD symptoms. Self-injurious behavior (SIB), aggressive/destructive behavior, and the frequency of stereotyped behavior positively correlated with GI symptoms and sleep problems and it was moderately negatively associated with age. Internalizing symptoms and age were positively associated with SIB. Aggression was significantly related to gender, but not the presence of ASD symptoms.

Conclusions: Findings highlight the relationships between comorbid conditions. They may lead to a deeper understanding of how comorbidities present in children and adolescents with Angelman Syndrome.

What this paper adds?

This study used a relatively large cross-cultural sample, of 98 children and adolescents, to add critical knowledge about the parent-reported comorbidities that occur in Angelman Syndrome. It adds to the small body of existing literature on this rare genetic condition, and for the first time, it provides important detailed and nuanced knowledge about relationships between comorbidities that commonly present in children and adolescents with AS. It adds new knowledge concerning the characteristics of comorbidities regarding the presence of ASD, gender, and age, and how comorbidities are associated with aggression, stereotypy, and self-injury. The study identified a high prevalence of comorbid symptoms, which indicates that comorbidities in AS are an important area of

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investigation. It found that the majority of the children and adolescents presented with sleep problems, challenging behavior, and at least one GI symptom. In comparison, internalizing symptoms occurred less frequently. It also found positive associations between gastrointestinal symptoms, sleep problems, internalizing symptoms, and the severity of challenging behaviors. This knowledge facilitates understanding that could facilitate improvements in the identification, management, and treatment of challenging behaviors in clinical care. It also identifies the direction for future research.

1. Introduction

Angelman Syndrome (AS) is a rare clinical, neurogenetic disorder that affects approximately 1 in 12,000–20,000 people (Buckley, Dinno, & Weber, 1998; Galván-Manso et al., 2002). Symptoms of AS present within the first year of life (Bird, 2014) and they include craniofacial abnormalities, an ataxic gait, limbic weakness, seizures, severe intellectual disability (ID), hyperactivity, and a perceived happy demeanor (Adams, Horsler, Mount, & Oliver, 2015; Holland, Whittington, & Butler, 2002; Williams et al., 1995). A minority of individuals can speak using word phrases (Bird, 2014) but most individuals are nonverbal (Andersen, Rasmussen, & Strømme, 2001).

AS is caused by dysfunctionality on the maternally derived chromosome 15 and a biparental contribution to the 15q11–13 chromosome that affects its expression (Bird, 2014; Kishino, Lalande, & Wagstaff, 1997; Matsuura et al., 1997). It can also be caused by paternal uniparental disomy and maternally inherited denovo deletion (Clayton-Smith & Laan, 2003) or genetic imprinting defects (La Fevre et al., 2017). Between 85% and 90% of confirmed diagnoses with clinical phenotypes contain genetic mechanisms that impact the expression of the UBE3A gene, but some clinical symptoms of AS have no association with specific genetic defects. However, genetic abnormalities in chromosome 15q11-q13 region succumb to genomic imprinting (Clayton-Smith & Laan, 2003; Williams et al., 1995).

Comorbidity is the presence of two or more disorders occurring in the same individual at the same time (Matson & Nebel-Schwalm, 2007). Comorbid symptoms are present in AS and Fragile X Syndrome (Newman, Leader, Chen, & Mannion, 2015), another rare genetic condition, and they affect 78.7–95% of individuals with autism spectrum disorder (ASD) (Joshi et al., 2010; Mannion & Leader, 2013). Indeed, ASD is an important comorbidity in AS because for between 42% and 79.9% of individuals with AS, ASD is a comorbid disorder (Peters, Beaudet, Madduri, & Bacino, 2004; Trillingsgaard & Østergaard, 2004), and there is an overlap between ASD and AS symptomology (Summers & Impey, 2011; Walz, 2007). Therefore it is probable comorbid conditions that are common in ASD may also impact individuals with AS. In ASD, typical comorbidities include gastrointestinal (GI) symptoms, epilepsy, and feeding problems (Leader & Mannion, 2016; Leader, Tuohy, Chen, Mannion, & Gilroy, 2020; Mannion & Leader, 2014). To date, a small amount of research has focused on the comorbid symptoms that occur in children and adolescents with AS. The research that concerns GI symptoms, sleep problems, psychopathology, and challenging behavior will now be introduced.

Glassman et al. (2017) found that GI symptoms, including constipation, gastroesophageal reflux disease, cyclic vomiting, issues swallowing, and eosinophilic esophagitis, occurred in 87% of children and adults with AS. Furthermore, the presence of GI symptoms has been associated with a higher frequency of seizures in AS (Grocott, Herrington, Pfeifer, Thiele, & Thibert, 2017) and, in mice with AS, they are associated with mitochondrial dysfunction (Rossignol & Frye, 2012; Su et al., 2011).

Sleep problems, which can refer to sleep deprivation, sleep loss, insomnia, and sleep disturbance, are an associated feature of AS in 20 – 80% of individuals (Williams et al., 2006). Goldman, Bichell, Surdyka, and Malow (2012) identified daytime sleepiness, parasomnias, and bedtime resistance as the most common types of sleep problems in children and adolescents with AS and they remain consistent with age (Bruni et al., 2004). Sleep problems cause constant fatigue and daytime sleepiness, which may lead to impaired cognitive functioning and behavior problems in children with AS (Zhdanova, Wurtman, & Wagstaff, 1999). They also negatively impact parental well-being (Didden, Korzilius, Smits, & Curfs, 2004). Opposite imprinting defects have been implicated in sleep phenotypes and neurodevelopmental disorders in AS (Tucci, 2016). In mouse models, where the UBE3A is maternally expressed, circadian rhythm can be significantly impacted. Whereas, paternal additions or maternal deletions can result in reduced sleep and prolonged night wakings (Tucci, 2016).

Psychopathologies, defined as a mental illness that leads to impairment, dysfunction, and disability (Masten, Burt, & Coatsworth, 2006), are found in children with AS. In this context, psychopathologies include hyperactivity, attention problems (Walz & Benson, 2002), severe ID (Ludwig et al., 2005), and an unusually happy demeanor (Horsler & Oliver, 2006). The prevalence of many psychopathologies including internalizing emotional problems in children and adolescents have not yet been investigated, but the prevalence of happy demeanor, behavioral uniqueness, and inappropriate laughter has been found to range from 57% (Clarke & Marston, 2000) to 100% (Williams et al., 1995). It has also been argued that a perceived happy demeanor may not accurately depict the emotional state of children with AS, because UBE3A deficiency has been associated with increased levels of cortisone, demonstrating increased stress has been identified in rodent samples (Godavarthi, Dey, Maheshwari, & Jana, 2012).

Challenging behaviors can include aggression, self-injury, destructiveness, inappropriate social or sexual conduct, hyperactivity, unusual mannerisms, and pica (Emerson, 2001). In AS, challenging behaviors are stressful to caregivers and they adversely impact the quality of family life (Sadhwani et al., 2019). Common challenging behaviors include feeding issues, excessive chewing, a strong attraction to water, stereotypy, tantrums, and self-injury (Horsler & Oliver, 2006; Williams et al., 2006). The occurrence of physical aggression is higher in individuals with AS than those with ID without AS (Arron, Oliver, Moss, Berg, & Burbidge, 2011) and pre-schoolers with AS are more likely than children with other neurogenetic syndromes to display withdrawn behavior, attention-deficit/hyperactivity problems, depressive symptoms, and ASD symptoms (Neo & Tonnsen, 2019). It has also been demonstrated that hyperactivity and irritability increase with the age in children and adolescents with AS (Sadhwani et al., 2019).

To date, minimal research has focused on how comorbid symptoms relate to one another in children and adolescents with AS. One study has examined the relationship between challenging behavior and sleep problems and found improving challenging behavior

reduced sleep problems (Allen, Kuhn, DeHaai, & Wallace, 2013). However, further research needs to increase understanding about the characterization and presentation of comorbid symptoms in children and adolescents with AS. This is needed because relationships between comorbidities may differ in strength particularly regarding the presence of ASD symptomology, and in relation to other demographic features such as age and gender. More detailed knowledge about the relationship between comorbidities and their presentation could facilitate the early identification of comorbid symptoms, improve their clinical management (Neo & Tonnsen, 2019), and improve quality of life for children and adolescents with AS and their caregivers.

1.1. Current Study

This study examines the relationship between common comorbidities that occur in children and adolescents with AS. The study aims to increase understanding as to how challenging behavior problems, including SIB, aggression, and stereotypical behavior relate to GI symptoms, sleep problems, internalized problems, to the presence of ASD, age, and gender. The study objectives are (i) to determine the prevalence of coexisting ASD symptomology, gastrointestinal (GI) symptoms, sleep problems, internalized symptoms, and challenging behavior problems, (ii) to determine how these factors correlate with each other, (iii) to investigate which factors are associated with challenging behavior in children and adolescents with AS. Therefore the analyses are exploratory and do not aim to predict the direction of effects.

2. Method

2.1. Sample

The sample consisted of 98 children and adolescents, aged 3 − 18 years (M=9.11; SD=4.67), 61.2% male), with a diagnosis of AS. Diagnoses were parent-reported and they were not confirmed during the study. The majority of AS diagnoses were given by doctors (69.4%), and geneticists (19.4%). Eleven percent of children and adolescents received diagnoses from other sources, such as neurologists (3.06%, $n = 3$), professors (2.04%, $n = 2$), and psychologists (1.02%, $n = 1$). At diagnosis, the mean age of the children was 2.6 (SD=1.98) years. ID was reported in 94 children and adolescents (95.9%). Of these children and adolescents, ID was mild (5.1%, one female, four males); moderate (33.7%, 13 females, 20 males), and severe (57.1%, 23 females, 33 males). The majority of children and adolescents (40.8%) were from the USA ($n = 40$), while the UK and Australia accounted for 10.2% ($n = 10$) of children and adolescents each. Ireland, Greece, Spain, South Africa, Brazil, Italy, and Finland accounted for 3.1% ($n = 3$) each, and France, Germany, Canada, and Israel had 2.04% ($n = 2$) each. Children and adolescents were also from Austria, Croatia, India, New Zealand, Chile, Norway, and Turkey.

2.2. Procedure and Informants

Ethical approval was granted by the School of Psychology Research Ethics Committee at the National University of Ireland, Galway. Parents and guardians were made aware of the study through international AS organizations, parent support groups, and online forums. Informants were parents of children and adolescents with AS, aged 3–18 years. Data collection took place over four-months. During the recruitment process, a flyer was used where it was stated that this study was looking for parents of children and adolescents with AS to participate. If parents wished to participate in the study, they were provided with a participant information sheet and a consent form to complete. Parents provided consent for their children as they were completing questionnaires on their behalf. Assent for minors was not obtained. Once consent was obtained, questionnaires that are described below were distributed online via qualtrics. The questionnaires were in English and informants completed them independently in their own time. Informants were also given written instructions, written in plan non-scientific language, printed on the top of each questionnaire. Informants were also provided an email address and they were invited to contact researchers for further assistance via email if they had any queries.

2.3. Measures

2.3.1. Demographic information

Demographic data were gathered using a self-constructed questionnaire. This included the participant's age, gender, country of residence, presence of ID, level of ID, aged of AS diagnosis, and presence of other comorbid conditions such as epilepsy, ADHD, and an anxiety disorder. This questionnaire was also used to ascertain whether the child was on medication and if so, the type of medication and what condition it was used to treat. It also elicited information concerning the child's ability to form words/ short phrases or to successfully use body language,

2.3.2. Social Communication Questionnaire (SCQ)

The SCQ (Rutter, Bailey, & Lord, 2003) is an informant-based questionnaire, which screens for symptoms of ASD. The questionnaire contains 40 items. However, if a child is unable to form words or short phrases, as assessed in the first question, items 2–7 are deemed inappropriate and so the informant skips to item 8. In this instance, only 34 items are assessed. Questions assess behavior throughout the lifetime, with certain questions specifically targeting the year between the child's fourth and fifth birthdays. Parents whose children are under the age of four are required to answer these questions in relation to the past 12 months. Items address the child's social interaction and communication abilities, as well as stereotyped, repetitive behavior. Items assessing the presence of a behavior

are answered in a "yes/ no" format. If a participant engages in a behavior associated with ASD, they receive a score of 1. If a participant does not engage in a behavior associated with ASD, they receive a score of 0.

The SCQ demonstrates varying degrees of specificity in the differentiation between ASD and non-ASD cases (0.58 – 0.88), and so is used to assist clinicians in diagnosis, but is not appropriate as a sole diagnostic tool (Allen, Silove, Williams, & Hutchins, 2007; Chandler et al., 2007). With high convergent validity (70%) with the Autism Diagnostic Interview-Revised (ADI-R; Rutter, Le Couteur, & Lord, 2003) and high factor-based reliability, based on the Social-Communication, and Stereotyped Behaviors and Unusual Interest scales (83%−96%), the tool showed effectiveness when measured on a sample of children with Down Syndrome (Magyar, Pandolfi, & Dill, 2012).

2.3.3. GI Symptoms Inventory

The GI Symptoms Inventory (Autism Treatment Network, 2005) is an informant-based questionnaire designed to assess GI symptoms in the past three months. It consists of 35 questions, however, there are additional items should a participant exhibit certain symptomatology, and therefore includes 77 items in total. This is a non-validated measure designed from previous questionnaires regarding GI symptoms and symptoms identified during the clinical assessment of children with ASD. It has been used previously in published research with children and adolescents with ASD and other developmental and genetic conditions (Leader, Francis, Mannion, & Chen, 2018; Mazefsky, Schreiber, Olino, & Minshew, 2014; Mazurek et al., 2013; Williams, Christofi, Clemmons, Rosenberg, & Fuchs, 2012a, 2012b; Williams, Fuchs, Furuta, Marcon, & Coury, 2010).

2.3.4. Children's Sleep Habits Questionnaire (CSHQ)

The CSHQ (Owens, Spirito, & McGuinn, 2000), a 52-item, informant-based questionnaire for measuring sleep problems. Previous research employed this measure with children presenting with ASD, developmental delay, as well as with children with AS (Goldman et al., 2011, 2012; Goodlin-Jones, Sitnick, Tang, Liu, & Anders, 2008). Research identifies the CSHQ as a reliable, valid questionnaire, with the cut-off score of 41 recording high sensitivity (0.80) and specificity (0.72; Owens et al., 2000). Four of the items record descriptive information regarding time and duration of sleep. The other items are measured on a three-point Likert scale, with responses being "Usually (5 + times)" or "Falls Asleep", scored at 3, "Sometimes (2–4 times)" or "Very Sleepy", scored at 2, and "Rarely (0–1 time)" or "Not Sleepy", scored at 0. Items are also categorized into eight subscales, Bedtime Resistance, Sleep Onset Delay, Sleep Duration, Sleep Anxiety, Night Wakings, Parasomnias, Sleep Disordered Breathing, and Daytime Sleepiness.

2.3.5. Child Behavior Checklist (CBCL)

The CBCL (Achenbach & Rescorla, 2000, 2001) is a 113-item, parental-report questionnaire, used to assess emotional and behavior problems in children and adolescents, aged between 1 ½ to 18 years, within the past six months. Results are separated according to age groups, i.e. 1 ½ to 5-year-olds versus 6–18-year-olds, and assessed using age-based normative scales. Each item on the CBCL represents an emotional or behavioral problem. Parents rate each item, as being true or not true of their child, on a three-point Likert scale. Responses include "not true (as far as you know)", rated at 0, "somewhat or sometimes true", rated at 1, and "very true or often true", rated at 2. Behaviors are categorized into seven behavior subscales for children aged between 1 ½ to 5 years, and eight subscales for children and adolescents aged between 6 and 18 years. Subscales are grouped into internalizing problems, externalizing problems, and other problems.

Schmeck et al. (2001) demonstrated that the CBCL had high discriminative validity (83.8%) in a sample of German children and adolescents aged 4–18 years. High comparative validity was also found between the CBCL and the Rutter Parental Questionnaire ($r =$ 0.79; Rutter, Tizard, & Whitmore, 1981) in a sample of 6–11-year-old children attending a psychiatric (Fombonne, 1989). The Rutter Parental Questionnaire (Rutter et al., 1981) screens for psychiatric disorders in 9–13-year-old children. The CBCL has been used in populations such as ASD and Cerebral Palsy (Hartley, Sikora, & McCoy, 2008; Leader et al., 2021).

2.3.6. Behavior Problems Inventory – Short Form (BPI-S)

The BPI-S (Rojahn et al., 2012a) is a 30-item, parental-report questionnaire designed to assess the frequency and severity of maladaptive behaviors in individuals with intellectual disabilities during the past two months. Frequency is measured on a five-point Likert scale, with responses being "Never/ No Problem", scored at 0, "Monthly", scored at 1, "Weekly", scored at 2, "Daily", scored at 3, and "Hourly", scored at 4. Severity is measured on a four-point Likert scale, with responses being "Never/ No Problem", scored at 0, "Mild", scored at 1, "Moderate", scored at 2, and "Severe", scored at 3. Behaviors were categorized into three subscales, SIB (8 items), aggressive/ destructive behavior (10 items), and stereotyped behavior (12 items).

Mascitelli et al. (2015) investigated the reliability of the BPI-S. Cronbach's alpha (α) coefficients (Cronbach, 1951) were calculated to determine internal consistency. The BPI-S received a total α-coefficient of 0.91, with total frequency and severity scales receiving α-coefficients of 0.89 and 0.83 respectively, demonstrating high internal consistency (Mascitelli et al., 2015). Correlations depicting test-retest reliability and inter-rater reliability ranged from $r = 0.65$ to.91 and interclass correlation coefficient (ICC) = 0.38 to.74 respectively for the different subscales (Mascitelli et al., 2015).

Rojahn et al. (2012b) investigated construct validity between the BPI-S, the original BPI (BPI-01), and relevant subscales of the Aberrant Behavior Checklist, the Diagnostic Assessment for the Severely Handicapped-II, the Nisonger Child Behavior Rating Form, and the Inventory for Client and Agency Planning. Mean differences of β-values for the SIB, aggressive/ destructive behavior, and stereotyped behavior subscales were 0.00 ($SD = 0.03$, max = 0.06), 0.00 ($SD = 0.01$, max = 0.03), and 0.00 ($SD = 0.04$, max = 0.08) respectively (Rojahn et al., 2012b). It has been used in published studies on children with ASD and other developmental disabilities (Leader, Tuohy, Chen, Mannion, & Gilroy, 2020).

2.4. Analyses

Descriptive statistics including means, standard deviations, and frequencies were calculated for the variables. Pearson's correlation coefficients were conducted to analyze the relationships between demographic factors, the presence of ASD, challenging behavior, total GI symptoms, total sleep problems, and total internalizing symptoms. To avoid potential measurement issues resulting from overlap with the aggression subscale of the BPI=S, this study only utilized data from the internalizing problems subscale of the CBCL. Scores from each subscale of the BPI-S were transformed due to the violation of the assumption of normality. Five hierarchical multiple regressions were conducted to analyze whether GI symptoms, sleep problems, and internalizing symptoms were associated with each of the five BPI-S subscales of challenging behavior, i.e. frequency and severity of SIB, frequency and severity of aggressive/destructive behavior, and the frequency of stereotyped behavior. For stereotyped behavior in the BPI-S, there is no severity subscale. There are no cut-offs for the BPI-S. Age, gender, and total SCQ scores were controlled for.

3. Results

3.1. Descriptive statistics

3.1.1. Current comorbid diagnoses

Demographic information is provided in Table 1. Eighty-two percent of children and adolescents (61.7% males) had a comorbid diagnosis which did not include gastrointestinal, sleep, behavior problems, and or comorbid psychopathology. Comorbid diagnoses included epilepsy, $n = 68$ (69.4%), ADHD, $n = 18$ (18.4%), and an anxiety disorder, $n = 6$ (6.1%).

3.1.2. Medication for comorbid disorders

Ninety-one percent ($n = 89$) of the children and adolescents were taking some form of medication. Table 2 shows the reported medication usage for particular symptoms amongst this sample.

3.1.3. ASD symptoms

Applying the recommended cut-off score of 15 or greater, the SCQ indicated that 72.4% of children and adolescents (66.2% males) displayed symptoms of ASD. Nine percent (55.6% males) demonstrated verbal ability. This was demonstrated in 11.3% of children and adolescents with ASD symptoms, compared to 3.7% without ASD symptoms.

3.1.4. GI symptoms

Table 3 presents the number of children and adolescents who presented with various types of GI symptoms. Eighty-three percent of the sample ($n = 81$, 64.2% males) had experienced at least one GI symptom within the last three months. Whereas thirty-three percent ($n = 32$, 62.5% male) had three to five GI symptoms. Sixty-one percent of the sample ($n = 60$, 58.3% male) had received treatment of at least one GI symptom. The most common treatments were stool softeners like Miralax (11.2%), Movicol (6.1%), probiotics (5.1%), and dietary changes (8.2%).

3.1.5. Sleep problems

Table 4 presents the means and standard deviations for scores on each of the eight subscales of the CSHQ. The mean total score on the CSHQ was 52.61 ($SD = 7.71$). Ninety-six percent of children and adolescents (62.8% male) demonstrated sleep problems, with a score of 41 or greater.

3.1.6. Internalizing symptoms

The CBCL scores were translated to *t* scores based on set age norms for 1 ½ to 5 year-olds and for 6–18-year-olds. The total CBCL *t* scores for all children and adolescents had a mean of 57.56. For children aged between 1½ to 5 years, the mean was 58.41. The mean

Table 1
Demographic Variables of children and adolescents with AS.

Variable	Features	*n*	%
Age of children and adolescents in years	3–5	27	27.6
	6–11	36	36.7
	12–18	35	35.7
Gender	Female	38	38.8
	Male	60	61.2
Country of Residence	USA	40	40.8
	Other	29	29.6
	Australia	10	10.2
	UK	10	10.2
	Greece	3	3.1
	Spain	3	3.1
	Ireland	3	3.1

Table 2
Medications used by children and adolescents with AS.

Medication used for following Symptom	% of children and adolescents with AS
Epilepsy/Seizures	64.3
Sleep problems	35.7
Constipation	16.3
Reflux	7.1
Anxiety	5.1

Table 3
Number of children and adolescents with AS presenting with each type of GI symptom.

GI Symptom	No. of children and adolescents with AS	% of children and adolescents with AS
Constipation	66	67.3%
Diarrhea	29	29.6%
Abdominal Pain	28	28.6%
Bloating	25	25.5%
Nausea	24	24.5%
Other GI Symptoms	16	16.3%

Table 4
Means, standard deviations and range for CSHQ and BPI-S.

Subscale	*M*	*SD*	*Range of Possible Scores*
CSHQ			
Daytime Sleepiness	12.11	2.99	8.00–19.00
Parasomnias	10.33	2.16	7.00–20.00
Bedtime Resistance	9.46	3.21	6.00–17.00
Sleep Anxiety	6.81	2.06	4.00–12.00
Night Wakings	5.88	1.69	3.00–9.00
Sleep Duration(hrs)	5.84	1.90	3.00–9.00
Sleep Disordered Breathing	3.90	1.35	3.00–9.00
Sleep Onset Delay	1.69	0.79	1.00–3.00
BPI-S			
SIB Frequency	4.84	3.93	0.00–18.00
SIB Severity	3.28	2.97	0.00–16.00
Aggressive/ Destructive Behavior Frequency	8.64	6.80	0.00–28.00
Aggressive/ Destructive Behavior Severity	5.65	4.54	0.00–22.00
Stereotyped Behavior Frequency	11.41	8.08	0.00–34.00

Note: CSHQ = Children's Sleep Habits Questionnaire - Higher scores indicate more sleep problems; BPI-S = Behavior Problems Inventory-Short Form - Higher scores indicate more behaviour problems

for children aged 6–11 years was 60.29, and for those aged 12–18 years it was 62.54.

3.1.7. Challenging behavior

Means and standard deviations associated with challenging behavior were calculated from the BPI-S data. Results were calculated for each of the five subscales, frequency of SIB, aggressive/ destructive behavior, and stereotyped behavior, as well as the severity of SIB and aggressive/ destructive behavior. The analysis found that 98% of children and adolescents presented with at least one form of challenging behavior and 6.1% ($n = 6$) displayed one type of challenging behavior only i.e. SIB, aggressive/destructive behavior, or stereotyped behavior. Whereas $n = 12$ (12.2%) displayed two types of challenging behavior, and $n = 78$ (80.0%) displayed all three types of challenging behavior. Eighty-nine percent of children and adolescents, $n = 87$ (35.6% females) engaged in SIB, whereas, 88.8%, $n = 87$ (34.5% females) and engaged in aggressive/ destructive behavior, and stereotyped behavior was exhibited by 91.8%, $n = 90$ (35.6% females).

3.2. Inferential statistics

A series of hierarchical multiple regression models were conducted to determine whether GI symptoms, sleep problems, and the internalizing symptoms predicted scores on each of the BPI-S subscales (SIB frequency, SIB severity, aggression frequency, aggression severity, stereotyped behaviors) when controlling for age, gender, and SCQ scores. To determine if one variable impacted the relationship between the other two variables, age, gender, and total SCQ scores were entered in the first block. Total GI symptoms were entered in the second block. Total sleep problems followed in block three. Total internalizing symptoms *t* scores were entered in block four. For all five models, there was independence of residuals; Durbin-Watson statistics ranged from 1.84 to 2.18. Partial scatterplots of

the predictor variables and the criterion variable were examined. These demonstrated that linearity was present in the data. The plot of studentized residuals versus unstandardized predicted values, on examination demonstrated homoscedasticity, in the data. Multicollinearity was not present in the data. Table 5 presents the Pearson's correlation statistics, which were less than.7 for predictor variables. The Variance Inflation scores (VIF) were less than 10, and tolerance scores were greater than 0.1. There was no standardized residual greater than + /- 3 standard deviations, leverage values greater than 0.2, or values for Cook's distance above 1. The assumption of normality was met, as assessed by a Q-Q Plot.

With respect to the model for SIB frequency, the overall model was significant. It accounted for 19% of the variance in SIB frequency ($F_{(6,91)} = 5.00$, $p < .001$, $R^2 = 0.25$, *Adj* $R^2 = 0.19$). Age, gender, and total SCQ scores, contributed to the model significantly. These explained 9% of the variance in the frequency of SIB ($F_{(3,94)} = 3.98$, $p = .010$, $\Delta R^2 = 0.11$, *Adj* $\Delta R^2 = 0.09$). Total GI symptoms, contributed to the model significantly. These accounted for 6% of the variance ($F_{(1,93)} = 6.73$, $p = .011$, $\Delta R^2 = 0.06$, *Adj* $\Delta R^2 = 0.06$). Sleep problems, also contributed to the model significantly, accounting for 5% of the variance explained ($F_{(1,92)} = 6.21$, $p = .014$, $\Delta R^2 = 0.05$, *Adj* $\Delta R^2 = 0.05$). Internalizing symptoms did not significantly contribute to the model ($F_{(1,91)} = 13.60$, $p = .098$, $\Delta R^2 = 0.02$, *Adj* $\Delta R^2 = 0.02$). Gender ($\beta = -0.19$, $p = .060$), age ($\beta = -0.08$, $p = .406$), and internalizing symptoms ($\beta = 0.17$, $p = .098$) did not significantly contribute to the variance explained. Total SCQ scores ($\beta = 0.26$, $p = .009$), GI symptoms ($\beta = 0.27$, $p = .011$), and sleep problems ($\beta = 0.24$, $p = .014$) were significant contributors to the variance explained.

With respect to the model for SIB severity, the overall model was significant, accounting for 16% of the variance in SIB severity ($F_{(6,91)} = 4.91$, $p < .001$, $R^2 = 0.24$, *Adj* $R^2 = 0.16$). Step one accounted for 11% of the variance ($F_{(3,94)} = 4.86$, $p = .003$, $\Delta R^2 = 0.13$, *Adj* $\Delta R^2 = 0.11$). Step two did not significantly contribute to the model ($F_{(1,\ 93)} = 2.63$, $p = .108$, $\Delta R^2 = 0.02$, *Adj* $\Delta R^2 = 0.02$). Step three accounted for 5% of the variance ($F_{(1,\ 92)} = 6.35$, $p = .013$, $\Delta R^2 = 0.05$, *Adj* $\Delta R^2 = 0.05$). Step four did not significantly contribute to the variance ($F_{(1,\ 91)} = 3.85$, $p = .053$, $\Delta R^2 = 0.03$, *Adj* $\Delta R^2 = 0.03$). Gender ($\beta = -0.27$, $p = .006$), total SCQ score ($\beta = 0.23$, $p = .020$), and sleep problems ($\beta = 0.25$, $p = .013$), were significant contributors to the variance explained.

With respect to the model for aggression frequency, the overall model was significant, accounting for 8% of the variance in aggression frequency ($F_{(6,91)} = 2.64$, $p = .021$, $R^2 = 0.15$, *Adj* $R^2 = 0.08$). Step one was not a significant contributor to the model ($F_{(3,94)} = 1.93$, $p = .129$, $\Delta R^2 = 0.05$, *Adj* $\Delta R^2 = 0.03$). Step two accounted for all 8% of the variance ($F_{(1,\ 93)} = 6.63$, $p = .012$, $\Delta R^2 = 0.12$, *Adj* $\Delta R^2 = 0.08$). Neither step three ($F_{(1,\ 92)} = 2.38$, $p = .127$, $\Delta R^2 = 0.02$, *Adj* $\Delta R^2 = 0.01$) nor step four ($F_{(1,\ 91)} = 0.58$, $p = .450$, $\Delta R^2 = 0.01$, *Adj* $\Delta R^2 = 0.01$) significantly contributed to the variance. GI symptoms ($\beta = 0.27$, $p = .012$) was the only significant contributor to the variance explained.

With respect to the model for aggression severity, the overall model was significant, accounting for 10% of the variance in aggression severity ($F_{(6,91)} = 2.86$, $p = .014$, $R^2 = 0.16$, *Adj* $R^2 = 0.10$). Step one did not significantly contribute to the variance ($F_{(3,94)} = 2.12$, $p = .103$, $\Delta R^2 = 0.06$, *Adj* $\Delta R^2 = 0.03$). Step two accounted for 7% of the variance ($F_{(1,\ 93)} = 4.81$, $p = .031$, $\Delta R^2 = 0.11$, *Adj* $\Delta R^2 = 0.07$). Step three accounted for 3% of the variance ($F_{(1,\ 92)} = 4.40$, $p = .029$, $\Delta R^2 = 0.04$, *Adj* $\Delta R^2 = 0.03$). Step four did not significantly contribute to the variance ($F_{(1,\ 91)} = 0.92$, $p = .340$, $\Delta R^2 = 0.01$, *Adj* $\Delta R^2 = 0.01$). Gender ($\beta = -0.21$, $p = .044$), GI symptoms ($\beta = 0.23$, $p = .031$), and sleep problems ($\beta = 0.22$, $p = .039$) significantly contributed to the variance explained.

With respect to the final model for stereotyped behaviors, the overall model was significant, accounting for 31% of the variance in stereotyped behaviors ($F_{(6,91)} = 8.37$, $p < .001$, $R^2 = 0.36$, *Adj* $R^2 = 0.31$). Step one accounted for 18% of the variance ($F_{(3,94)} = 7.92$, $p < .001$, $\Delta R^2 = 0.20$, *Adj* $\Delta R^2 = 0.18$). Step two accounted for 11% of the variance ($F_{(1,\ 93)} = 15.05$, $p < .001$, $\Delta R^2 = 0.11$, *Adj* $\Delta R^2 = 0.11$). Step three did not significantly contribute to the overall model ($F_{(1,\ 92)} = 1.95$, $p = .166$, $\Delta R^2 = 0.01$, *Adj* $\Delta R^2 = 0.01$). Step four accounted for the final 2% of the variance ($F_{(1,\ 91)} = 4.01$, $p = .048$, $\Delta R^2 = 0.03$, *Adj* $\Delta R^2 = 0.02$). Gender ($\beta = -0.20$, $p = .036$), total SCQ scores ($\beta = 0.27$, $p = .005$), GI symptoms ($\beta = 0.36$, $p < .001$), and internalizing symptoms ($\beta = 0.19$, $p = .048$) were significant contributors to the variance explained. Table 6 presents the model summary for each of the five regression models, including standardised beta coefficients.

4. Discussion

This study examined the relationships between common comorbidities that occur in children and adolescents with AS and it ascertained how challenging behavior problems relate to sleep and internalized problems, GI symptoms, demographic factors, and the presence of ASD. The findings will now be discussed in relation to the prevalence of the comorbidities in this sample and the degree and direction of the relationships between these comorbidities.

Table 5
Summary of Pearson's Correlations for Predictor variables used in hierarchical regression models.

	1.	2.	3.	4.	5.
1. Age					
2. Gender	.08 * *				
3. Total SCQ	.12	-0.06			
4. Total GSI	.25 * *	-0.08	.31 * *		
5. Total CSHQ	-0.04	-0.13	.17 *	.30 * *	
6. Internalizing symptoms	-0.13	-0.14	.16	.38 * **	.30 * *

*p < .05; * * p < .01; * ** p < .001.

Note: GSI=Gastrointestinal Symptom Inventory; CSHQ=Children's Sleep Habits Questionnaire; CBCL=Child Behavior Checklist; SCQ=Social Communication Questionnaire

Table 6
Multiple Regression Predictors of Challenging Behavior.

Variable	β	R^2	*Adj* R^2	*F* change
Model 1: SIB frequency				
Overall model		0.25	0.19	5.00 * **
Step 1		0.10	0.11	4.04 *
Age	-0.08			
Gender	-0.19			
Total SCQ	0.26 * *			
Step 2		0.06	0.06	6.73 *
Total GI symptoms	0.27 *			
Step 3		0.05	0.05	6.21 *
Total CSHQ	0.24 *			
Step 4		0.02	0.02	13.60
Internalizing symptoms	.17			
Model 2: SIB severity				
Overall model		0.24	0.16	4.91 * **
Step 1		0.13	0.11	4.86 * *
Age	-0.05			
Gender	-0.27 * *			
Total SCQ	0.23 *			
Step 2		0.02	0.02	2.63
Total GI symptoms	0.17			
Step 3		0.05	0.05	6.35 *
Total CSHQ	0.25 *			
Step 4				
Internalizing symptoms	0.20	0.18	0.12	3.85
Model 3: Aggression frequency				
Overall model		0.15	0.08	2.64 *
Step 1		0.05	0.03	1.93
Age	-0.15			
Gender	-0.22			
Total SCQ	0.04			
Step 2		0.12	0.08	6.63 *
Total GI symptoms	0.27 *			
Step 3		0.02	0.01	2.38
Total CSHQ	0.15			
Step 4		0.01	0.01	0.58
Internalizing symptoms	0.04			
Model 4: Aggression severity				
Overall model		0.16	0.10	2.86 *
Step 1		0.06	0.03	2.12
Age	-0.07			
Gender	-0.21 *			
Total SCQ	0.12			
Step 2		0.11	0.07	4.81 *
Total GI symptoms	0.23 *			
Step 3		0.04	0.03	4.40 *
Total CSHQ	0.22 *			
Step 4		0.01	0.01	0.92
Internalizing symptoms	0.11			
Model 5: Stereotyped behavior				
Overall model		0.36	0.31	8.37
Step 1		0.20	0.18	7.92 * **
Age	-0.30			
Gender	-0.20 *			
Total SCQ	0.27 * *			
Step 2		0.11	0.11	15.05 * **
Total GI symptoms	0.36 * **			
Step 3		0.01	0.01	1.95
Total CSHQ	.16			
Step 4		0.03	0.02	4.01 *
Internalizing symptoms	0.19 *			

*p < .05, * *p < .01, * **p < .001

Analysis of data from the current study sample revealed that comorbid disorders are highly prevalent in children and adolescents with AS. This finding concurs with that of previous research (Joshi et al., 2010; Mannion & Leader, 2016). The prevalence of the individual comorbidities is also similar to previous samples of children and adolescents with AS. In the current study, an extremely large percentage of children and adolescents presented with challenging behavior (98%), and 80% of children and adolescents presented with all three forms of challenging behavior; SIB, aggressive/destructive behavior, and stereotyped behavior. Furthermore,

89% of children and adolescents engaged in aggressive/ destructive behavior and the same percentage exhibited SIB. A similar high incidence of aggression in children with AS has been noted previously. Strachan et al. (2009) reported aggression was exhibited by 83.3% of children with AS and physical aggression was reported by 70.2% of another sample of children and adolescents (n = 104) (Arron et al., 2011). In the latter study, 92% of participants also engaged in stereotyped behavior, and individuals who showed aggression showed lower levels of autistic-like social interaction (Arron et al., 2011).

Regarding the prevalence of GI symptoms, the findings of the current study were similar to Glassman et al. (2017). In the current study 82.7% of individual children and adolescents with AS had at least one GI symptom, and constipation was the most common. Sleep problems were also extremely common, presenting in 95.9% of the examined sample. This prevalence rate is similar to previous research that found sleep problems to be a common issue in individuals with AS (Bruni et al., 2004; Goldman et al., 2012; Zhdanova et al., 1999), occurring in 90% of children and young adults with AS (Clayton-Smith, 1993). Previous research has also found that epilepsy, with multiple seizures, affects 79% of individuals who have sleep disorders (Conant, Thibert, & Thiele, 2009). In the current study, epilepsy may also have been a prevalent comorbidity in children and adolescents with AS because epilepsy medication was the most frequently prescribed medication. However, this finding should be treated with caution because anti-epileptics can be used off-label for behavioral concerns without a confirmed epilepsy diagnosis (Kuchenbuch et al., 2018; Munshi et al., 2010).

Symptoms of ASD were present in 72.4% of children and adolescents. This finding is similar to that of Trillingsgaard and Østergaard (2004) who demonstrated symptoms of ASD in 79.9% of individuals with AS. But evidence of ASD was somewhat larger than the 42% incidence in the sample examined by Peters et al. (2004). In terms of verbal ability, as measured through the SCQ, only 9% of children and adolescents in the current study were able to form words or short phrases. Not being able to form any words or less than short phrases demonstrates severe verbal impairment. Speech impairment has been found consistently in AS (Williams et al., 2006), and the ability to successfully form up to three-word phrases has been previously demonstrated in 19.4% of children with AS (Robb, Pohl, Baraister, Wilson, & Brett, 1989). And it is possible that the relatively severe limited verbal ability of this sample may have contributed to the high prevalence of aggression as in the absence of verbal language aggression may be used by the children to initiate and maintain social contact with other people (Strachan et al., 2009).

Regarding the prevalence of internalizing symptoms, 38% of children and adolescents in the current sample met the clinical cut-off for these symptoms on the CBCL. A greater prevalence of internalizing symptoms has previously been noted amongst children with AS who displayed more withdrawn behavior, attention-deficit/hyperactivity problems, and depressive symptoms than children with Prader-Willi syndrome, and William's syndrome (Neo & Tonnsen, 2019). The discussion will now focus on the relationships between these comorbidities.

The current study examined the relationship between age and the other examined variables. A significant relationship was not found between sleep problems and age. This finding concurred with that of Bruni et al. (2004) who also demonstrated that sleep problems remain consistent with age in individuals with AS. However, a moderate negative relationship was found between age and the frequency of stereotyped behavior i.e. increased age was associated with decreased frequency of stereotyped behavior. In addition, the results of the regression analysis found that age contributed significantly to the frequency and severity of the variance in SIB.

The presence of ASD symptoms and gender also contributed significantly to the regression model concerning the severity and frequency of SIB. The findings overall suggest that there is an increased likelihood of SIB and that it may be more severe in male children and adolescents, and in the presence of ASD symptoms. The study also found that aggression severity is significantly related to gender but not the presence of ASD symptoms. These results suggest that aggression is, therefore, more likely to occur in male children and adolescents with AS who have or do not have co-occurring ASD symptoms.

Both GI symptoms and sleep problems were found to significantly positively correlate with the frequency and severity of SIB, the frequency of aggressive/ destructive behavior, and the frequency of stereotyped behavior. And GI symptoms and sleep problems were associated with stereotypy and the frequency of SIB respectively. These findings support those of previous research in which fatigue and daytime sleepiness was found related to behavior problems in children with AS (Zhdanova et al., 1999) and GI symptoms were also associated with challenging behavior (Glassman et al., 2017).

It is also noteworthy that internalizing symptoms did not, significantly contribute to the frequency of SIB. But the presence of internalizing symptoms significantly contributed to the variance explained in the regression model regarding stereotyped behaviors and the presence of autism symptoms.

4.1. Study strengths and limitations

This study is the first to examine relationships between GI symptoms, sleep problems, and challenging behavior in children and adolescents with AS and it expanded upon previous literature by using multiple regression analysis to investigate the variables associated with challenging behavior. This study benefited from a good sample size, given that it examined a rare genetic condition. It also used validated measures, and it involved participants from a range of geographical locations. The study limitations include that data were not collected regarding whether the diagnoses of AS were confirmed by genetic testing and because it relied on parental-report questionnaires. It should however be noted that there can be a high concordance (88.9–92.1% agreement) between parental and clinician evaluations of GI dysfunction in children and adolescents with ASD (Gorrindo et al., 2012). This suggests that parental reports can be accurate measures of some comorbid symptoms. However, alternative methods of assessment via professionals may also have limitations. For example, if the sample is geographically dispersed, as is typically the case when investigating rare diseases, there may be an over representation of respondents in higher socio-economic groups who have the resources to seek healthcare (Pereira, 2020). This may be problematic for the generalization of study findings to the wider populations, especially when the socio-economic status of respondents may impact the severity of behavior problems. Bias may also have been introduced in the current study if families

with children and adolescents who have more severe behavior problems were more likely to enroll in the study.

4.2. Implications for clinical practice

Findings from the current study emphasize the prevalence of comorbid symptoms in children and adolescents with AS and may lead to a deeper understanding of symptom profiles and how to treat certain collections of symptoms. Therefore the findings have implications for the management and treatment of challenging behavior in clinical practice.

Due to the co-occurrence of, and the association between SIB, aggression, and stereotyped behavior with internalizing symptoms, GI symptoms, and sleep problems, the challenging behaviors may be reduced by improving the identification of these co-occurring symptoms. Indeed, these co-occurring symptoms could be regarded as potential modifiers of challenging behavior. Individuals with AS who present with challenging behavior are thoroughly and systematically screened for these related and co-occurring problems. Having identified underlying internalizing, GI, and sleep problems, their treatment needs to be prioritized. Indeed, recent research has shown the effectiveness and tolerability of three commonly prescribed medications that significantly reduced sleep disturbances and improved behavior (Pereira, 2020).

Furthermore, efforts to manage and treat these co-occurring problems should take place in conjunction with direct measures that target the challenging behavior. This management needs to include working in partnership with parents and caregivers, but it should also involve where possible, the direct assessment by clinicians of the specific behavior that is reported by parents as problematic (Pelc, Cheron, & Dan, 2008).

The results of the current study have also revealed new knowledge about the relationship between non-modifiable demographic characteristics, including gender and age with comorbidities in AS. This provides new knowledge about the characteristics in which these comorbidities are likely to present. The results reveal that clinicians should be particularly vigilant in attending to underlying GI and sleep problems when children and adolescents and AS present with challenging behaviors.

4.3. Future research

The current study found a small negative correlation that was not statistically significant between age and internalizing problems (-0.121; $p = .24$). However, relying on parent reporting, in populations with limited communication ability may affect the detection of internalizing symptoms (Durbeej et al., 2019). To accurately assess the internalizing symptoms in children and adolescents with AS, future research may benefit from using data collection methods that complement parental reporting. For example, using structured observation tools administered by professionals may increase the accurate detection of internalizing problems.

The current study also found that as children and adolescents with AS age, they display less stereotyped behavior. Future investigations need to replicate and clarify the trajectory of the relationships between both stereotypical behavior and internalizing behavior with age, and their association with each other. Further research also needs to examine the potential functional benefits of stereotypical behaviors to children and adolescents with AS. In children with ASD, internalized behavior problems increase with age (Kuusikko, Sanna et al., 2008), and it has been argued that stereotypical behaviors may be a way in which individuals with ASD can exhibit and relieve negative feelings, anxiety, and stress (Fuld, 2018). Therefore, stereotypical behaviors, may be of functional benefit to a child and adolescents with AS, who has ASD comorbidity and stereotypical behaviors may not always be regarded as negative and challenging behavior problems.

Future longitudinal and prospective studies also need to provide knowledge about the direction of causality between the common comorbidities that are experienced by children and adolescents with AS. These studies will facilitate identifying possible shared mechanisms that may underlie the comorbidities. For example, current studies in related populations with ASD are prospectively investigating potential gut-brain pathways between GI symptoms and the development of ASD (Troisi et al., 2020). The underlying factors that are being investigated include the genome, environment, metabolome, and the microbiome. Such factors are likely to have relevance for children and adolescents with AS, especially those who also have ASD symptomology.

In addition, longitudinal research should also focus on the trajectory of the relationship between comorbid symptoms in individuals with AS, as they develop into adulthood. This work will determine the relative stability of comorbid symptoms over time. Further knowledge about the presentation of comorbidities will also be gained through conducting cross-cultural investigations, to determine whether the presentation of AS is consistent regardless of country of origin and culture.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the National University of Ireland Galway and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent

Informed consent was obtained from all individual participants included in the study.

CRediT authorship contribution statement

Geraldine Leader: Conceptualization, Methodology, Supervision, Writing – review & editing, Visualisation. **Rebecca Gilligan:**

Investigation, Formal analyses, Writing – original draft. **Sally Whelan**: Writing – review & editing. **Rory Coyne:** Formal analyses of Data, Writing – review & editing. **Aoife Caher:** Formal Analyses, Writing – review & editing. **Keeley White:** Writing – original draft, Supervision. **Ivan Traina:** Resources. **Shellita Muchenje:** Formal analyses, Writing – review & editing. **Rudo L. Machaka:** Formal Analyses, Writing – review & editing. **Arlene Mannion:** Conceptualization, Methodology, Supervision, Writing – original draft, Writing –- review & editing, Visualisation.

Conflict of Interest

All the authors declare that they have no conflict of interest.

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