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Association Between Feeding Problems and Gastrointestinal Symptoms, Language, and Developmental History in Adults With Angelman Syndrome

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ABSTRACT

Angelman syndrome (AS) is a neurodevelopmental disorder characterized by severe developmental delays, typical facial features, ataxia, seizures, speech impairments, sleeping difficulties, and a happy demeanor. Caregivers of individuals with AS often report feeding problems, with difficulties including issues with obesity, failure to gain weight at the expected rate, food-seeking behaviors, and the requirement of tube-feeding. This study examined the frequency of feeding problems in 57 adults with AS, the most common types of issues, the associations and differences between those who experience feeding problems, and the predictors of feeding problems. Caregivers provided information through the Global Angelman Syndrome Registry, a global database that gathers information on individuals with AS. High rates of feeding problems were found, with 83% of adults experiencing feeding problems. The most common issue reported was food-seeking behaviors. Analyses found significant associations between feeding problems and gastrointestinal symptoms, and language and communication. Analyses did not find these variables to significantly predict feeding problems in adults with AS. The results of this study extend the current literature by highlighting the variables that are associated with feeding problems, the most common types of problems, and the high rates of feeding problems among adults with AS.

1 | Introduction

1.1 | Angelman Syndrome

Angelman Syndrome (AS) is a rare, genetic, neurodevelopmental disorder that is characterized by typical facial features, absent speech, ataxia, severe developmental delay, sleep disorders, seizures, and a uniquely happy demeanor (Bindels-de Heus et al. 2020). The estimated prevalence of AS is 1:15,000–24,000 globally (Napier et al. 2017).

1.2 | Genetic Basis of Angelman Syndrome

AS is caused by the lack of expression of the maternally imprinted gene *UBE3A*, which is biallelically expressed in all tissues except

in the brain (Abu-Amero et al. 2006; Mertz et al. 2014). There are various genetic classifications of AS, with approximately 70% of individuals having maternal deletions of chromosome 15q11-13. Additional classifications include a pathogenic variant of the maternally imprinted *UBE3A*, an imprinting center defect, and paternal uniparental disomy (Salminen et al. 2019; Williams et al. 2006).

1.3 | Feeding Problems in Angelman Syndrome

The term "feeding problems" encompasses a wide range of concerning behaviors that frequently occur during mealtime (Aponte and Romanczyk 2016). Feeding problems can result in an individual with AS engaging in refusal to eat, and a significant failure to gain weight, resulting in failure to gain weight at the expected rate (Benoit 2000). Berry et al. (2005) reported that the prevalence rate of overeating and food-seeking behaviors associated with obesity ranged from 7% to 50% in individuals with AS. Welham et al. (2015) examined food-related behavior problems in Prader–Willi syndrome (PWS) and other genetic neurodevelopmental syndromes, including AS. Welham et al. (2015) reported that PWS had the most severe food-related issues, but in some areas, individuals with AS exhibited equally severe problems, with over 50% of AS participants scoring above the median PWS score in food-taking and storing. Welham et al. (2015) concluded that food-related issues in AS required further study.

1.4 | Relationship Between Feeding Problems and Developmental History

The developmental history of an individual is an account of how and when they met various developmental milestones compared to children of similar age (Bellman et al. 2013). When examining feeding problems in adults, it is important to note infancy history, as findings suggest that infants with AS may experience issues with sucking, swallowing, gastroesophageal reflux, and limited ability to effectively breast- and bottle-feed (Dagli et al. 2017). There is evidence that feeding difficulties such as oral motor difficulties and mouthing behaviors that occur during the first year of life may be associated with feeding problems in childhood, adolescence, and so forth (Dagli et al. 2017; Thibert et al. 2013).

1.5 | Feeding Problems and Gastrointestinal Symptoms

Leader, Whelan, et al. (2022) found that the high frequency of gastrointestinal (GI) symptoms among individuals with AS was associated with feeding problems including vomiting, arching, and refusal to nurse. Leader, Whelan, et al. (2022) identified a significant association between GI symptoms and history of tube feeding, highlighting the positive relationship between feeding problems and GI issues. It is important to further examine feeding problems in AS, as it is known that GI symptoms cause discomfort that can contribute to sleep problems, behaviors of concern, and restrict social development (Bird 2014).

1.6 | Feeding Problems and Challenging Behavior

Individuals with AS exhibit challenging behaviors including overactivity, hyperactivity, sleeping difficulties, self-injurious behaviors, and feeding issues such as excessive chewing (Clarke and Marston 2000; Larson et al. 2015). Challenging behavior can result in refusal to eat, aggression, tantrums, and ritualized feeding behaviors, leading to issues such as failure to gain weight at the expected rate (Fodstad and Matson 2008; Matson and Fodstad 2009). Larson et al. (2015) noted that weight management in adults with AS is a complex issue, with contributing factors including challenging behavior related to food (Larson et al. 2015).

1.7 | Feeding Problems and Communication

Feeding problems in individuals with AS can be heightened due to lack of or inability to communicate (Glassman et al. 2017). Most adolescents and adults with AS can communicate by pointing and reaching, use of gestures, using communication boards, and pointing to body parts (Dagli et al. 2017). Individuals with AS have profound communication deficits including little to no functional speech or expressive language skills, which can result in few diagnoses of feeding problems in people with AS (Dagli et al. 2017; Larson et al. 2015). While investigating sleep disturbances in children with AS, Leader et al. (2024) identified a significant association between the ability to use spoken words and computerized communication devices and sleep issues. Given these associations, the relationship between various communication methods—including gestures, augmentative and alternative communication (AAC) devices, and Pragmatic Organisation Dynamic Display (PODD) formal books—is being examined to further understand the impact of communication abilities on feeding difficulties.

1.8 | AS and Adaptive Behavior

Adaptive behaviors that may be related to feeding problems include the ability to hold a bottle, to chew various textures, whether feeding support is needed, skills to indicate they are full, and whether food supplementation is required (Kanne et al. 2011; Roche et al. 2022; Sparrow et al. 2005). Researchers investigated adaptive behavior in children with AS and reported that gross and fine motor difficulties with feeding were negatively associated with age (Roche et al. 2022). However, this negative relationship has not been thoroughly investigated in an adult population, as existing studies have primarily focused on infants and children.

1.9 | Current Study

The current study aimed to investigate the most common types of feeding problems in adults with AS. There has been a limited number of studies focusing on adults with AS (Clayton-Smith 1993; Den Besten et al. 2021; Giroud et al. 2015). Recent findings demonstrated over 50% of caregivers reported feeding problems in the individual with AS, 46% of adults were

overweight, and 9% of adults were underweight (Den Besten et al. 2021). Feeding problems can result in an individual being at greater risk for other serious health issues and can have both short and long-term consequences, including weight loss, choking, failure to gain weight at the expected rate, malnutrition, iron deficiency anemia, physical pain and GI discomfort (Ball et al. 2012; Leader et al. 2021; Meral and Fidan 2015). The current study aimed to promote understanding of the factors associated with feeding problems in adults with AS, through investigating how these factors predicted their occurrence. Further investigation is required to better understand the nature and extent of this relationship in order to facilitate the identification of these feeding problems and the factors that may predict them.

2 | Method

2.1 | Sample

The sample consisted of 57 adults with a diagnosis of AS. Adults with AS were enrolled in the Global Angelman Syndrome Registry and caregiver information was obtained. The mean age of the sample was 26.9 years (*S.D* = 7.73), ranging from 18 to 47 years. The sample consisted of 53% males ($n = 30$) and 47% females ($n = 27$). There were no participants who reported indeterminate for gender. All participants had a confirmed diagnosis of AS following a genetic test from a geneticist, pediatrician, neurologist, neuropediatrician, or other professionals. The following results were received regarding the genetic test results of the participants: 54% ($n = 31$) had a chromosome deletion (class unknown) result for AS; 32% ($n = 18$) had a chromosome deletion (Class 1) result for AS; and 14% ($n = 8$) did not disclose the results of their genetic test. The Registry is eligible for individuals with an imprinting center defect (ICD), mutation, uniparental disomy (UPD), clinical, or mosaic; however, this study consisted of participants with a chromosome deletion or nondisclosed result, as these individuals had completed the relevant module for inclusion in the current study (Tones et al. 2018). Prior to receiving an AS diagnosis, some participants ($n = 35$) also had received a misdiagnosis of one of the following; Autism Spectrum Disorder (ASD); Seizure Disorder; Cerebral Palsy; Global Development Delay.

2.2 | Procedure and Informants

Data collected by the Global Angelman Syndrome Registry were used for secondary analysis to investigate feeding problems. The registry is patient-reported, with respondents including parents and/or caregivers of individuals with AS (Napier et al. 2017). The Foundation for Angelman Syndrome Therapeutics (FAST) Australia, researchers and clinicians, pharmaceutical companies and caregivers of individuals with AS have contributed to the development of the registry's aims, objectives, design, and content (Tones et al. 2018). The registry is governed by the Global Angelman Syndrome Registry Governance Board, while the Data Curator manages all registry activities including data requests (Napier et al. 2017). Data was collected from participants globally, with 49% based in the United States. Other regions included Europe (23%), Australia (14%), and Canada (7%) (Tones et al. 2018). The Global Angelman Syndrome Registry developed a Rare Disease Registry Framework (RDRF) to deploy a modular and web-based questionnaire (Napier et al. 2017). The questions included in all modules are based off standardized clinical scales (Tones et al. 2018). Each module, along with their respective questions and answering format—such as Likert scale or text box, are available to view at https://www.angelmanregistry.info/modules/. Parents and caregivers were advised to consult their clinicians when completing sections of the modules that they found challenging (Tones et al. 2018).

2.3 | Measures

2.3.1 | Demographic Information

Gender was reported on in Module 0, Demographics, with participants answering Male, Female, or Indeterminate. Participants disclosed the age at diagnosis and current age in Module 2, History of Diagnosis and Results. Questions regarding the clinician who made the diagnosis, a misdiagnosis, any dual diagnosis and the results of a genetic test for AS used Likert scales with answers scoring from 1 to 5 and "Unknown" depending on the question. For instance, participants were asked: Who made the diagnosis? Informants chose from: Pediatrician/GP; Neuropediatrician; Neurologist; Geneticist; Other. Weight was reported as part of Module 7 Medications and Interventions.

2.3.2 | Feeding Problems

Data about feeding problems were obtained using Module 3 Illnesses or Medical Problems, and focused on four of the subscales of this module; Dental Issues, Obesity; Failure to gain weight at the expected rate; and Tube-Feeding. Likert 1 to 3 scales were used to report on the frequency and status of the issue. For example, informants were asked: What is the current status of your child/adult's failure to thrive? Answers included: Currently experiencing; Intermittently experiencing/episodic; Resolved; Unknown. Further data were obtained via questions involving the age at onset, height, weight, and BMI. Informants reported any dental issues the individual had.

2.3.3 | Developmental History

Data concerning developmental history was collected using Module 1 Newborn and Infancy History. Twenty questions from this module were used and a Likert scale 1–6 was employed with questions focusing on feeding during infancy, including nursing difficulties such as failure to latch, ineffective sucking, biting or vomiting issues, irritability in association with feeding or nursing, gaining weight, and any challenges transitioning to solid food. For instance, participants were asked: Does/did the individual with Angelman Syndrome experience feeding difficulties as a newborn? Answers included: Yes, all the time; Yes, most of the time; Yes, some of the time; Yes, rarely; No, never; Unknown.

2.3.4 | Gastrointestinal Symptoms

GI symptoms were examined via Module 3 Illness or Medical Problems. Subscales of this module that were focused on included gastroesophageal reflux, constipation, vomiting with feeds, and gagging, by answering twenty-seven questions in total. The occurrence, severity, and history of each of these issues were reported on using a Likert scale scoring 1–6. For instance, participants were asked: Has the individual with Angelman Syndrome ever vomited with feeds? Informants chose from: Yes, all the time; Yes, most of the time; Yes, some of the time; Yes, rarely; No, never; Unknown.

2.3.5 | Challenging Behavior

Challenging behavior was examined using Module 5 Behavior and Development module. Informants were asked to rate how problematic the individual's behavior was on a scale of 1–10. The occurrence and frequency of repetitive behaviors were reported using thirty questions with a Likert scale scoring 1–6. These behaviors included slapping the wall, whole body movements, mouthing or chewing, fear of strangers, irritations in new situations, anxious behaviors, as well as self-harming and aggressive behaviors. For example, informants were asked: Does he/she exhibit any of the following behaviors? Oppositional behaviors.

2.3.6 | Language and Communication

The "Communication" module was utilized by informants to answer questions on expressive language, verbal communication ability, and the different forms of communication used, including assisted and augmented methods, as well as the preferred method of communication. This module used Likert scales scoring from 1 to 5 when answering fifteen questions on various communication methods. For example, caregivers were asked: Please rate the individual's ability to use the following communication methods/systems: Signing. Participants could select from various options: Doesn't use; Rarely uses; Uses for single requests regularly; Communicates effectively with known people; Communicates effectively with known and unknown people.

2.3.7 | Adaptive Behavior

Adaptive behavior was reported on using Module 5 Behavior and Development. Caregivers were asked about the frequency and ability of behaviors from eight subscales, including the individual's history of holding a bottle, any tastes or textures the individual does not enjoy, fussiness with food, capability of chewing all textures, ability to self-feed or whether assistance is required, and whether food supplementation occurs. A 1–5 Likert scale with an "Unknown" option was used to gather data, with questions including: He/she indicates that he/she is full: Frequency (How often does the individual with Angelman Syndrome do this?). Participants then select from: Yes, all the time; Yes, most of the time; Yes, some of the time; Yes, rarely; No, never; Unknown.

2.3.8 | Medical History

Medical history was examined using Module 4 Medical History and focused on allergies and intolerances. Caregivers reported on the occurrence of allergies or intolerances and answered on the type of allergy and status using Likert scales 1–4. For instance, they were asked: What is the current status of your child/adult's intolerances? The options given were: Currently experiencing; Intermittently experiencing/episodic; Resolved; Unknown.

2.4 | Analyses

The data was divided into two groups: adults with feeding problems and adults without feeding problems, whereby a feeding problem is classified as the presence of at least one of the following symptoms during their lifetime: problems with obesity, food-seeking behaviors, issues with failure to gain weight at the expected rate, and if they are/were ever tube-fed. A default alpha level of 0.05 was used for analysis. A Bonferroni correction for multiple comparisons was used. The Shapiro–Wilk test was performed and showed that the distribution of age of diagnosis departed significantly from normality ($W = 0.53$, $p < 0.01$). As a result, a Mann–Whitney U test was run to examine whether there was a difference between age of diagnosis of AS and whether individuals present with feeding problems or not. The assumption of minimum expected cell frequency (> 5) was violated, as various cells had expected counts less than five. Therefore a series of 2×2 Fisher's Exact test were run to examine the association between feeding problems in adults with AS and developmental history, adaptive behavior, language and communication, and GI symptoms. Shapiro–Wilk test showed that challenging behavior departed significantly from normality ($p < 0.01$). Therefore, Mann–Whitney U tests were run to identify the differences in challenging behavior between those who had feeding problems and those who did not. A logistic regression analysis was conducted to examine the predictors of feeding problems in adults with AS. The results of Fisher's Exact tests and Mann–Whitney U tests indicated which predictor variables to include in the logistic regression.

3 | Results

3.1 | Feeding Problems

The frequency of feeding problems in adults with AS was examined, with 83% ($n = 47$) of adults presenting with at least one feeding problem, and 17% ($n = 10$) without feeding problems. Food-seeking behaviors were the most common feeding problem, with 72% ($n = 41$) of adults experiencing this issue. The second most common feeding problem was failure to gain weight at the expected rate, with 37% ($n = 21$) experiencing difficulties. Obesity was identified in 26% ($n = 15$) of adults. Finally, tube-feeding occurred in 11% ($n = 6$) of adults.

3.2 | Feeding Problems and Demographic Information

The mean age at diagnosis of adults with feeding problems was 5.4 years (SD = 8.49) and ranged from 0.5 to 28.9 years. It is

important to note that 14% ($n=8$) of participants did not disclose the results of their genetic test for AS, and this should be considered when interpreting the findings of the study. A Mann–Whitney U test was conducted to examine whether a difference existed between the age of diagnosis and the presence of feeding problems. Feeding problems in early infancy are often one of the symptoms that contribute to a diagnosis of AS (Williams et al. 2010). The results from the Mann–Whitney U test indicated that there was no significant difference between the age of diagnosis and feeding problems ($U=12.50$, $p=0.20$). The mean weight of those with feeding problems was 65.6 kg (SD = 23.66), ranging from 37.0 to 150.0 kg. The mean weight of those without feeding problems was 53.9 kg (SD = 10.04) and ranged from 45 to 72.57 kg.

3.3 | Relationship Between Feeding Problems and Developmental History

A Fisher's Exact test was conducted to investigate if there was an association between feeding problems and developmental history. The crosstab included 13 variables, and were scored with "Yes," "No," or "Unknown." Among individuals with a history of feeding problems, 86% ($n=37$) reported to having experienced feeding difficulties in childhood. Difficulties with suck/swallowing were highly prevalent in both those with and without feeding problems (85%). Vomiting was notably more frequent among those with feeding problems (85%) than those without (50%). Gastroesophageal problems were also more commonly reported in those with feeding problems (72%) compared to participants without (57%). Difficulties with weight gain were more frequently reported in those with feeding problems (64%) than in those without feeding problems (29%). There was no significant association found between feeding problems and developmental history.

3.4 | Feeding Problems and Gastrointestinal Symptoms

The association between feeding problems and GI symptoms was examined using Fisher's Exact test. As can be seen in Table 1, six variables were included in the crosstab, and were scored with "Yes," "No," or "Unknown." An association was observed between feeding problems and gastroesophageal reflux ($p=0.02$). An association was found between adults with feeding problems and vomiting with feeds ($p=0.04$). An association was seen between feeding problems and experience of gagging ($p=0.01$). It was found that 77% ($n=36$) of adults with feeding problems experienced gagging, compared to 75% ($n=6$) of those without.

3.5 | Feeding Problems and Language and Communication

Fisher's Exact test was conducted to examine whether an association existed between feeding problems and language and communication. As can be seen in Table 2, 17 variables were included in the crosstab, and were scored with "Uses," "Doesn't Use," or "Unknown." A significant association was found between feeding problems and an individual using moans to communicate ($p=0.03$). An association was observed between feeding problems and use of formal (PODD) books ($p=0.04$). An association was also observed between feeding problems and use of low-tech augmentative and alternative communication (AAC) ($p=0.01$).

3.6 | Feeding Problems and Adaptive Behavior

A series of Fisher's Exact tests were conducted to investigate if there was an association between feeding problems and adaptive behavior in adults with AS. As can be seen in Table 3, eight variables were included in the crosstab, and were scored with "Yes," "No," or "Unknown." There were no significant associations observed among adaptive behavior and feeding problems.

3.7 | Feeding Problems and Medical History

A series of Fisher's Exact tests were conducted to examine the association between feeding problems and medical history. Of the adults with feeding problems, 33% ($n=19$) had diagnosed allergies and 19% ($n=11$) had diagnosed intolerances. No significant associations were identified between feeding problems and medical history among this sample.

3.8 | Feeding Problems and Challenging Behavior

A series of Mann–Whitney U tests were conducted to examine whether there is a difference between challenging behaviors in those with feeding problems and those without. As can be seen in Table 4, the results of the Mann–Whitney U tests indicated there were no significant differences in challenging behavior between those with feeding problems and those without.

3.9 | Predictors of Feeding Problems

A logistic regression analysis was conducted to determine the predictors of feeding problems in adults with AS. The dichotomous criterion variable was feeding problems (with/without), and the predictor variables were gastrointestinal symptoms and language and communication, as determined by the findings from Fisher's Exact tests. Multicollinearity was not present in the data as Pearson's correlation statistic for the predictor variables was less than 0.7. The logistic regression model was not statistically significant ($\chi^2(7)=5.92$, $p=0.550$). The model explained 28% (Nagelkerke R^2) of the variance in feeding problems and explained 90% of adults with AS. Results of the regression are reported in Table 5. Analysis of the Wald statistics suggested that none of the variables significantly added to the model.

4 | Discussion

The results indicate that there is a high frequency of feeding problems among adults with AS. In this study, 83% of adults with AS experienced feeding problems. Food-seeking behaviors were the most common feeding problem in 84% of this sample. These findings are consistent with those from Mertz et al. (2014), who found that children with AS exhibited significant overeating and food-seeking behavior. Failure to gain weight at the expected rate was found among 39% of adults

TABLE 1 | GI symptoms and level of activity and food intake of adults with AS with and without feeding problems.

Gastrointestinal (GI) symptom	**Feeding problems 83% (*n* = 47)**			**No feeding problems 17% (*n* = 10)**			***Fisher's exact test***
	Yes	No/unknown		Yes	No/unknown		*p*
	Percentage (*n*)	Percentage (*n*)		Percentage (*n*)	Percentage (*n*)		
Gastroesophageal reflux	80% (*n* = 35)	20% (*n* = 9)		40% (*n* = 4)	60% (*n* = 6)		0.02
Constipation	89% (*n* = 42)	11% (*n* = 5)		100% (*n* = 10)	0% (*n* = 0)		0.57
Vomited with feeds	67% (*n* = 31)	33% (*n* = 15)		22% (*n* = 2)	78% (*n* = 7)		0.04
Gagging	77% (*n* = 36)	23% (*n* = 11)		75% (*n* = 6)	25% (*n* = 2)		0.01
Dental problems	51% (*n* = 24)	49% (*n* = 23)		22% (*n* = 2)	78% (*n* = 7)		0.11
Strep throat	57% (*n* = 27)	43% (*n* = 20)		40% (*n* = 4)	60% (*n* = 6)		0.46
GI Symptom	Increased	Normal	Decreased	Increased	Normal	Decreased	x^2
	Percentage (*n*)	Percentage (*n*)	Percentage (*n*)	Percentage (*n*)	Percentage (*n*)	Percentage (*n*)	Percentage (*n*)
Activity Level	7% (*n* = 3)	33% (*n* = 14)	60% (*n* = 25)	25% (*n* = 1)	50% (*n* = 2)	25% (*n* = 1)	2.54
Food intake	23% (*n* = 10)	63% (*n* = 27)	14% (*n* = 6)	0% (*n* = 0)	100% (*n* = 4)	0% (*n* = 0)	2.39

Note: Not all caregivers reported on GI symptoms; therefore, some data were missing. Missing data existed for gastroesophageal reflux (*n* = 3), vomiting with feeds and gagging (*n* = 2), dental problems (*n* = 1), activity level (*n* = 10), and food intake (*n* = 8).

TABLE 2 | Language and communication of adults with AS with and without feeding problems.

Adaptive behavior item	Feeding problems 83% ($n=47$)		No feeding problems 17% ($n=10$)		*Fisher's exact test*
	Uses	Does not use/ unknown	Uses	Does not use/ unknown	*p*
	Percentage (*n*)	Percentage (*n*)	Percentage (*n*)	Percentage (*n*)	
Expressive language	79% ($n=23$)	21% ($n=6$)	100% ($n=8$)	0% ($n=0$)	0.66
Uses babbles	32% ($n=15$)	68% ($n=32$)	30% ($n=3$)	70% ($n=7$)	1.00
Uses moans	49% ($n=23$)	51% ($n=24$)	10% ($n=1$)	90% ($n=9$)	0.03
Uses single words	21% ($n=10$)	70% ($n=37$)	30% ($n=3$)	70% ($n=7$)	0.68
Uses intentional sound	49% ($n=23$)	51% ($n=24$)	70% ($n=7$)	30% ($n=3$)	0.30
Uses 2/3 word phrase	2% ($n=1$)	98% ($n=46$)	20% ($n=2$)	80% ($n=8$)	0.08
Uses longer phrase speech	0% ($n=0$)	100% ($n=47$)	10% ($n=1$)	90% ($n=9$)	0.18
Uses spoken words	50% ($n=14$)	50% ($n=14$)	63% ($n=5$)	37% ($n=3$)	0.70
Uses gestures	89% ($n=25$)	11% ($n=3$)	88% ($n=7$)	12% ($n=1$)	1.00
Uses signing	59% ($n=17$)	41% ($n=12$)	88% ($n=7$)	12% ($n=1$)	0.22
Uses visual pictures	63% ($n=17$)	37% ($n=10$)	100% ($n=8$)	0% ($n=0$)	0.07
Uses formal (PODD) books	4% ($n=1$)	96% ($n=23$)	37% ($n=3$)	63% ($n=5$)	0.04
Uses iPad apps, picture to voice	56% ($n=15$)	44% ($n=12$)	88% ($n=7$)	12% ($n=1$)	0.21
Uses eye tracking devices	12% ($n=3$)	88% ($n=21$)	0% ($n=0$)	100% ($n=7$)	1.00
Uses low-tech augmentative and alternative communication (AAC)	17% ($n=4$)	83% ($n=20$)	75% ($n=6$)	25% ($n=2$)	0.01
Uses mid-tech AAC	21% ($n=5$)	79% ($n=19$)	29% ($n=2$)	71% ($n=5$)	0.64
Uses high-tech AAC	75% ($n=12$)	25% ($n=14$)	71% ($n=5$)	29% ($n=2$)	0.40

Note: Not all caregivers reported on language and communication; therefore, some data were missing. Missing data existed for expressive language and signing ($n=20$), use of spoken words and gestures ($n=21$), use of visual pictures and iPads ($n=22$), PODD books and low-tech AAC ($n=25$), mid-tech AAC ($n=26$), and high-tech AAC ($n=24$).

in the current study, reflecting findings that highlight failure to gain weight at the expected rate as an early symptom of AS that leads to a diagnosis (Lalande and Calciano 2007; Mertz et al. 2013). Obesity presented in 27% of participants, supporting the findings of Den Besten et al. (2021), who reported that 37% of adults with AS were overweight, with one third of those considered obese. The current study found that 11% of participants had been tube fed, which is supported by Bindels-de Heus et al. (2020), who reported that 13% of children with AS required tube-feeding.

A positive relationship was found between feeding problems and GI symptoms, including gastroesophageal reflux, vomiting with feeds, and experiencing gagging. This is supported by Prasad et al. (2018) who reported that 53% of adolescents and adults experienced gastroesophageal reflux. Larson et al. (2015) observed that episodic gagging was a common GI symptom among adults with AS and was associated with feeding issues. Glassman et al. (2017) found that cyclic vomiting episodes were a notable GI issue reported by both children and adults with AS.

A relationship was found between feeding problems and use of moans to communicate, use of formal PODD books, and use of low-tech AAC. Glassman et al. (2017) illustrated the association between communication deficits and feeding and GI issues, outlining that feeding problems can be heightened when an individual struggles to communicate their feeding wants, needs, and preferences.

There was no relationship identified between feeding problems and developmental history. However, Leader, Whelan, et al. (2022) examined early and current GI symptoms in children and adolescents with AS and found significant associations between high-frequency GI symptoms groups and variables associated with infancy history. The contradiction in the above results may be related to how this study categorized the variable feeding problems. Food-seeking behaviors and failure to

TABLE 3 | Adaptive behavior of adults with AS with and without feeding problems.

Adaptive behavior item	Feeding problems 83% ($n=47$)		No feeding problems 17% ($n=10$)		*Fisher's Exact Test*
	Yes	No/unknown	Yes	No/unknown	*p*
	Percentage (*n*)	Percentage (*n*)	Percentage (*n*)	Percentage (*n*)	
Ability to hold a bottle	81% ($n=21$)	19% ($n=5$)	100% ($n=6$)	0% ($n=0$)	0.56
Texture/tastes disliked	69% ($n=20$)	31% ($n=9$)	67% ($n=2$)	33% ($n=1$)	1.00
Fussy about food	67% ($n=18$)	33% ($n=9$)	33% ($n=2$)	67% ($n=4$)	0.18
Ability to chew all textures	85% ($n=23$)	15% ($n=4$)	60% ($n=6$)	40% ($n=4$)	1.00
Feeds themselves using fingers/utensils	96% ($n=27$)	4% ($n=1$)	100% ($n=6$)	0% ($n=0$)	1.00
Support with feeding from parent/caregiver	85% ($n=23$)	15% ($n=4$)	83% ($n=5$)	17% ($n=1$)	1.00
Indicates that they are full	81% ($n=22$)	19% ($n=5$)	83% ($n=5$)	17% ($n=1$)	1.00
Uses supplementation in forms of additional formulas	18% ($n=5$)	82% ($n=23$)	0% ($n=0$)	100% ($n=5$)	0.57

Note: Not all caregivers reported on adaptive behavior; therefore, some data were missing. Missing data existed for the ability to hold a bottle, textures disliked, and the ability to chew all textures ($n=25$), fussy about food ($n=24$), feed themselves ($n=23$), and support with feeding, indicates they are full, and food supplementation ($n=24$).

TABLE 4 | Means and standard deviations of challenging behavior of adults with AS with and without feeding problems.

Challenging behavior subscale	Feeding problems 83% ($n=47$)		No feeding problems 17% ($n=10$)		Mann–Whitney *U* test
	M	SD	*M*	SD	*U*
Appropriate affect	4.00	0.67	4.42	0.58	54.00
Self-injury	1.73	0.94	1.50	0.63	82.50
Spontaneous affect	2.16	0.87	2.22	0.81	81.50
Anxiety	2.59	0.98	2.64	0.89	74.00
Behavior Dysregulation	2.47	0.63	2.31	0.85	73.50
Repetitive behaviors	2.19	0.85	2.19	0.76	76.00
Poor attention & hyperactivity	3.05	0.99	2.00	0.71	31.50

TABLE 5 | Logistic regression of feeding problems in adults with AS.

	β	SE	Wald	OR
Vomited with feeds	−1.54	1.19	1.68	0.21
Experiencing gagging	−0.17	1.33	0.02	0.85
Experienced gastroesophageal reflux	−0.95	1.56	0.37	0.39
Communicated using moans	−0.69	1.39	0.25	0.50
Communicated using 2 or 3 word phrases	−18.62	40192.97	0.00	0.00

gain weight at the expected rate were both considered feeding problems. However, failure to gain weight at the expected rate is most commonly seen in infants, whereas food-seeking behaviors can occur at any stage during one's lifetime. Therefore, individuals who experienced failure to gain weight at the expected rate as an infant should not be compared to an adult currently demonstrating food-seeking behaviors.

There was no relationship found between challenging behavior and feeding problems. These findings contradict previous literature, which suggested that challenging behavior often exacerbated feeding difficulties during mealtimes (Ball et al. 2012; Williams et al. 2010). However, these studies were mainly conducted among individuals with ASD or intellectual disabilities and did not specifically focus on AS.

There was no relationship found between feeding problems and adaptive behavior. In studies examining feeding difficulties and adaptive behaviors in individuals with ASD, researchers found no significant association between the two variables (Leader et al. 2021).

GI symptoms, and language and communication were not found to predict feeding problems in adults with AS. These findings may have been impacted by the fact an adult sample was studied, and caregivers may have had difficulty recalling information from infancy. Johnson et al. (2014) investigated the relationship between feeding problems and behavioral characteristics and reported that the severity of communication deficits did not predict mealtime or feeding problems in children with ASD (Johnson et al. 2014).

The generalizability of the study was strengthened as the Global Angelman Syndrome Registry was used, consisting of data from participants worldwide, resulting in greater participant diversity in terms of age, race, and genetic classifications of AS. The use of the registry also resulted in access to a large sample size, thereby strengthening the external validity of the study. The use of an online questionnaire reduces social desirability bias, as research has demonstrated that participants are more likely to give socially desirable answers in the presence of a researcher (Chung and Monroe 2003).

This study has several limitations. Self-selection into the Registry may create biases in the sample, as those within the target population will be more likely to participate in the modules if they are interested in the work (Tones et al. 2018). Given that participants do not have to fill out all modules or questions, it is possible they might only complete modules that are relevant to their own needs and experiences, creating a self-selection bias. The generalizability of the results may also be limited as the regression does not include age, sex, or molecular subtype. A further limitation of the study is the inclusion of adults with a history of feeding difficulties in childhood, regardless of whether those difficulties have since resolved. While this provides a broad perspective on feeding issues in adults with AS, it does not distinguish between persistent and resolved difficulties, which may impact the interpretation of the findings, such as identifying factors contributing to long-term feeding problems in adults with AS. The cells are rather small for some of the analyses in the study; however, the data were not powered for analysis. The small sample size and lack of information on the family environment, including siblings, household income, and employment status, may limit the validity and generalizability of the study, as it cannot be determined whether these findings accurately represent the population. It is important to note that correlations were used in the analyses of the current study, and while correlations can identify relationships between variables, they do not establish causation. The direction of these relationships may not infer causality. Therefore, future research is necessary to replicate and further investigate the associations observed in this study.

The sample does not consist of those with a nondeletion etiology (imprinting center defect, uniparental disomy, and pathogenic variance of *UBE3A*). Given there are significant phenotypic differences between deletion and nondeletion etiologies for multiple variables in the analyses and established differences in feeding behavior, the findings can only be extended to adults with AS caused by a deletion. While the inclusion into the registry requires individuals as having a confirmed molecular diagnosis, the results of their genetic test and disclosing the molecular diagnosis are up to the discretion of the participant. In the current study, 14% ($n = 8$) did not disclose the results of their genetic test, and therefore results involving molecular subgroups should be interpreted with this in mind. The difference in obesity prevalence between individuals with deletion and nondeletion (e.g., UPD) is an important consideration. Mertz et al. (2014) found that individuals with paternal uniparental disomy (pUPD) are more prone to overeating behaviors and obesity from an early age, whereas those with Class I deletions tend to have lower birth weights and may not follow the same trajectory toward obesity. This suggests that genotype may play a role in feeding behaviors and weight regulation in AS. Future research should avail of the Global Angelman Syndrome Registry's data to explore how genotype influences feeding difficulties and the prevalence of obesity in the different genetic groups. Additionally, there is a lack of subclassification for over half of the participants with a chromosome deletion, as specific information about deletion class (e.g., Class 1 vs. Class 2) was not available for 54% of cases. This may reflect variability in how genetic information was reported at the time of registry enrollment, rather than an actual absence of this data. As a result, it is possible that individuals with Class 2 or atypical deletions were included in the "class unknown" group. Future research would benefit from more detailed and standardized molecular data to enable clearer genotype–phenotype analyses.

It is recommended for future studies to consider using translated versions of the Global Angelman Syndrome Registry, rather than using participants exclusively from English-speaking countries. This would allow for a greater accessibility of the Registry for non-English speaking families, as well as increasing representation and participation. Given the nonsignificant association between feeding problems in adults and developmental history, it would be advisable and clinically useful for future studies to examine potential current predictors of adult feeding behaviors in order to generate more reliable and accurate results. A further limitation of the study involves the analysis of feeding problems as a construct, given that food-seeking behaviors and obesity have a different etiology compared to tube-feeding and failure to gain weight at the expected rate. Future research might consider focusing their analyses exclusively on obesity and food-seeking behaviors given these behaviors are less prone to recall bias. Additionally, conditions like obesity and tube feeding may not commonly coexist in an individual, suggesting the need for separate analyses for these conditions. Future research should examine these feeding difficulties individually to better understand their unique contributors to feeding problems and the management of these conditions. Alternatively, tube-feeding and failure to gain weight at the expected rate could be examined together as these conditions might be interrelated, and likewise with obesity and food-seeking behaviors. Of the participants, 19% ($n = 9$) had received a dual diagnosis of ASD, with all nine individuals having reported a feeding problem. While these individuals met inclusion criteria and were retained in the analysis, it should be noted that co-occurring conditions may influence GI symptoms and other clinical features. Given the significant association between ASD and co-occurring GI issues (Leader, Abberton, et al. 2022), future research may benefit from exploring the relationship of feeding problems in individuals with and without

a co-occurring ASD diagnosis, or similar co-occurring conditions, to better understand their impact on feeding issues.

Findings may inform clinicians about the co-occurring symptoms of feeding problems in adults with AS, including obesity, failure to gain weight at the expected rate, tube-feeding, and food-seeking behaviors. Due to the association between feeding problems and GI symptoms, and language and communication, clinicians could potentially develop a more thorough screening process to identify feeding issues with the aid of these predictors. Practitioners may recognize the relationship between communication ability and feeding issues, and prioritize those individuals who cannot verbally express their symptoms when screening for these issues. The high prevalence rates of feeding problems may encourage the priority in treating these difficulties in a clinical setting.

In conclusion, this study has extended current literature by highlighting the high rates of feeding problems among this population and identifying variables associated with these issues. This study provided novel findings on the outcomes of feeding problems in adults such as failure to gain weight at the expected rate and food-seeking behaviors, as these issues had previously been associated with feeding disorders in infancy and childhood. The findings expand the current theoretical understanding of feeding problems in AS, as feeding issues had previously been primarily associated with PWS, the sister-imprinted disorder of AS, with AS patients even being misdiagnosed with PWS as infants when presenting with feeding difficulties (Williams et al. 2010).

Author Contributions

Ciara Cassidy: formal analysis, investigation, methodology, writing – original draft, writing – review and editing. **Arlene Mannion:** conceptualization, investigation, methodology, supervision, writing – original draft, writing – review and editing. **Sally Whelan:** supervision, writing – original draft, writing – review and editing. **Megan Tones:** data curation, writing – review and editing, resources. **Helen Heussler:** data curation, writing – review and editing, resources. **Matthew Bellgard:** data curation, resources, writing – review and editing. **Geraldine Leader:** conceptualization, methodology, writing – original draft, writing – review and editing.

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Ethics Statement

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

Consent

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

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data on which this research is based is accessible on request through the Global Angelman Syndrome Registry (hhtps://angelman-registry.info/).

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