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# Parent Description of Anxiety in Angelman Syndrome

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## Abstract

Anxiety is being increasingly identified in Angelman syndrome (AS). Qualitative questions and quantitative assessments were used to evaluate for anxiety in 50 subjects with AS. In-person evaluations assessed behaviors concerning for anxiety and circumstances wherein they occurred. Caregivers completed anxiety and other behavioral rating scales. Caregiver responses were categorized and compared to items from anxiety rating scales. The most common behavioral manifestation of anxiety was "aggression." The most common circumstance was "separation from caregiver/parent." Subjects had elevated scores on anxiety, irritability and hyperactivity scales with lower mean scores among subjects with a maternal deletion. The Pediatric Anxiety Rating Scale best captured behaviors described by caregivers. Existing anxiety scales should be adapted for use in AS.

**Keywords** Angelman syndrome · Anxiety · Rating scale · Irritability · Hyperactivity

Angelman syndrome (AS) is a neurogenetic disorder characterized by intellectual disability (ID), severely limited expressive language, epilepsy, ataxia, sleep impairment and a specific behavioral phenotype of frequent smiling and paroxysms of laughter (Williams et al., 2006). Angelman syndrome is caused by impaired expression of the maternally-inherited ubiquitin-protein ligase E3A gene (UBE3A) on Chromosome 15 (Albrecht et al., 1997). Molecular mechanisms that result in AS include deletion of the maternal 15q11.2-13.1 region, mutation of the maternal UBE3A gene, paternal uniparental disomy (UPD), and imprinting center defects. Interfering behaviors are a common source of morbidity and can include hyperactivity (Williams, 2010),

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aggressive behavior (Arron et al., 2011), and manifestations of anxiety (Clayton-Smith, 2001).

An increasing body of research indicates that caregivers are especially concerned about anxiety in patients with AS, particularly among adolescents and adults. Detailed case series (Clayton-Smith, 2001; Giroud et al., 2015), as well as a larger phone survey (Larson et al., 2015) have described and determined that anxiety in adolescents and adults with AS is a consistent concern among caregivers. Larson et al. (2015) found that 46% of caregivers reported their adult dependent with AS as "showing signs of anxiety." A separate retrospective chart review identified an increasing prevalence of anxiety into adulthood with 71% of caregivers reporting anxiety in the 26–43 years old cohort (Prasad et al., 2018). While caregiver report indicated anxiety was increasing with age, other features of the syndrome, such as ongoing seizures or sleep disorder, were more likely to have stabilized.

The determination of internal mood states is difficult in the largely minimally verbal population of individuals with AS. Considering this, some studies have explored observable behaviors in AS that may be indicative of anxiety. One cohort of 248 subjects with AS identified 45% as becoming upset when routines were changed (Walz, 2007). Another study of 68 subjects with AS found half had a fear of crowds and a third had a fear of noise (Artigas-Pallares et al., 2005).

In a more recent study a modified anxiety questionnaire was administered to 100 caregivers of subjects with AS and found high levels of distress with separation from a preferred caregiver (Wheeler et al., 2019). It remains to be determined if these behaviors that caregivers describe are representative of internal states of anxiety in patients with AS.

Rodent models of AS have lent additional evidence to the likelihood that anxiety may be a common feature in the syndrome. One study found manifestations of anxiety in rodents wherein there was a maternal chromosome deletion including UBE3A but not in rodents with a paternal chromosome deletion involving the same region (Jiang et al., 2010). Disruptions in the glucocorticoid receptor signaling pathway found that hyperactivity in the hypothalamic–pituitary–adrenal (HPA) axis resulted in increased susceptibility to anxiety and stress in the maternal UBE3A deficient mouse model (Godavarthi et al., 2012). Alternative hypotheses involve the serotonin neurotransmitter system. In Drosophila, the UBE3A equivalent gene is implicated in regulating monoamine synthesis (Ferdousy et al., 2011). In addition, case reports of serotonergic medications such as buspirone and mirtazapine have resulted in improvement in anxiety and disrupted sleep in patients with AS (Balaj et al., 2019; Hanzlik et al., 2020).

It is challenging to identify and quantify the severity of anxiety in patients with AS in light of the limited expressive language skills and cognitive ability. Many of the assessment tools used to elicit and quantify anxiety in patients with developmental disabilities depend on respondents having the verbal ability to identify emotion. Alternatively, caregivers may be asked to surmise the internal emotional states of a minimally verbal individual. Such conditions introduce variability that limits the reliability of an assessment tool. For instance, one caregiver might conclude that anxiety underlies a specific behavior whereas another may conclude frustration drives the behavior. A rating scale designed to measure irritability in populations with ID, such as the Aberrant Behavior Checklist (ABC) Irritability subscale, may capture some behavior described by caregivers as anxiety in AS but not capture other manifestations of anxiety such as a fear of crowds. It remains difficult to determine internal mood states and their relationship to behavior in individuals that are minimally verbal. It is critically important to better understand the emotion–behavior relationships in AS, however, due to the large impact such factors have on an individual's ability to function.

To better understand caregiver report of anxiety in AS, a combined qualitative and quantitative assessment evaluated a partially clinically referred sample of 50 children, adolescents and adults with AS. We compared caregiver responses to open-ended questions about behaviors they found concerning for anxiety and circumstances in which they occurred to items in rating scales of anxiety, irritability and hyperactivity commonly used in the ID subject population. We expected that caregiver descriptions of behavior concerning for anxiety would show better concordance with anxiety assessment measures than those of irritability and hyperactivity.

# Methods

## Ethical Considerations

The study was approved by the Human Research Committee institutional review board. Informed consent was provided by a parent for all subjects; no subjects were capable of providing assent due to impairments in cognitive function and expressive language.

## Subjects

Fifty children, adolescents and adults with AS and a primary caregiver met for a 2–4 h in-person interview with study staff for data collection. Subjects were recruited through materials to capture a "clinically referred" population including letters sent to outpatients and advertisements posted at an AS specialty clinic. Other subjects were recruited through materials to capture a "non-clinically referred" population including flyers on the "Current Research" page on the Angelman Syndrome Foundation website and advertisements at a biyearly family Angelman Syndrome conference. Twenty-three of the 50 subjects were seen for their study visits during the 2016 Angelman Syndrome Foundation annual meeting and others were seen for their visit at the AS specialty clinic. Subjects' caregivers were aware that assessment of anxiety was the focus of the study. Subjects' families were not asked how they heard about the trial so subjects could not be distinguished based on their methods of recruitment. The subject age, sex, and other demographic data, along with medical and family history of psychiatric diagnoses were obtained.

Inclusion criteria were a diagnosis of AS confirmed via genetic testing and availability of one of the subject's primary caregivers for the interview. Subjects were from 19 different states across the nation as well as Mexico and the United Kingdom and all interviewed caregivers were fluent in English. Interviews were conducted between 2016 and 2018.

## Qualitative Questions About Anxiety

Qualitative measures were designed to capture the phenomenon of anxiety as described by caregivers in their loved one with AS. Content analysis and constant comparative methods were used, deriving categories from caregiver responses

in the interviewer's notes. Caregivers were verbally asked a set of open-ended standardized questions designed to elicit symptoms of anxiety in their dependent with AS: (1) "Does your family member have anxiety?" (2) "Please describe what anxiety looks like in your family member?" (3) "During what situations or circumstances does anxiety occur in your family member?" The sole interviewer (CK) was a child/adolescent adult psychiatrist with experience working with patients with AS for treatment of behavioral concerns. Responses were written down in the interviewer's notes attempting to use caregivers' own words and reading back the response to the caregiver to allow opportunity for correction.

## Quantitative Rating Scales

The following rating scales were verbally administered (CK + JM) during the 2–4 h caregiver/subject clinical interview session:

### Anxiety, Depression and Mood Scale (ADAMS, Esbensen et al., 2003)

The ADAMS is a standardized instrument designed to measure mood and anxiety symptoms in patients with developmental disability. The measure is clinician rated based on caregiver report and contains subscales for mania, depression, social avoidance, generalized anxiety and obsessive/compulsive behavior. Each item is rated 0–3 with higher scores reflecting more severe symptoms. Subscales on generalized anxiety and social avoidance were the only two subscales used to measure anxiety.

### Pediatric Anxiety Rating Scale (PARS, Pediatric Psychopharmacology Anxiety Study Group, 2002)

The PARS is a clinician rated measure of anxiety in children and adolescents. Although not developed for subjects that are minimally verbal, previous studies have used the tool in mixed severity populations with developmental disability (Storch et al., 2012; Wood et al., 2015). The PARS assesses for the presence of symptoms in multiple anxiety domains including social interactions/performance situations, separation anxiety, generalized anxiety, specific phobia, acute physical signs & symptoms, and other. Caregivers rate anxiety symptoms from 0 to 5 on five separate variables: frequency, severity, avoidance and level of interference at home and in the community. Higher scores reflect greater severity. The 5-item total score was used to quantify overall anxiety as it is thought to be less sensitive to medication side effects. Cut-offs have been established for neurotypical youth (Ginsburg et al., 2011) and proposed for youth with ASD (Kerns et al., 2015).

### Anxiety Scale of the Child and Adolescent Symptom Inventory (CASI-Modified)

The CASI (Gadow & Sprafkin, 2005) is a caregiver completed questionnaire with items that map directly onto DSM diagnostic criteria for anxiety disorders in children and adolescents. Twenty anxiety specific questions were selected from the CASI based on previous use of this tool to assess anxiety in subjects with developmental disability (Sukhodolsky et al., 2008). Items are scored as 0 = never, 1 = sometimes, 2 = often, and 3 = very often. Total symptom severity scores are generated by tabulating all items. The CASI-modified contains items across seven anxiety disorders as follows: separation anxiety disorder is covered by 8 items; generalized anxiety disorder by 5 items; somatization and social phobia each by 2 items; and obsessive–compulsive disorder, specific phobia and panic disorder each by one item. Higher scores reflect greater severity. Responses were scored by the examiner based on interview with caregivers.

### Aberrant Behavior Checklist (ABC-Community, Aman & Singh, 1994)

The ABC is a caregiver rated instrument that measures psychiatric symptoms and behavioral disturbance in subjects with developmental disability across multiple domains. It was used to assess the severity of irritability and hyperactivity in subjects. The ABC has been used in subjects with AS (Clarke & Marston, 2000; Sadhwani et al., 2019). Items are scored on a scale from 0 to 3 and include subscales for Irritability, Social Withdrawal, Stereotypy, Hyperactivity and Inappropriate Speech. Higher scores indicate greater symptom severity.

### ADHD-Rating Scale IV (ADHD-RS-IV; DuPaul et al., 1998)

The ADHD-RS-IV is an 18-item scale that includes two domains: inattention and hyperactivity/impulsivity. Caregivers use a 0–3 scale to rate the subject with higher scores indicating greater symptom severity, with scores of 2–3 representing a significant symptom. The tool has been used to elicit symptoms of ADHD in subjects with autistic disorder in previous studies (Sinzig et al., 2009).

### Clinical Global Impression-Severity (CGI-S, Guy, 1976)

The CGI-S is a clinician administered rating scale wherein the evaluator rates overall disease severity on a 7-point scale from a rating of 1 (normal/not at all impaired) to 7 (among the most extremely impaired). One consistent

evaluator (CK) experienced in the care of patients with AS administered the CGI-S, rating overall disease severity of AS for each subject.

## Qualitative Response Coding

Based on the observed parental free responses on signs of anxiety and circumstances associated with anxiety, two study team members who administered the clinical interviews (CK and JM) collaboratively created categories for classification of signs and circumstances. Themes that made up coding categories were derived from review of the data and not established in advance. The written parental responses were then provided to two additional non-clinical study team members (CR and HS), who independently classified the responses into the newly created categories. Cohen's kappa quantified agreement between the two non-clinical team members for each category. Categories with estimated Cohen's kappa > 0.6 were retained for data analysis and comparison with items on quantitative rating scales. For categories with estimated Cohen's kappa > 0.6 but observed agreement < 100%, the principal investigator (CK) determined the final categorization used for results reporting. Three study team members, two clinical (CK and JM) and one non-clinical (CR), independently reviewed the quantitative rating scales to determine if each sign and circumstance category identified in the parental responses was covered by one or more items on each rating scale. Team members recorded the item numbers corresponding to coverage for each symptom and situation so that sources of disagreement could be identified. Two out of three rater agreement was used to determine if an anxiety rating scale had a question item corresponding to a specific caregiver concern.

## Data Analysis

Characteristics of the sample were tabulated using means and standard deviations (SDs) for continuous and ordinal variables and frequencies and percentages for categorical variables. Clinical ratings were summarized using means and standard errors (SEs), and means were compared between subgroups based on sex and genetic subtype using Welsh's t-test. Linear regression models with clinical rating as the outcome and linear and quadratic functions of age as predictors associated clinical ratings with age. Ninety-five percent confidence intervals (CIs) for prevalence estimates were calculated using Wilson's method.

Data analysis was conducted using SAS (version 9.4) statistical software. Cohen's kappa estimates were calculated using the psych package (Revelle, 2018) for R (version 3.5.2) statistical software. Statistical tests based on linear regression used robust (type HC3) variance estimation. All statistical tests were two-sided and performed at the test-wise alpha = 0.05 significance level.

## Results

### Demographics

The characteristics of the sample are summarized in Table 1. The mean age of the sample is 16.8 years (SD = 9.8 years), with a relatively even distribution of children, adolescents and adults. Participants were generally white (96%) and male (60%), coming from households making over $90,000 per year (67%). Half of caregivers held an advanced graduate or professional degree (50%). All participants had a CGI-S score between 4 and 6, with most having a score of 5 ("markedly ill") (68%). Participants with a deletion positive mechanism of genetic inheritance accounted for 68% of the sample which is representative of the overall AS population.

### Caregiver-Report Anxiety Symptoms and Circumstances

Ninety-two percent (46/50; 95% CI 81%, 97%) of participants with AS had informants who answered positively to the question "Does your family member have anxiety?" The four participants who answered "no" were not asked the two following open-ended questions describing anxiety and circumstances.

Categories for caregiver responses to the prompt "Please describe what anxiety looks like in your family member?" among the 46 caregivers who endorsed anxiety are shown by age group in Fig. 1, with categories displayed if they were reported by at least 10% of caregivers. "Aggression", included by 33/46 (72%; 95% CI 57%, 83%) caregivers overall, 14/19 (74%; 95% CI 51%, 88%) of caregivers of children 12 and under, 11/13 (85%; 95% CI 58%, 96%) of caregivers of children age 13–17, and 8/14 (57%; 95% CI 33%, 79%) caregivers of adults 18 and over, was the most commonly reported anxiety-like behavior overall and within each age group. In addition to response items identified in Fig. 1, four caregivers of subjects endorsed "banging," three caregivers each endorsed "pacing," "repetitive mouthing/chewing," and "repetitive requests," two caregivers each endorsed "hand wringing," "stereotypy," "distractibility" and "hypervigilance," and one caregiver each endorsed "body shaking," "myoclonus," "finger picking," "nail biting," "rubbing of skin," "confusion," and "euphoria/giddiness." "Myoclonus" and "body shaking" may represent the same clinical phenomenon but were kept separate as this was not certain. Three symptom categories were excluded due to poor agreement (Cohen's kappa estimates < 0.6): "social avoidance/shyness," "tiredness," and "angry facial expression."

**Table 1** Sample characteristics

| Mean age (SD) | Age | |
|---|---|---|
| | Number of participants in each age group (%) | |
| 16.8 (9.8) years | ≤ 12 years old | 21 (42) |
| | 13–17 years old | 13 (26) |
| | ≥ 18 years old | 16 (32) |
| Demographic information | | |
| Male | | 30 (60%) |
| White | | 48 (96%) |
| Hispanic | | 6 (13%[†]) |
| Parental information | | |
| Parental education (%) | | Annual household income[‡] (%) |
| High school graduate or GED | 3 (6) | < $20,000 | 1 (2) |
| Some college/post-high school or 2 years degree | 5 (10) | $20,001–$40,000 | 3 (6) |
| College degree | 17 (34) | $40,001–$60,000 | 2 (4) |
| Advanced graduate or professional degree | 25 (50) | $60,001–$90,000 | 10 (20) |
| | | ≥ $90,000 | 33 (67) |
| Angelman syndrome characteristics | | |
| CGI-S score of participants (%) | | Genetic subtype (%) |
| 4—moderately ill | 7 (14) | Deletion positive | 34 (68) |
| 5—markedly ill | 34 (68) | Uniparental disomy | 5 (10) |
| 6—severely ill | 9 (18) | Imprinting defect | 4 (8) |
| | | UBE3A mutation | 7 (14) |

*SD* standard deviation, *GED* general education diploma, *UBE3A* ubiquitin protein ligase E3A, *CGI-S* Clinical Global Impression-Severity
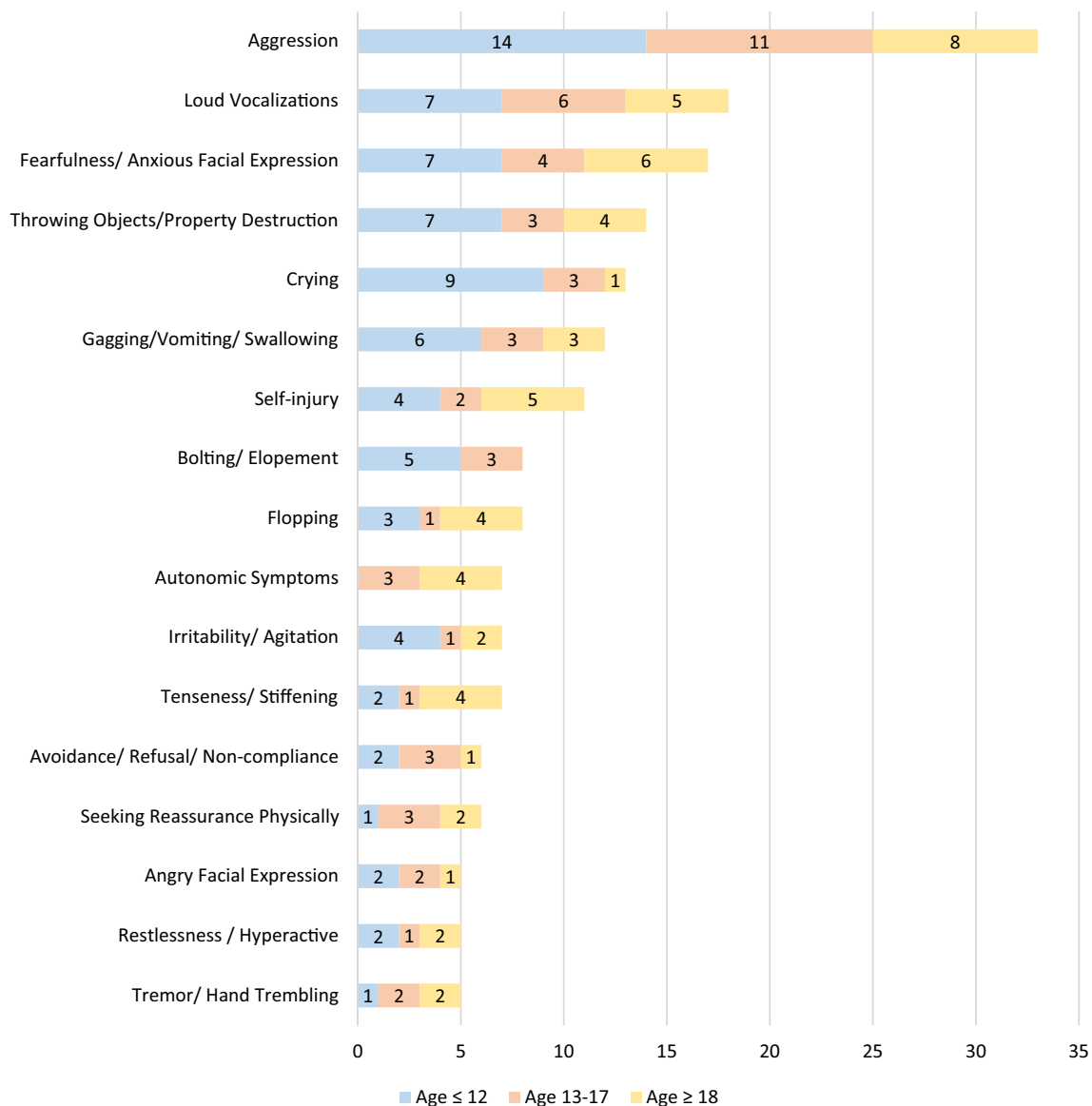
[†]4% did not report if the participant was Hispanic (n = 2)

[‡]2% did not report an annual household income (n = 1)

Categories for caregiver responses to the prompt "During what situations or circumstances does anxiety occur in your family member?" are shown in Fig. 2. "Separation from caregiver/parent", included by 24/46 (52%; 95% CI 38%, 66%) total caregivers and 11/19 (58%; 95% CI 36%, 77%) caregivers of children 12 and under who endorsed anxiety, was the most commonly reported circumstance associated with anxiety-like behaviors overall and for those age 12 and under. For children age 13–17 "crowds," included by 9/13 (69%; 95% CI 42%, 87%) caregivers, was the most frequently endorsed circumstance. For adults age 18 and over, "separation from caregiver/parent" and "new places/environment" were reported with the same frequency (7/14 caregivers; 50%; 95% CI 27%; 73%). In addition to response items identified in Fig. 2, four caregivers each endorsed "conflict/arguing," "caregiver's attention drawn from subject" and "sleeping alone/separating at night only," three caregivers each endorsed "fear of falling/unsteady terrain," "natural environment (i.e. heights)," "waiting," and "lack of sleep," two caregivers each endorsed "bathrooms/using restrooms," "clinginess/attached at the hip," "children," "overstimulation," "boredom/unstructured time" and "in pain/not feeling well," and one caregiver each endorsed "being hurried/rushing," "strong smells," "getting ready to eat," "hunger," "medication side effects," "menstruation" and "going to school program." Two categories were excluded due to poor agreement (Cohen's kappa estimates < 0.6): "performance anxiety/trying something new" and "other situational."

Direct description of the categories/themes used by researchers to code the caregivers' responses is listed in supplementary material (Online Resource 1). Researchers attempted to err on the side of creating more distinct categories to capture the maximum heterogeneity of caregiver response. The range of parent quotes coded as aggression included "hitting," "hair pulling," "kicks at others," "biting, pinching," "striking others," "head butting," "grabbing mom," and "aggression." The range of parent quotes coded as "separation from caregiver/parent" included "separation from mom," "separation from family," "separation from parents," "anticipated separation" and "goodbyes."
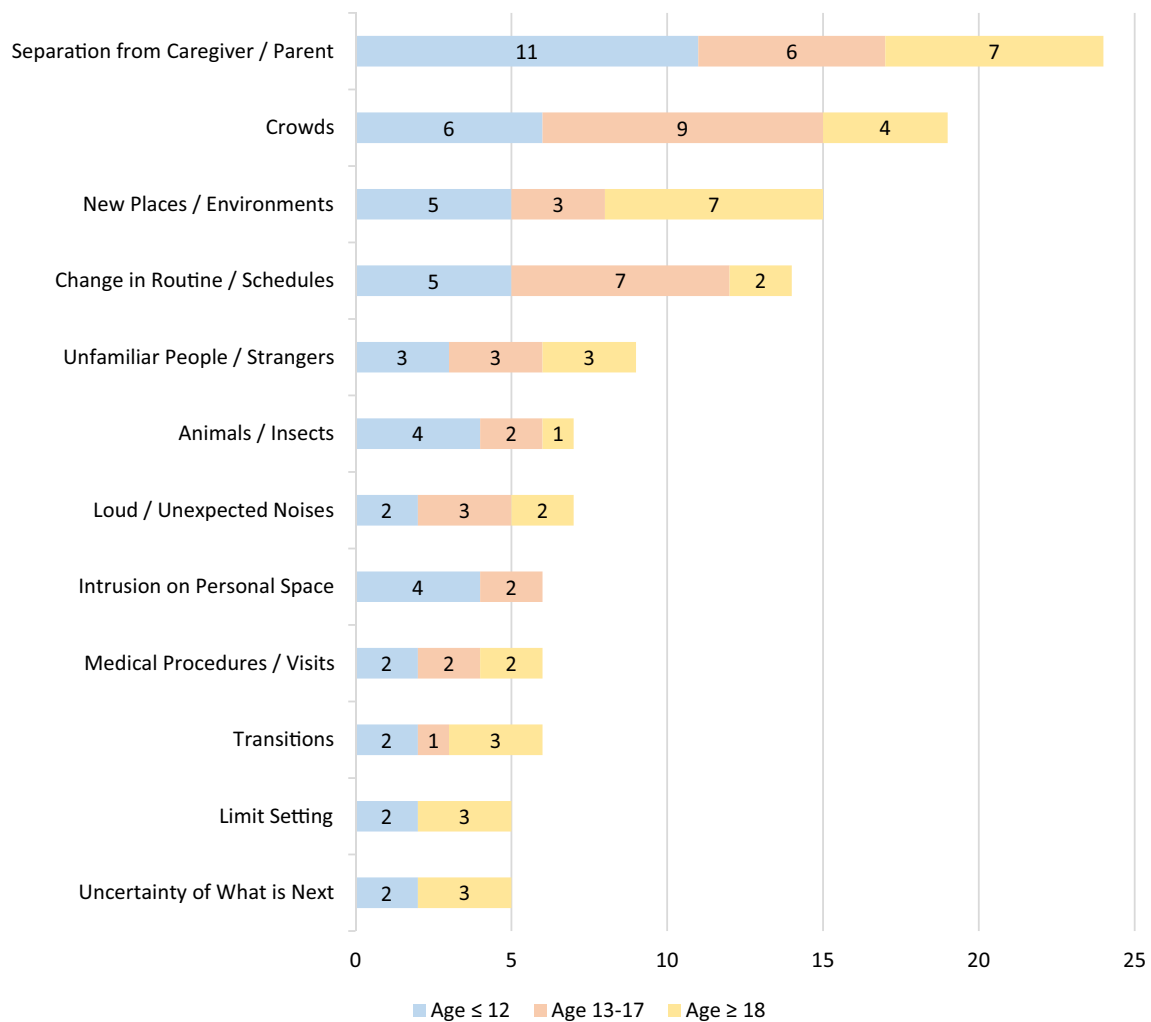
Fig. 1 Frequency of behaviors associated with anxiety by caregiver open-ended response. Four parents/caregivers denied anxiety in their dependent with AS

## Rating Scales, General Results

Mean (standard error) total anxiety rating scores on the three candidate anxiety rating scales by age group, sex, and mechanism of inheritance are presented in Table 2. The observed mean total score on the PARS (12.6; 95% CI 11.1, 14.1) was above proposed cutoffs for discriminating anxious from nonanxious neurotypical youth (11.5) and youth with autism spectrum disorder (7) (Ginsburg et al., 2011; Kerns et al., 2015); 33/50 subjects (66%; 95% CI 52%, 88%) had scores at or above the neurotypical cutoff, and 41/50 (82%; 95% CI 69%, 92%) had scores at or above the autism spectrum disorder cutoff. Total mean score on the ADAMS General Anxiety subscale (7.2; 95% CI 6.1, 8.4) was below the proposed cut-off (10) for anxiety disorder from a study of adults over the age of 50 years with intellectual disability (Hermans et al., 2012); 14/50 (28%; 95% CI 17%, 42%) met this threshold. Cut-offs were not available for the modified CASI, however, the lower limit of the confidence interval for the mean score (12.6; 95% CI 10.3, 14.9) was equal to the mean score (10.3) observed for a sample of clinically referred minimally verbal children and adolescents with autism spectrum disorder (Hallett et al. 2013).

**Fig. 2** Frequency of circumstance associated with anxiety by caregiver open-ended response. Four parents/caregivers denied anxiety in their dependent with AS

No pattern emerged by age or sex consistently across scales. Of note, the CASI-modified subscale items pertaining to separation anxiety were endorsed by caregivers for all three age groups including children (≤ 12 years), teens (13–17 years) and adults (≥ 18 years). When comparing mean total scores on anxiety rating scales by genetic molecular inheritance pattern, means for maternal deletion inheritance (the most common type) were compared to means for all other mechanisms of inheritance. Mean anxiety scores as assessed by the CASI-modified Total Anxiety score and the PARS 5-Item Total score were significantly lower for maternal deletion inheritance than other mechanisms of inheritance (CASI mean difference = − 7.3, 95% CI − 12.5, − 2.0, $t_{22}$ = 2.86, p = 0.009; PARS mean difference = − 3.1, 95% CI − 6.1, − 0.1, $t_{35}$ = 2.11, p = 0.04). Mean scores on the ADAMS General Anxiety scale were similar between mechanisms of inheritance (mean difference = − 0.1, 95% CI − 2.7, 2.5, $t_{28}$ = 0.08, p = 0.93).

Table 2 also presents mean ratings for additional clinical scales assessing symptoms other than anxiety. Subscale ratings for the ABC for hyperactivity (mean = 20.9, 95% CI 17.6, 24.3) and irritability (mean = 12.8, 95% CI 10.2, 15.4) were above mean scores from a community referred population of children with ID (hyperactivity mean ♀ = 8.1 and ♂ = 13.4; irritability mean ♀ = 6.6 and ♂ = 7.7) (Marshburn & Aman, 1992). Ratings were also high on the hyperactivity (mean = 11.6, 95% CI 9.9, 13.3) subscale of the ADHD-RS as compared to normative data in community populations for the scale (DuPaul et al., 1998). ADHD-RS scores decreased by age ($\chi_{(2)}^2$ = 9.05, p = 0.01), and ABC irritability (ABC-I) subscale scores were lower and social withdrawal subscale scores higher for those with a deletion positive mechanism

Table 2 Mean (SE) clinical ratings by age, sex, and mechanism of inheritance

| | Age (years) | | | | | Sex | | | Mechanism of inheritance | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| | All (N=50) | ≤12 (n=21) | 13–17 (n=13) | ≥18 (n=16) | p[a] | Males (n=30) | Females (n=20) | p[b] | Deletion positive (n=34) | Other (n=16) | p[b] |
| *Anxiety scales* | | | | | | | | | | | |
| ADAMS, general anxiety | 7.2 (0.6) | 6.3 (1.0) | 7.5 (0.7) | 8.2 (1.0) | 0.53 | 6.9 (0.7) | 7.7 (1.0) | 0.53 | 7.2 (0.7) | 7.3 (1.1) | 0.93 |
| *CASI-modified* | | | | | | | | | | | |
| Anxiety total | 12.6 (1.1) | 11.2 (1.6) | 15.5 (1.7) | 12.1 (2.4) | 0.008 | 13.1 (1.5) | 11.9 (1.8) | 0.59 | 10.3 (1.1) | 17.6 (2.3) | 0.009 |
| Separation anxiety | 4.3 (0.5) | 3.5 (0.7) | 5.8 (1.0) | 4.3 (1.1) | 0.07 | 4.5 (0.7) | 4.1 (0.8) | 0.71 | 3.7 (0.6) | 5.8 (1.0) | 0.54 |
| PARS 5-item total | 12.6 (0.8) | 11.2 (1.1) | 15.7 (0.8) | 11.9 (1.5) | 0.79 | 13.8 (1.0) | 10.7 (1.1) | 0.04 | 11.6 (0.9) | 14.7 (1.1) | 0.04 |
| *Other clinical ratings* | | | | | | | | | | | |
| *ABC* | | | | | | | | | | | |
| Irritability | 12.8 (1.3) | 12.3 (1.9) | 13.7 (2.2) | 12.8 (2.7) | 0.54 | 13.1 (1.8) | 12.4 (1.8) | 0.77 | 10.6 (1.3) | 17.4 (2.5) | 0.02 |
| Hyperactivity | 20.9 (1.7) | 23.7 (2.8) | 20.9 (2.6) | 17.3 (2.9) | 0.21 | 22.8 (2.1) | 18.2 (2.7) | 0.19 | 19.5 (2.0) | 24.0 (2.7) | 0.20 |
| Stereotypy | 3.3 (0.6) | 4.7 (1.1) | 2.1 (0.7) | 2.6 (0.8) | 0.17 | 3.8 (0.8) | 2.7 (0.9) | 0.35 | 3.9 (0.8) | 2.2 (0.6) | 0.11 |
| Social withdrawal | 3.9 (0.6) | 3.3 (0.9) | 3.5 (1.1) | 5.1 (1.4) | 0.07 | 4.4 (0.9) | 3.3 (0.9) | 0.40 | 4.7 (0.9) | 2.4 (0.7) | 0.04 |
| Inappropriate speech | 1.0 (0.3) | 0.7 (0.3) | 1.2 (0.5) | 1.3 (0.5) | 0.54 | 1.0 (1.0) | 1.1 (0.5) | 0.81 | 0.8 (0.3) | 1.5 (0.4) | 0.19 |
| ADHD-RS, hyperactivity[c] | 11.6 (0.9) | 13.9 (1.4) | 11.3 (1.3) | 8.9 (1.4) | 0.01 | 12.8 (1.0) | 9.9 (1.5) | 0.11 | 10.8 (1.0) | 13.4 (1.6) | 0.18 |

Scale ranges are 0–21 for ADAMS General Anxiety, 0–60 for CASI Anxiety Total, 0–24 for CASI Separation Anxiety, 0–25 for PARS 5-Item Total, 0–45 for ABC Irritability, 0–48 for ABC Hyperactivity, 0–21 for ABC Stereotypy, 0–48 for ABC Social Withdrawal, 0–12 for Inappropriate Speech, and 0–27 for ADHD-RS Hyperactivity

*SE* standard error, *ADAMS* Anxiety, Depression, and Mood Scale, *CASI* Child and Adolescent Symptom Inventory, *PARS* Pediatric Anxiety Rating Scale, *ABC* Aberrant Behavior Checklist, *ADHD-RS* ADHD Rating Scale

[a]Tests for association with age are based on linear regression with linear and quadratic functions of age as predictors and robust standard errors

[b]Welch's t-test compared means between males and females and genetic subtypes

[c]Mean ratings for the inattention subscale are not reported because 37/50 (74%) of participants considered 2 or more items not applicable

of inheritance (ABC-I subscale mean difference $= -6.8$, 95% CI $-12.7$, $-1.0$, $t_{24} = 2.41$, $p = 0.02$; ABC social withdrawal subscale mean difference $= -2.3$, 95% CI $-4.5$, $-0.6$, $t_{47} = -2.07$, $p = 0.04$).

## Rating Scales, Concordance with Caregiver Report

Tables 3 and 4 present concordance of caregiver reported symptoms and circumstances with items on the rating scales. Disagreement among the three reviewers about whether caregiver concerns had a corresponding item within the anxiety rating scales was common.

Based on agreement of two or three raters, 11 of the 23 (48%) caregiver-report symptom categories endorsed by two or more caregivers were not covered on any of the anxiety scales. These 11 included the three symptom categories reported by the greatest percentage of caregivers. Eight (35% of all categories) of the 11 were covered by at least one of the non-anxiety rating scales, of which the most commonly endorsed categories were "aggression," "loud vocalizations," and "self-injury," all covered by items on the ABC-I subscale. The remaining three categories (13% of all categories), "fearfulness/anxious facial expression," "throwing objects/property destruction," and "flopping" were not covered by items on any of the scales included in the study.

Of the 12 symptom categories (52%) that were covered by items included on one or more of the anxiety rating scales, seven (30% of all categories) were covered by items on one or more anxiety rating scales only. These seven were "gagging/vomiting/swallowing," "bolting/elopement," "tenseness/stiffening," "autonomic symptoms," "seeking reassurance physically," "tremor/hand trembling," and "pacing." Of the five symptom categories (22% of total) covered both by one or more anxiety rating scales and one or more non-anxiety rating scales, the most commonly endorsed were "crying," covered by the ABC-I subscale and the ADAMS Depressed Mood scale, "irritability/agitation," covered by the ABC-I subscale, and "avoidance/refusal/noncompliance," covered by the ABC Irritability and Hyperactivity subscales and the ADHD-RS hyperactivity subscale.

For 15 of the 23 symptom categories (65%), all three raters agreed about coverage of the category on anxiety and non-anxiety scales (though not necessarily about coverage on each individual scale). Of these 15 categories, five were covered only by items on anxiety scales, four were covered only by items on non-anxiety scales, five were covered by items on both anxiety and non-anxiety scales, and one ("flopping") was not covered by any item.

Based on agreement of two or three raters, 12 of the 25 (48%) caregiver-reported circumstance categories endorsed by at least two caregivers were covered by one or more items on the anxiety scales, but no items on the non-anxiety scales. These 12 covered categories included three of the five most commonly endorsed: "separation from caregiver/parent," "crowds," and "unfamiliar people/strangers." The remaining 13 circumstance categories (52%) were not covered by items on either the anxiety or non-anxiety scales. The three most commonly endorsed categories that were not covered were "new places/environments," "change in routine/schedules," and "loud/unexpected noises."

For the 12 caregiver-endorsed circumstance categories covered by the anxiety scales, all three raters agreed that the category was covered by the anxiety scales only for nine of them (36% of total categories). However, one rater disagreed about coverage for eight of the 13 situations not covered by any scale. Five disagreements were about coverage on an anxiety scale, two were about coverage on a non-anxiety scale, and one was about coverage on both kinds of scales. Overall, though no caregiver-endorsed situation was associated with one or more items on non-anxiety rating scales by two or more raters, six of the 25 (24%) categories were associated with one or more non-anxiety scale items by only one rater.

## Discussion

The goal of this study was to report on the behavioral expression of anxiety in AS as described by caregivers and the applicability of three anxiety rating scales commonly used in patients with developmental disorders. The study used qualitative questions to elicit behavioral description of parent/caregiver concerns with respect to anxiety in children, adolescents and adults with AS. Specific behaviors that may represent manifestations of anxiety and the circumstances in which they occur were sought in individuals with AS unable to describe their internal mood states. Three anxiety rating scales previously used in subjects with developmental disability were administered and evaluated for their coverage of caregivers' conceptualization of anxiety. While not definitive, the results of the study may prove useful to caregivers, clinicians and researchers attempting to identify, diagnose, treat and better understand anxiety in individuals with AS.

Separation from caregiver was the most common circumstance associated with concern for anxiety among the parents/caregivers. Separation from preferred caregivers was also the most common precipitant of anxiety in AS found by Wheeler et al. (2019) in their development of a parent-rated anxiety questionnaire for AS. Similarly, their assessment instrument contains items for multiple other parental concerns identified in the current study such as "fear of crowds," "trembling," and "clingy." The overlap in behavioral symptoms suggests this new scale may be able to capture caregiver concern about anxiety. That the modified CASI identified symptoms of separation anxiety disorder in adolescent and adult subjects indicates this phenomenon in

**Table 3** Anxiety symptoms endorsed by parent report, in order of percent endorsement

| | Anxiety scales and subscales | | | Non-anxiety scales and subscales | | | | |
|---|---|---|---|---|---|---|---|---|
| | ADAMS General or social anxiety | CASI General or separation anxiety | PARS | ABC-I | ABC-H | ABC Other | ADAMS Other | ADHD-RS |
| Aggression | | | * | | | | | |
| Loud vocalizations | | | | | * | | | |
| Fearfulness/anxious facial expression | * | * | * | | | | | |
| Throwing objects/property destruction | | | * | * | | | | |
| Crying | | | | | | | | |
| Gagging/vomiting/swallowing | | * | | | | | | |
| Self-injury | | | | | | | | |
| Bolting/elopement | | | | | * | | | * |
| Flopping | | | | | | | | |
| Irritability/agitation | | * | | | | | | |
| Tenseness/stiffening | | | | | | | | |
| Autonomic symptoms | * | * | | | | | | |
| Avoidance/refusal/non-compliance | * | * | * | * | | | | * |
| Seeking reassurance physically | | | | | | | | |
| Tremor/hand trembling | | | * | | | | | |
| Restlessness/hyperactive | * | | | | | | | |
| Banging | | | * | * | | | | |
| Pacing | * | * | * | | * | | * | * |
| Repetitive mouthing/chewing | | | | | | | * | |
| Repetitive requests | | | | | * | * | | |
| Hand wringing | | | | | | * | | * |
| Stereotypy | | | | | | | * | |
| Distractibility | | | | | | | | |
| Hypervigilance | * | | | | | | | |

**Table 3** (continued)

*ADAMS* Anxiety, Depression, and Mood Scale, *CASI* Child and Adolescent Symptom Inventory, *PARS* Pediatric Anxiety Rating Scale, *ABC-I* Aberrant Behavior Checklist, Irritability subscale, *ABC-H* Aberrant Behavior Checklist, Hyperactivity subscale, *ABC Other* Aberrant Behavior Checklist, Stereotypy, Social Withdrawal, and Inappropriate Speech subscales, *ADAMS Other* ADAMS Manic/Hyperactive Behavior, Depressed Mood, and Compulsive Behavior subscales, *ADHD-RS* ADHD Rating Scale

Symptom categories endorsed by two or more caregivers are included. Shading indicates the symptom was covered in the corresponding scale according to two or more reviewers. Stars indicate two out of three reviewer agreement only

patients with AS may frequently extend past childhood when separation anxiety would be expected to be rare. In fact, the majority of parent reported symptoms and situations were represented across age groups. Notable exceptions were the lack of autonomic symptoms in children 12 and under and low frequency of crying in adults 18 and over. However, our sample size does not allow us to draw definitive conclusions about differences in prevalence of individual symptoms and situations by age.

Aggression was the most common behavioral concern presented by caregivers as representative of anxiety. This is consistent with previous studies (Sadhwani et al., 2019; Wink et al., 2015) that have identified aggression as a common concern. Similarly, self-injury was identified by 11 out of 46 (24%) caregivers but at lower rates than aggression (33/46, 72%). Our study did not have the statistical power to draw definitive conclusions about how mean total scores on anxiety rating scales were affected by differences in sex, age or genetic subtype. However, similar to previous studies (Buntinx et al., 1995; Sadhwani et al., 2019), we observed decreasing hyperactivity levels (on the ADHD-RS) with increasing age and less irritability (on ABC-I) in subjects with maternal deletion compared with the other genetic subtypes. The results of our study highlight the importance of ongoing use of rating scales that capture aggressive and self-injurious behavior when examining behaviors of parental concern in AS populations.

Despite the relevance of the ABC-I subscale in this population, many behaviors and circumstances reported by parents in our study were not captured by question items on the ABC. This raises concerns about the content validity of the ABC to capture parental concerns of anxiety when used without additional measures. Moreover, it should not be assumed that aggression is synonymous with the construct of irritability as measured by the ABC-I subscale. Aggression in patients with AS may serve to seek or maintain attention from a preferred caregiver (Strachan et al., 2009) which may represent a different construct than "tantrums" or "melt-downs" in response to limit setting. This may explain why one large study in AS failed to find elevations in the ABC-I subscale as compared to community ID populations (Clarke & Marston, 2000).

The results from anxiety rating scales used in this study should be interpreted with caution. Subjects' mean total score on the PARS is above proposed cutoffs for high risk anxiety populations (Ginsburg et al., 2011; Kerns et al., 2015) and below proposed cutoffs on the ADAMS (Hermans et al., 2012). Our findings argue that the PARS is better for capturing parental concerns for anxiety than the ADAMS which has no question items for separation anxiety. A limitation of rating scales is the inclusion of items that ask parents to judge internal mood states. Furthermore, it is not clear that proposed cutoffs are appropriate for use in the minimally verbal subject population. Our study found higher mean scores on the PARS and modified CASI in subjects with non-deletion mechanisms of inheritance as compared to deletion mechanisms of inheritance. This is consistent with anxiety severity differences found by Wheeler et al. (2019) and the finding mirrors the lower levels of irritability seen in deletion mechanisms in inheritance.

The PARS was superior for content validity as compared to other rating scales in terms of capturing caregivers' concept of anxiety. The PARS covered the highest number of "anxiety symptoms" (11) and "anxiety circumstances" (11) reported by caregivers. The trade-off for this benefit was that the PARS included many question items more appropriate for subjects with verbal language abilities, for example many questions pertaining to the content of worries. Indeed, there were many occasions when the three evaluators disagreed as to whether a parental concern for anxiety had a corresponding question item in an anxiety rating scale. In the design of our study we chose three anxiety rating scales used commonly in previous studies of patients with developmental disability. However, the challenges with content validity and applicability for the AS population highlight the need for assessments tools specific for AS to capture caregivers' concept of anxiety.

Our results highlight the challenge of separating symptoms concerning for anxiety and symptoms concerning for irritability in a minimally verbal population. Many symptoms and circumstances reported by the caregivers are not reflected in the items on the anxiety scales and are reflected on the non-anxiety scales. Disagreement among the three reviewers about whether caregiver concerns had a corresponding item within the anxiety rating scales was common. This raises the possibility that results would have varied for a different set of raters. Adding to this challenge, some of the symptoms described by parents as concerning for anxiety were physiological ("autonomic symptoms," "tremor") and may be difficult to evaluate in the context of taking

**Table 4** Anxiety circumstances endorsed by parent report, in order of percent endorsement

| | Anxiety scales and subscales | | | Non-anxiety scales and subscales | | | | |
|---|---|---|---|---|---|---|---|---|
| | ADAMS General or social anxiety | CASI General or separation anxiety | PARS | ABC-I | ABC-H | ABC Other | ADAMS Other | ADHD-RS |
| Separation from caregiver/parent | | | | | | | | |
| Crowds | * | | | | | * | | |
| New places/environments | | * | | | | | | |
| Change in routine/schedules | | | | | | | | |
| Unfamiliar people/strangers | * | * | | | | * | | |
| Animals/insects | | | | | | | | |
| Loud/unexpected noises | | * | * | | | | | |
| Intrusion on personal space | | | * | | | | | * |
| Medical procedures/visits | | | | | | | | |
| Transitions | | | * | | | | | |
| Uncertainty of what is next | | | * | | | | | |
| Limit setting | | | | | * | | | |
| Conflict/arguing | | | | | | | | |
| Caregiver's attention drawn from subject | | * | * | * | | | | |
| Sleeping alone/separating at night only | | * | | | | | | |
| Fear of falling/unsteady terrain | | * | * | | | | | |
| Natural environment | | * | | | | | | |
| Waiting | | | | | * | | | * |
| Lack of sleep | | | * | | | | | |
| Bathrooms/using restrooms | | | | | | | | |
| Clinginess/attached at the hip | | | | | | | | |
| Children | | | * | | | | | |
| Overstimulation | | | | | | | | |
| Boredom/unstructured time | | | | | | | | |
| In pain/not feeling well | | | | | | | | |

**Table 4** (continued)

*ADAMS* Anxiety, Depression, and Mood Scale, *CASI* Child and Adolescent Symptom Inventory, *PARS* Pediatric Anxiety Rating Scale, *ABC-I* Aberrant Behavior Checklist, Irritability subscale, *ABC-H* Aberrant Behavior Checklist, Hyperactivity subscale, *ABC Other* Aberrant Behavior Checklist, Stereotypy, Social Withdrawal, and Inappropriate Speech subscales, *ADAMS Other* ADAMS Manic/Hyperactive Behavior, Depressed Mood, and Compulsive Behavior subscales, *ADHD-RS* ADHD Rating Scale

Circumstance categories endorsed by two or more caregivers are included. Shading indicates the symptom was covered in the corresponding scale according to two or more reviewers. Stars indicate two out of three reviewer agreement only

medications. These challenges highlight the need for the development of question items for anxiety in AS that are focus-group tested to capture caregiver concern. Circumstance items tended to be more specific to anxiety scales and may be a promising approach to measuring anxiety in individuals with AS.

Participants in this study were predominantly white and highly educated. It is possible that race, ethnicity, and socioeconomic status may impact parent report of behavioral concerns in patients with AS in ways this study doesn't capture. Future research in this area should prioritize diversity and more than fifty subjects to ensure findings are applicable to the larger population of individuals with AS.

In our study we used qualitative questions to capture caregivers' description of behaviors concerning for anxiety and their precipitating circumstances. Some additional desirable qualitative methods were not used. These include pilot testing open ended questions prior to usage, tape recording interviews, allowing caregivers to give feedback on the coding scheme, and performing additional measures to test data saturation. These methods should be considered by future studies in order to reduce the risk that the researchers' own concept of anxiety may bias results.

It is possible that parents misunderstood questions about anxiety and instead described general behavioral concern in their dependent with AS. We attempted to address this by describing the study to caregivers as specifically addressing "Anxiety in Angelman Syndrome" and worded questions to elicit qualitative data consistently to emphasize anxiety. Conversely, this study design may have biased caregivers to score higher on rating scales for anxiety as compared to rating scales for other behavioral symptoms. Anxiety scale question items are worded to ask about the appearance of symptoms in the context of anxiety, the explicitly stated purpose of the study.

We anticipate the results of the study can be used to develop clinician as well as caregiver rated scales for behavioral concerns in patients with AS that do not rely on suppositions regarding internal mood state. Given the significant impact of mood and behavioral concerns on daily

functioning and quality of life, we believe there is great value in studying the behavioral and emotional challenges of patients with AS rather than conceding to the current limitations of assessment instruments available to minimally verbal populations.

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