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Angelman Syndrome in Adulthood

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Abstract

Angelman syndrome (AS) is a neurogenetic disorder. The goal of this study was to investigate the primary health issues affecting adults with AS and to further characterize the natural history and genotype-phenotype correlations. Standardized phone interviews with caregivers for 110 adolescents and adults with AS were conducted. The impact of age, gender, and genotype on specific outcomes in neurology, orthopedics, internal medicine, and psychiatry were investigated. The mean age of individuals with AS was 24 years (range 16–50y). Active seizures were present in 41% of individuals, and 72% had sleep dysfunction. Significant constipation was present in 85%, and 32% were overweight or obese, with obesity disproportionately affecting women. Scoliosis affected 50% with a mean age at diagnosis of 12 years, and 24% of those diagnosed with scoliosis required surgery, an intervention disproportionately affecting men. Sixty-eight percent were able to walk independently, and 13% were able to speak 5 or more words. Self-injurious behavior was exhibited in 52% of individuals. The results of this study indicate that epilepsy severity may assume a bimodal age distribution: seizures are typically most severe in early childhood but may recur in adulthood. While late-adolescent and adult sleep patterns were improved when compared to the degree of sleep dysfunction present during infancy and childhood, the prevalence of poor sleep in adults remained quite high. Primary areas of clinical management identified include the following: seizures, sleep, aspiration risk, GERD, constipation, dental care, vision, obesity, scoliosis, bone density, mobility, communication, behavior, and anxiety.

Keywords

Angelman syndrome; adults; seizures; behavior; self-injury

INTRODUCTION

Angelman syndrome (AS) is a neurogenetic disorder clinically characterized by features of epilepsy, poor sleep, ataxia, frequent smiling/sociability, and scoliosis. Individuals typically have severe cognitive impairment and limited expressive speech. Eighty to 90% of individuals with AS develop seizures, which may include multiple semiologies [Thibert et al., 2009]. Children may have gross motor delays, sitting at an average age of 20.5 months

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and walking at 3.7 years, and 10% of individuals with AS do not develop the ability to walk independently [Williams et al., 2010]. Although many children with AS have significant receptive language skills, the majority of individuals gain very few words [Jolleff et al., 1993, Williams 2005].

AS has an estimated incidence of approximately 1 in 12,000–20,000 live births, but life expectancy by epidemiologic measures remains unknown [Williams et al., 2010]. The molecular etiology of AS is a loss of function of the maternally inherited *UBE3A* gene, which codes for E6AP-3A ubiquitin protein ligase [Knoll et al., 1989, Albrecht et al., 1997, Kishino et al., 1997]. There are 4 molecular subtypes of AS, and deletion of the 15q11.2–13.1 region (Del) is the most common. Mutation of the maternal *UBE3A* gene, paternal uniparental disomy (UPD), and imprinting defects also cause an AS phenotype [Knoll et al., 1989, Malcom et al., 1991, Buriting et al., 1995, Kishino et al., 1997, Matsuura et al., 1997].

The first individuals to undergo genetic testing for AS in early childhood during the late 1980s are now young adults. Over the past 3 decades, there has been significant progress in diagnostics and care for adults with AS. Drs. Jill Clayton-Smith and Charles Williams were the pioneers of this field and among the first to characterize the adult phenotype and to study the impact of age [Williams et al., 1982, Clayton-Smith et al., 1993]. In 1984, Bjerre et al. contributed a case report of a 75-year-old patient with a clinical diagnosis of AS from Sweden who was described to be in generally good health [Bjerre et al., 1984]. The case, which features the oldest patient reported in the literature, played a pivotal role in AS research, as it provided some evidence that the disease was not a degenerative process [Bjerre et al., 1984, Sandanam et al., 1997]. Today, research on aging in the setting of AS continues to advance, and quality of life for the majority of individuals with AS has been found to be maintained into adulthood [Bjerre et al., 1984, Clayton-Smith et al., 2003]. In this study, investigators aimed to further characterize the natural history and current clinical manifestations of AS in adulthood.

MATERIALS AND METHODS

This institutional review board-approved study conducted at the Massachusetts General Hospital investigated AS in adulthood with subject data collected by a series of phone interviews with primary caregivers. Subject recruitment information was sent by e-mail to close to 1,120 addresses from the Angelman Syndrome Foundation (ASF) database. Study information was also posted to the “Current Research” page on the ASF website. Subject inclusion criteria were as follows: diagnosis of AS by a physician, 16 years of age or older, interviewee self-identification as one of the subject’s primary caregivers. Subjects were from 34 states in the United States, Puerto Rico, and 2 Canadian provinces. All interviews were completed over a period of 4 months in 2011. The impact of age, gender, and genotype on specific outcomes in neurology, internal medicine, orthopedics, and psychiatry were investigated. The interview consisted of a set of standardized questions developed by the investigators. In addition, there were several designated points in the interview during which participants were asked to describe additional pertinent medical history not specifically covered in the standardized questions. The investigators were contacted by 3 families with a son or daughter with AS who had previously died. These caregivers completed the

standardized interview, and their responses were included in the full data set. In one case, the subject had died prior to an AS diagnosis; however, his sibling, who had a similar phenotype, was subsequently diagnosed with AS, identified by a mutation in *UBE3A*. Both siblings were therefore included and reported as having the same associated genotype. One subject had a diagnosis of mosaicism (unknown to investigators if the individual's genotype was an imprinting defect or a chromosomal type). Because she was a genotypic outlier, her case data were not included in the full cohort analyses.

The interview included a modified Early Childhood Epilepsy Severity Scale (E-Chess) [Humphrey et al., 2008]. The score was modified from the rubric initially described by Humphrey et al. in two ways: (a) "time period over which seizure occurred" was eliminated, given that the full cohort would receive the same score ("more than 6 months"); (b) "response to treatment" was reduced to 1 of 2 possible responses, "complete cessation" or "partial/no improvement" [Humphrey et al., 2008]. Caregivers were asked the age range during which seizures were most severe, and the median age was calculated. Episodes reported by caregivers as seizures were recorded as such; however, in many cases, the patients had not recently undergone electroencephalography (EEG).

Categorical data were presented as frequencies and compared using a 2-sided Fisher exact test. Continuous data were presented as mean ± standard deviation (SD). Covariate impact was measured by linear regression for continuous variables and logistic regression for nominal or ordinal variables. Multivariate regression analyses assessing gender and age included the full cohort (n=109). Univariate regression analyses assessing genetic impact included the cohort of individuals with a known genotype (Del, *UBE3A*, UPD) (n=93). Alpha was set at 0.05.

RESULTS

Cohort demographic data are presented in Table I. There were no statistically significant differences in age or gender between the known genotype (n=93) cohort and the subset of individuals with a clinical diagnosis or unknown genotype (n=16). Epilepsy and sleep data are reported in Tables II and III. There was no association between having active seizures and sleep problems (p=0.506) and/or co-sleeping (p=0.423). Five cases were reported to have prolonged episodes of rhythmic shaking of their arms, legs, face, or whole body (F22, F24, M24, M29, M49). Events occurred only when the individuals were awake, and maximum duration ranged from 1 to 6 hours. Event frequency ranged from 3 events per year to 2 events per day prior to treatment. Triggers included menstruation, systemic illness, constipation, exhaustion, stress, and anger.

Table IV presents internal medicine data. In the treatment of gastroesophageal reflux disease (GERD), 6 individuals underwent Nissen fundoplication: 4 had the procedure before the age of 2 years (F18, M21, M24, M32), and 2 had the procedure in their twenties (F24, M20). Four individuals had a history of gastroparesis (F21, F26, M17, M24). From an ophthalmologic perspective, F32 had extreme sensitivity to bright sun in her eyes; M26 developed keratoconus from persistent eye rubbing behavior; M32 was legally blind; and M24 had been diagnosed with cortical visual impairment. Tables V and VI present

anthropomorphic, orthopedic, mobility, and exercise data. Mean female height was 1.55 meters (sd: 0.084), and male height was 1.68 meters (sd: 0.099). Scoliosis was not associated with the independently mobile (p=0.816) or non-ambulatory (p=0.242) covariates.

Table VII presents data on communication and activities of daily living. Recurrent themes included the following: significant receptive language skills; typically able to communicate needs and wants using direct objects; highly sensitive to voice tone, specifically when aggressive or confrontational; a demonstrated ability to make meaningful connections with people, despite limited expressive language. Table VIII presents data on challenging behaviors in AS. The most commonly cited challenging behaviors were as follows: pulling others' hair (31%), hitting others (28%), yelling/screaming (21%), pulling on others (19%), dropping to the floor (18%), hugging too tightly and/or hugging strangers (17%), biting others (17%), chewing clothing (16%), chewing plastic (13%), pinching others (13%), hitting self (12%), biting nails (12%), kicking others (11%), banging head (10%). The majority of the AS cohort had never been evaluated by a psychiatrist; however, 46% (n=48) of caregivers felt that the individual had shown some signs of anxiety. Alternatively, only 2% of caregivers endorsed possible signs of depression.

M16 died in a drowning accident in the home. F24 died of pneumonia in the setting of severe seizures, and M38 died of metastatic lung cancer. Of the interviewed caregivers, 55% endorsed having back pain or other chronic pain symptoms. Thirty-seven percent endorsed feelings of isolation, and 19% were unable to identify a source of emotional support. Caregivers endorsed significant anxiety about the future: 30% described the anxiety as moderate, and 18% described it as severe.

DISCUSSION

The results of this study were limited by the interview design, which did not include a physical exam by a physician or medical record review. Given that participants were recruited through the ASF, this study may have a response bias toward a more severe medical phenotype. Additionally, a larger proportion of the study cohort was living with parents (75%) compared to a clinical series of adults with AS (ages 16 to 40 years) reported by Clayton-Smith et al., in which about half the study cohort continued to live with parents [Clayton-Smith et al., 2001]. The study cohort provided a relatively close representation of the genotypic distribution seen in the general AS population, with the exception of a mildly increased UPD subset and an absence of any subjects with an imprinting defect: Del 65–75% (study 68%), *UBE3A* 5–11% (8%), imprinting defect 3% (0%), UPD 3–7% (9%) [Williams et al., 2010].

Neurology

Epilepsy is one of the primary health concerns for adults with AS and is the leading cause of hospitalization across age groups [Thomson et al., 2006]. The literature suggests that the period of greatest epilepsy severity is typically early childhood and that seizures often improve over the first decade and a half of life [Matsumoto et al., 1992, Clayton-Smith et al., 1993, Smith et al., 1996, Viani et al., 1995, Valente et al., 2006, Thibert et al., 2009, Pelc et

al., 2008, Uemura et al., 2005]. According to the literature, individuals with AS may then experience a quiet period or seizure remission through their late teens and early twenties, followed by a possible recurrence of seizure severity during their third and fourth decades [Clayton-Smith et al., 1993, Thibert et al., 2009, Laan et al., 1996, Laan et al., 1997, Clayton-Smith et al., 2001, Williams et al., 1982, Matsumoto et al., 1992, Moncla et al., 1999, Thomson et al., 2006, Buckley et al., 1998]. Consistent with prior series, the vast majority of this study cohort (94%) had a history of seizures [Thomson et al., 2006, Smith et al., 1996, Laan et al., 1997], and the majority of adults (77%) experienced their most severe seizures before age 11. We found a similarly bimodal distribution of seizure severity, with decreased rates of seizure-freedom and increased seizure severity scores, for individuals over 25 years compared to those 16 to 20 years of age.

Previously, across age groups, the Del genotype has been found to confer the most severe epilepsy phenotype, followed by *UBE3A*. The UPD population has been found to exhibit the least severe epilepsy phenotype [Minassian et al., 1998, Clayton-Smith et al., 2003, Lossie et al., 2001, Moncla et al., 1999]. In our study we found that individuals with *UBE3A* had significantly decreased odds of developing seizures under the age of 3 compared to the Del cohort, and no one with this genotype had more than one seizure semiology. The UPD cohort had significantly decreased odds of developing epilepsy compared to the Del cohort, and no one with this genotype experienced daily seizures.

With an EEG correlate, sustained shaking episodes without loss of consciousness have been described in individuals with AS as myoclonic status in non-progressive encephalopathy (MSNE) [Pelc et al., 2008, Dalla Bernardina et al., 1985, Elia et al., 2009, Valente et al., 2006, Guerrini et al., 1996, Ogawa et al., 1996, Dalla Bernardina et al., 1995, Viani et al., 1995]. Without an EEG correlate, similar episodes of sustained shaking have also been clinically identified in AS and have been described as cortical myoclonus [Guerrini et al., 1996, Stecker et al., 2003, Pelc et al., 2008, Guerrini et al., 2003]. Based on clinical experience with other adult AS patients, the investigators hypothesize that the shaking episodes described by the caregivers in this study are likely consistent with cortical myoclonus; follow-up studies that incorporate electrophysiological data are being conducted to further characterize this pathology in the adult AS population.

AS may also confer significant sleep problems [Walz et al., 2005, Conant et al., 2009]. The pathophysiologic mechanism of epilepsy and sleep dysfunction in AS may be secondary to haploinsufficiency and decreased expression of a GABA receptor gene, specifically GABRB3 on 15qll-13, adjacent to *UBE3A* [Minassian et al., 1998, Lossie et al., 2001, DeLorey et al., 1996, Nolt et al., 2003]. While significant sleep problems during infancy and early childhood are nearly universal among individuals with AS, it has been previously reported that sleep dysfunction may improve with age [Smith et al., 1996, Miano et al., 2004, Clayton-Smith et al., 2001, Sandanam et al., 1997]. The results of this study support this hypothesis: the majority of caregivers described current sleep patterns as improved when compared to the degree of sleep dysfunction experienced during infancy and childhood. The prevalence of poor sleep in adults, however, remained quite high, affecting the majority (72%) of the cohort.

Our results indicate sleep dysfunction in multiple domains for adults with AS, including increased sleep latency, night waking, and daytime sleepiness. Consistent with prior rates of increased sleep latency (48–50.5%) across age groups [Walz et al., 2005, Conant et al., 2009], 65% of this study's cohort had trouble falling asleep. Sandanam et al. found that 54% of adults (Del) had significant nighttime waking, and, similarly, 66% percent of this cohort was reported to have difficulty staying asleep [Sandanam et al., 1997]. Prior studies have shown a decreased need for sleep in children with AS [Conant et al., 2009, Clayton-Smith et al., 1993]. However, our results indicate a reported average of 7.4 hours of sleep per night and some evidence of daytime sleepiness. These findings suggest that adults may not show the same degree of decreased need for sleep as younger individuals [Clayton-Smith et al., 1993]. The interaction between epilepsy and sleep dysfunction is not well understood, but these pathologies often coexist in the general epilepsy population, as well as in the AS population [Conant et al., 2009]. In this study, however, ongoing seizure activity was not significantly associated with sleep problems.

Internal medicine

The pathophysiologic impact of AS on the pulmonary, endocrine, and gastrointestinal systems has not been formally investigated in the adult population. We report high rates of pneumonia, choking episodes with eating, and resistant behavior surrounding drinking fluids. Very few individuals had undergone a formal speech and swallow study in the past, but our findings suggest that many adults with AS may have some degree of orapharyngeal dysfunction. Episodic gagging unrelated to eating was also common and for some, these gagging episodes had an olfactory trigger or anxiety component. These episodes appear quite uniform across the study population and may represent a form of stereotypy. Further, although AS is not traditionally associated with true hyperphagia, as is common in Prader-Willi syndrome [Clayton-Smith et al., 2001], we found that half the individuals were reported to not self-regulate food intake and/or to exhibit a (suspected) limited sense of fullness. Caregiveres of females more often reported limited satiety.

Gastrointestinal health issues, specifically gastroesophageal reflux disease (GERD) and constipation, are common among adults with AS and often require ongoing medical management [Clayton-Smith et al., 2001]. Previously, Clayton-Smith et al. reported potentially severe reflux in adulthood, including a case of stricture requiring surgical intervention [Clayton-Smith et al., 2001]. Similarly, a substantial proportion of our cohort with GERD did not improve with medical treatment, and 2 individuals underwent Nissen fundoplication in adulthood. Constipation was nearly universal, often requiring medical management. These results show that diagnostics in internal medicine often pose a significant clinical challenge, and common pathologies of the alimentary tract can be severe and may require long-term medical management.

Ophthalmology

The prevalence and natural history of visual impairment in AS remains unclear. In the AS adult literature, there have been several reports of keratoconus, typically developing secondary to recurrent eye rubbing behaviors as was described in this study [Laan et al., 1996, Williams et al., 1982, Bjerre et al., 1984, Clayton-Smith et al., 2003, Sandanam et al.,

1997]. In an adult series, strabismus and/or a pale fundus were the primary issues identified on ophthalmologic exam [Buntinx et al., 1995]. In a second report, retinochoroidal atrophy (RCA) with optic disk paleness was described in 2 adult patients, and Rufa et al. hypothesized that the RCA may be secondary to impaired ubiquitination and subsequent retinal photooxidative damage with age [Rufa et al., 2003].

Anthropometrics

Obesity is a major health concern for adults with AS [Van Buggenhout et al., 2009, Laan et al., 1996, Clayton-Smith et al., 2001, Smith et al., 1996, Thomson et al., 2006]. Thirty-two percent of the adults in this study were overweight or obese. We found that women in the cohort had increased odds of developing obesity, consistent with a prior report [Clayton-Smith et al., 2001]. Alternatively, Smith et al. observed obesity disproportionately affecting men [Smith et al., 1996]. Genotypic differences in the rates of obesity have been reported, with Del cohorts showing lower BMIs compared to non-deletion [Moncla et al., 1999]. In this study, however, no statistically significant genotype-phenotype correlations were observed. Weight management in the AS population is a complex issue potentially involving multiple factors, including genetic predisposition, aberrant sense of satiety, limited access to opportunities for exercise, and challenging behaviors related to food.

Orthopedics

Many adults with AS have had previous orthopedic care. Thoracic scoliosis affects about 10% of children with AS, but with age, scoliosis becomes more pervasive [Clayton-Smith et al., 2001, Clayton-Smith et al., 2003]. Prior reported prevalence rates of scoliosis span a broad range in adult AS cohorts (38.8%–71%) [Buntinx et al., 1995, Laan et al., 1996, Thomson et al., 2006], but in this study half the individuals had scoliosis. Clayton-Smith et al. observed that scoliosis progressed faster in non-ambulatory patients [Clayton-Smith et al., 1993], but Laan et al. alternatively hypothesized that this may not be causative, given that scoliosis can be identified in both ambulatory and non-ambulatory individuals [Laan et al., 1996]. In this study, no association was found between scoliosis and mobility parameters, but further prospective investigation is indicated. Laan et al. reported a significant difference in the rates of scoliosis by sex, with 92% of females and 56% of males affected [Laan et al., 1996]. Clayton-Smith et al. described a similar female predominance [Clayton-Smith et al., 2003]. Conversely, in this study, statistically significant differences in rates of scoliosis by sex, age, or genotype were not observed, but males did have increased odds of undergoing surgical intervention. Coppola et al. suggested that given the combination of limited mobility and chronic AED treatments, individuals with AS may have increased risk of fractures due to decreased bone density [Coppola et al., 2007]. We found that the individuals in their early twenties had increased odds of being diagnosed with osetopenia/osteporosis. This result is confounded by the fact that this age group may be more likely to have undergone bone density screening compared to the 16- to 20-year-old cohort. Based on these findings, primary orthopedic issues for adults with AS include scoliosis, contractures, and fractures.

Mobility

In the AS population, there is a complex interplay between independent mobility and many distinct parameters, including ataxia and gross motor development, obesity, scoliosis, hypertonia, bone density, and voluntary behavior [Clayton-Smith et al., 2001, Clayton-Smith et al., 2003, Van Buggenhout et al., 2000, Van Buggenhout et al., 2009]. We found that the majority of our cohort was able to walk independently (68%), consistent with the rate previously reported for an adult cohort (75%) [Clayton-Smith et al., 2001]. From a genetic perspective, adults with *UBE3A* and UPD, compared to those with a Del, have been found to have increased mobility [Moncla et al., 1999, Clayton-Smith et al., 2001]. In this study, however, only the UPD cohort had a statistically significant increase in mobility. Further, we found that adults with AS showed a capacity to learn to swim independently and participate in a wide range of physical activities including riding an adaptive bike, hippotherapy, and yoga. Consistent access to opportunities for routine exercise, however, remains a significant challenge.

Communication

Severe oral motor dyspraxia with absent or limited expressive speech is nearly universal in AS across age groups, with a significant discrepancy between expressive and receptive language abilities [Clayton-Smith et al., 1993, Penner et al., 1993, Didden et al., 2009, Laan et al., 1996, Moncla et al., 1999, Jolleff et al., 1993]. Individuals with AS communicate through multiple modalities, including vocalizations, signs or gestures, pictures, and electronic devices [Clayton-Smith et al., 1993, Calculator et al., 2013]. Previously, Clayton-Smith et al. found that 68% of adults with AS were able to communicate their basic needs, primarily through the use of gestures [Clayton-Smith et al., 2001]. In this study, a minority of individuals (13%) had facility with 5 or more words. Individuals showed use of multiple communication modalities, with the use of signs or gestures (including reaching/pointing) and the use of sounds with meaning, the two most common. The speech-language phenotype for *UBE3A* and UPD is typically less severe [Lossie et al., 2001, Clayton-Smith et al., 2001, Clayton-Smith et al., 2003, Moncla et al., 1999]. In this study, individuals with *UBE3A* had increased odds of developing some speech, and both non-deletion sub-groups had increased odds of using signs or natural gestures. Didden et al. similarly found increased use of signs and gestures among individuals with UPD compared to Del [Didden et al., 2009]. Finally, music was nearly universally (90%) described as very important and independently motivating for our cohort.

Challenging behavior

Aggressive and self-injurious behavior can lead to significant morbidity. Every day, challenging behaviors directly impact opportunities for community involvement and social inclusion, which can lead to increased isolation, often perpetuating behavior problems. Importantly, aggressive behaviors in AS (behaviors with the potential of harming others) are often without malicious intent, but rather with goals of social engagement. Prior studies have reported the prevalence of aggressive behavior at much lower rates (6–10%) in individuals across age groups in comparison to our cohort (72%) [Summers et al., 1995, Adams et al., 2011]. Contributing to this difference may be variable definitions of aggression and the size

and strength of adults, as some behaviors considered benign in childhood may become more problematic when expressed in adulthood.

In a prior study of communication in AS, Didden et al. indicated that aggressive behaviors were often used as a communication method for rejection/protest, suggesting a negative reinforcement maintenance mechanism [Mudford et al., 2008, Didden et al., 2009]. Laan et al. described sensory stimulation behavior in adults with AS, with chewing/mouthing behavior affecting 75% of the study cohort [Laan et al., 1996]. Consistent with these reports, our data similarly suggests that behaviors in AS typically serve multiple functions, including seeking social attention, communicating tangible demand/avoidant escape, and seeking sensory stimulation. Clinically, acute changes in behavior require thorough evaluation for a possible as-yet unrecognized illness or injury.

Anxiety is likely under-recognized in this population and may also contribute to challenging behavior [Clayton-Smith et al., 2001]. The therapeutic impact of medical management of anxiety on self-injurious and/or aggressive behaviors in AS is largely unknown, but our data suggest a decrease in the use of antipsychotic and stimulant/antihypnotic medications, stable use of SSRIs, and an increase in the use of anxiolytics. From an environmental perspective, Clayton-Smith et al. previously described adults with AS as often quite sensitive to changes in routine, a trend also seen in this study [Clayton-Smith et al., 2001].

Conclusions

As part of the longitudinal clinical care of adults with AS, primary areas of clinical management include the following: seizures, sleep, aspiration risk, GERD, constipation, dental care, vision, obesity, scoliosis, bone density, mobility, communication, behavior, and anxiety. Given the results of this study, adults with AS may require lifelong epilepsy management, as seizures have the potential to recur and/or progress in severity with age in a subset of the population, though they tend to improve with age. Additionally, sleep dysfunction, though it often improves over an individual’s lifetime, continues to impact the majority of adults and may require behavioral and/or pharmacological intervention. The multiple domains of healthcare in AS are best served by a comprehensive approach and an interdisciplinary team, working towards the goals of health and wellness, safety, social inclusion, and autonomy.

The results of this study demonstrate a profound need for improved understanding of the natural history of seizures in AS and ongoing inquiry into innovative treatment options for epilepsy and other neurobehavioral issues in AS. Additional areas of future research include prospective and polysomnographic trials to better characterize sleep and the impact of age in AS. Our findings indicate a need for further research characterizing AS-associated ophthalmologic pathology and also suggest a great need for ongoing innovative research and the development of evidence-based weight management and fitness programs for individuals with AS. Finally, in the area of communication, future investigation of the neurocognitive processing of music in AS may be pursued to further characterize language development and to potentially yield improved adaptive communication technologies.

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Table I

Demographics of Angelman syndrome study cohort.

	Full Cohort % (n=109)	Known Genotype % (n=93)	p-value[a]
Mean age	24.3y (sd: 7.24)	24.3 y (sd: 7.46)	0.895[b]
16–20y	38%	38%	1.000
21–25y	27%	28%	0.552
26–30y	21%	19%	0.322
31–40y	11%	11%	0.689
41–50y	4%	4%	1.000
Sex			
Female	50%	51%	0.788
Male	50%	49%	
Interviewee			
Mother	89%	89%	0.689
Father	6%	5%	0.273
Both	2%	2%	1.000
Other	3%	3%	1.000
Genotype			
Maternal deletion	68%	80%	--
UBE3A mutation	8%	10%	--
UPD	9%	11%	--
Mosaic	Single case	--	--
Clinical	10%	--	--
Unknown	5%	--	--
Home environment			
Parents' home	75%	74%	0.756
Group home	17%	16%	0.731
Residential center	6%	7%	0.588
Other	3%	3%	1.000

[a]2-sided Fisher's Exact Test.

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[b] Independent Samples T-Test/Levene's Test for Equality (Sig. 0.510). *y*: years, UPD: uniparental disomy.

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TABLE II

Epilepsy parameters for individuals with Angelman syndrome, late-adolescence through adulthood

	Full Cohort % (n)	Female odds ratio	21–25y odds ratio	26–30y odds ratio	31–50y odds ratio	UBE3A odds ratio	UPD odds ratio
History of seizures	94% (109)	0.437	IS (100%, 29)	0.335	0.775	IS (100%, 9)	0.111 *
Current seizures							
Seizure free/off AEDs [a]	12% (103)	0.937	0.786	1.197	2.470	1.584	0.792
Seizure free/AED Tx [a]	48% (103)	0.844	0.525	0.238 *	0.202 *	0.945	1.970
Active seizures [b]	41% (103)	1.154	2.345	4.102 *	6.701 *	1.853	0.494
Current AED ≥2	45% (103)	0.676	2.241	1.445	1.556	0.625	0.750
≥ 2 semiologies [c]	12% (103)	0.497	1.418	2.966	1.832	IS (0%, 9)	0.886
Frequency							
Monthly [d]	29% (103)	1.021	3.051	4.558 *	7.802 *	1.214	0.810
Daily	16% (103)	2.266	2.11	10.328 *	6.883 *	0.567	IS (0%, 8)
Seizure severity							
Modified E-chess score [δ]	4.65 (SD: 2.754, n=103)	0.055	0.807	1.706 **	1.688 **	-0.139	-0.569
Score > 6	26% (103)	0.817	1.464	3.032	2.28	0.857	1.000
Current medications							
Valproate	39% (103)	0.673	1.614	2.234	1.493	0.424	0.890
Clonazepam	17% (103)	1.033	1.232	0.431	0.277	IS (0%, 9)	0.500
Lamotrigine	17% (103)	1.809	2.080	0.622	0.855	0.567	0.648
Levetiracetam	13% (103)	0.588	3.948	0.955	9.329 *	0.775	IS (0%, 8)
Ethosuximide	9% (103)	0.49	0.198	0.279	0.383	1.675	1.914
Topiramate	9% (103)	0.264	0.258	0.653	0.477	3.943	1.533
Lifetime seizure severity							
AEDs >2 lifetime	63% (103)	1.782	2.020	1.188	1.577	0.283	0.942
AEDs >3 lifetime	45% (103)	1.107	2.455	2.008	1.754	0.140	0.671
Seizure onset <3y	68% (103)	0.847	1.555	2.076	2.777	0.206 *	1.235
Most severe age [δ]	7.53 (SD: 7.035, n=100)	1.192	1.772	−0.111	4.041	−2.536	1.339
0–5 y	52% (100)	0.472	0.863	0.667	1.827	2.000	1.000

	Full Cohort % (n)	Female odds ratio	21–25y odds ratio	26–30y odds ratio	31–50y odds ratio	UBE3A odds ratio	UPD odds ratio
6–10 y	25% (100)	0.875	0.568	1.071	0.154	0.964	0.482
11–15 y	12% (100)	4.519 *	0.922	2.956	0.602	IS (0%, 9)	0.766
16–20 y	6% (100)	6.19	2.827	IS (0%, 18)	IS (0%, 15)	2.062	2.357
21–25 y	5% (62)	2.370	--	--	--	IS (0%, 5)	7.167
26–30 y	0% (33)	--	--	--	--	--	--
>31 y	20% (15)	0.500	--	--	--	IS (0%, 2)	IS (0%, 1)

Age sub-groups compared with the 16–20y cohort. Genotype sub-groups compared with the Del cohort.

[a] cohort of individuals with history of seizures who have not had an event in 1 year or more.

[b] includes 3 individuals who were not being treated with an AED.

[c] reported to have 2 or more types of seizure, i.e. events that look different to caregiver.

[d] events occurring at least monthly. δ. regression coefficient listed for each covariate.

* statistically significant odds ratio ($\alpha = 0.05$).

** statistically significant regression coefficient (α=0.05). IS: infinite solution (%, n), AED: anti-epileptic drugs, Tx: treatment, y: years.

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TABLE III

Sleep parameters for individuals with Angelman syndrome, late-adolescence through adulthood

	Full Cohort % (n)	Female odds ratio	21–25y odds ratio	26–30y odds ratio	31–50y odds ratio	UBE3A odds ratio	UPD odds ratio
Sleep							
Sleep problems	72% (109)	1.310	0.977	3.479	1.553	1.296	1.481
Melatonin Tx	22% (109)	0.997	3.070	1.228	1.945	1.812	0.906
Other sleep medication [a]	25% (109)	0.949	0.345	0.942	0.497	1.447	1.241
Sleep latency							
Trouble falling asleep	65% (85)	2.449	0.539	0.827	1.042	0.357	1.071
TV on to fall asleep	45% (85)	1.727	2.035	3.263	2.146	1.111	0.370
Night waking							
Difficulty staying asleep	66% (85)	2.139	0.907	0.587	3.036	5.469	2.344
Awake overnight weekly [b]	20% (85)	1.150	0.426	0.969	0.848	0.484	2.031
Never sleeps through the night [b]	11% (84)	3.985	0.522	3.026	3.420	IS (0%, 9)	1.000
Co-sleeping	17% (109)	1.373	1.468	4.080 *	2.131	IS (0%, 8)	1.173
TV on all night long	24% (85)	2.224	1.170	2.721	1.821	1.680	0.400
Close nighttime monitoring [c]	37% (109)	1.193	3.311 *	1.999	1.858	0.694	0.347
Daytime sleepiness							
Naps routinely	56% (108)	0.997	3.704 *	3.125 *	2.778	0.545	0.545
Often falls asleep							
Riding in the car	35% (108)	0.837	4.424 *	4.315 *	2.833	1.477	0.923
Watching TV or movies	40% (108)	1.282	3.214 *	3.304 *	1.803	0.375	0.656
Sleep quantity							
Hours of sleep per night [δ]	7.4 (sd:1.67, n=61)	−0.175	0.985 **	−0.439	1.470	−0.850	−0.207
≤5 hrs	18% (61)	3.762	0.261	2.073	2.619	4.714	1.886
≥8 hrs	59% (61)	0.948	4.526 *	0.871	0.273	0.905	1.206
Lifetime sleep severity							
Compared to infancy							
Improved	77% (108)	1.741	1.740	0.799	0.406	0.964	2.893

	Full Cohort % (n)	Female odds ratio	21–25y odds ratio	26–30y odds ratio	31–50y odds ratio	UBE3A odds ratio	UPD odds ratio
Worse	6% (108)	0.487	1.478	1.853	IS (0%, 15)	2.500	IS (0%, 10)
Unchanged	18% (108)	0.648	0.363	1.019	3.339	0.612	0.476
Compared to childhood							
Improved	68% (108)	1.995	1.344	1.426	0.748	0.903	4.333
Worse	7% (108)	0.302	6.852	6.292	IS (0%, 15)	1.971	1.725
Unchanged	24% (108)	0.650	0.346	0.333	1.470	0.841	IS (0%, 9)

Age sub-groups compared with the 16–20y cohort. Genotype sub-groups compared with the Del cohort.

[a] sleep medications included: trazadone, clonidine, clonazepam, seroquel, tranxene, eszopiclone, zolpidem, mirtazepine, temazepam, ramelteon, doxylamine.

[b] awake for a period of an hour or more overnight.

[c] awake caregiver overnight, audio/video monitoring, or posey bed. δ. regression coefficient listed for each covariate.

[*] statistically significant odds ratio ($\alpha = 0.05$).

[**] statistically significant regression coefficient (α=0.05). IS: infinite solution (%, n), Tx: treatment, hrs: hours.

TABLE IV

Internal medicine parameters for individuals with Angelman syndrome, late-adolescence through adulthood

	Full Cohort % (n)	Female odds ratio	21–25y odds ratio	26–30y odds ratio	31–50y odds ratio	UBE3A odds ratio	UPD odds ratio
HEENT							
History of severe choking	40% (84)	0.648	1.524	1.690	1.098	0.825	1.375
Abnormal swallow study [a]	56% (16)	0.631	0.926	0.459	IS (100%, 3)	IS (0%, 2)	(n=0)
History of severe pneumonia	38% (85)	0.916	1.254	1.211	2.988	1.478	0.493
Episodic gagging [b]	51% (85)	0.569	2.239	0.433	1.141	0.839	0.280
Progresses to vomiting	49% (43)	2.675	2.239	1.677	1.245	3.643	1.214
Triggered by a strong smell	53% (43)	3.836	0.928	0.738	0.277	3.200	1.067
Dental care non-sedated	64% (85)	1.191	1.589	1.117	0.624	2.029	1.127
Seasonal allergies	48% (85)	0.737	0.628	1.331	0.718	1.192	1.192
Gastrointestinal/nutrition							
Decreased satiety	50% (105)	3.152 *	0.318	1.866	1.137	0.600	7.000
Poor hydration [c]	49% (109)	1.761	0.924	1.526	1.153	0.758	0.947
Gastroesophageal reflux [d]	47% (109)	1.291	1.848	1.900	2.229	0.800	0.667
History of medication	61% (51)	0.743	0.764	1.594	0.247	0.682	0.682
Improvement with treatment	48% (31)	0.740	0.505	0.896	IS (100%, 3)	1.000	IS (100%, 2)
Cyclic vomiting	37% (109)	1.447	0.110	0.617	0.521	1.314	0.411
Episode >6hrs [e]	83% (40)	0.436	IS (100%, 8)	0.861	1.133	0.120	IS (100%, 2)
Constipation	85% (109)	1.333	0.527	0.661	2.079	0.366	0.940
Medication for constipation	43% (109)	0.825	0.917	1.890	2.903	2.625	1.313
Typically < 4 stools per week	40% (80)	0.715	0.731	1.042	2.300	IS (0%, 6)	0.346
Gynecology							
Average age at menarche [δ]	13.2 (sd: 2.18, n=52)		0.689	0.606	0.178	0.528	−0.347
Early menarche [f]	17% 52		1.308	3.643	2.833	IS (0%, 4)	3.333
Late menarche [g]	27% (52)		0.623	0.190	0.571	0.758	1.151
OCP/Depo-Provera [h]	31% (54)		2.000	4.800	1.333	0.571	0.429
Regular menstrual cycle [i]	62% (37)		2.333	4.000	2.000	1.429	0.238

	Full Cohort % (n)	Female odds ratio	21–25y odds ratio	26–30y odds ratio	31–50y odds ratio	UBE3A odds ratio	UPD odds ratio
Severe menstrual symptoms [j]	13% (54)		IS (0%, 15)	0.300	0.429	IS (0%, 4)	0.947

Age sub-groups compared with the 16–20y cohort. Genotype sub-groups compared with the Del cohort.

[a] abnormal results included swallow delay and silent aspiration.

[b] unrelated to eating.

[c] drinks <20 ounces of fluid per day.

[d] diagnosed over lifetime.

[e] >6hrs or necessitating trip to emergency room.

[f] ≤ 10 years or more than 2 years earlier than maternal menarche.

[g] ≥ 15 years or more than 2 years later than maternal menarche.

[h] depot medroxyprogesterone acetate.

[i] individuals not on OCP/Depo-provera.

[j] significant pain and/or increased irritability. δ. regression coefficient listed for each covariate.

[*] statistically significant odds ratio ($\alpha = 0.05$).

[**] statistically significant regression coefficient ($\alpha=0.05$). HEENT: Head eyes ears nose and throat, IS: infinite solution (%, n), OCP: oral contraceptive.

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TABLE V

Anthropometrics and orthopedics for individuals with Angelman syndrome, late-adolescence through adulthood

	Full Cohort % (n)	Female odds ratio	21–25y odds ratio	26–30y odds ratio	31–50y odds ratio	UBE3A odds ratio	UPD odds ratio
Anthropometrics							
Height (m)	1.62 (0.114, 109)	−0.135**	−0.003	0.025	−0.012	−0.010	0.030
Body Mass Index	23.72 (4.679, 109)	1.085	0.423	0.931	1.525	1.582	−0.210
Underweight	9% (109)	1.655	0.352	0.220	IS (0%, 16)	0.903	IS (0%, 10)
Overweight	22% (109)	0.415	0.637	0.349	0.553	0.889	0.346
Obese	10% (109)	12.468*	1.418	2.048	1.853	2.735	1.063
Orthopedics							
Hypertonia							
Knee contracture	43% (109)	1.107	1.266	1.005	2.007	2.933	3.422
Tendon lengthening surgery [a]	20% (85)	0.299*	0.503	0.151	1.178	1.778	0.762
Scoliosis	50 (109)	1.491	1.985	0.559	1.045	0.680	0.437
Age at scoliosis diagnosis [δ]	12.06 (sd: 5.603, n=49)	0.258	1.968	2.759	3.629	−3.974	1.259
Scoliosis, mild	61% (54)	2.521	0.793	1.239	1.239	IS (0%, 4)	IS (100%, 5)
Scoliosis, severe	39% (54)	0.397	1.261	0.807	0.807	IS (0%, 4)	IS (0%, 5)
Surgical intervention	24% (54)	0.207*	1.000	0.613	0.250	IS (0%, 4)	IS (0%, 5)
Bone density							
Osteoporosis/osteopenia	16% (109)	1.137	5.684*	1.208	2.920	IS (0%, 9)	1.071
History of broken hip or femur	7% (109)	1.776	1.423	1.873	2.783	1.417	1.259

Age sub-groups compared with the 16–20y cohort. Genotype sub-groups compared with the Del cohort.

[a] hamstring and/or achilles. δ. regression coefficient listed for each covariate.

* statistically significant odds ratio ($\alpha = 0.05$).

** statistically significant regression coefficient ($\alpha = 0.05$). IS: infinite solution (%, n), m: meters.

TABLE VI

Mobility and exercise for individuals with Angelman syndrome, late-adolescence through adulthood

	Full Cohort % (n)	Female odds ratio	21–25y odds ratio	26–30y odds ratio	31–50y odds ratio	UBE3A odds ratio	UPD odds ratio
Mobility							
Walks independently	68% (85)	4.544 *	1.110	2.290	0.251	0.500	3.500
Side arm assist	22% (85)	0.454	0.986	0.810	2.341	1.843	0.439
Non-ambulatory	4% (85)	0.433	1.203	IS (0%, 17)	2.331	3.929	IS (0%, 8)
Walks in the home							
Always	93% (109)	8.581	1.016	IS (100%, 23)	0.306	0.706	IS (100%, 10)
Almost never (<10%)	7% (109)	0.117	0.985	IS (0%, 23)	3.272	1.417	IS (0%, 10)
Walks in the community							
Always	38% (109)	1.789	1.207	1.123	0.779	1.667	
Almost never (<10%)	18% (109)	0.329 *	1.375	IS (0%, 23	1.968	1.224	IS (0%, 10)
Maximum distance							
< 50–100 yards	41% (108)	0.714	1.992	2.220	2.824	1.961	0.294
1/4 – 1 mile	35% (108)	1.426	0.479	0.682	0.455	0.249	1.160
No clear distance limit	25% (108)	0.904	0.923	0.508	0.607	1.564	4.692 *
Walking distance limited by							
Behavior	22% (101)	0.934	0.792	1.694	0.610	IS (0%, 8)	0.671
Physical symptoms	43% (101)	1.744	1.380	1.126	1.533	2.222	0.571
Exercise							
Able to run	35% (108)	1.953	0.683	0.685	0.753	1.739	1.449
Swimming	90% (109)	0.736	IS (100%, 29)	0.070	0.075 *	0.836	0.418
Shallow water or with float	77% (109)	1.073	0.986	0.386	0.452	0.552	0.414
Deep water without a float	13% (109)	0.723	1.228	0.553	0.390	2.063	1.806
Horseback riding							
Current routine	17% (84)	1.169	0.493	0.295	0.714	1.636	1.432
Lifetime	77% (84)	0.885	0.765	0.686	0.404	0.345	1.103
Positive experience	58% (84)	1.005	0.876	0.750	0.636	0.718	0.897
Adaptive bike lifetime							

	Full Cohort % (n)	Female odds ratio	21–25y odds ratio	26–30y odds ratio	31–50y odds ratio	UBE3A odds ratio	UPD odds ratio
Current routine	33% (84)	0.750	0.480	0.135	0.302	1.042	3.125
Lifetime	77% (84)	0.882	1.411	1.038	0.612	0.902	4.059
Positive experience	60% (84)	0.952	1.576	0.649	0.425	0.718	8.077

Age sub-groups compared with the 16–20y cohort. Genotype sub-groups compared with the Del cohort.

* statistically significant odds ratio ($\alpha = 0.05$). IS: infinite solution (%, n).

TABLE VII

Communication and activities of daily living for individuals with Angelman syndrome, late-adolescence through adulthood

	Full Cohort % (n)	Female odds ratio	21–25y odds ratio	26–30y odds ratio	31–50y odds ratio	UBE3A odds ratio	UPD odds ratio
ADLs							
Self feeds with utensils	71% (85)	1.443	1.104	1.724	1.876	3.500	3.500
Continent of bowel and bladder [a]							
Daytime	39% (85)	1.270	0.912	0.895	1.605	0.722	15.167*
Nighttime	20% (85)	0.603	0.742	0.815	1.612	2.381	7.143*
Communication							
Words	47% (109)	1.760	0.757	0.875	0.561	5.431*	3.621
≥5 words	13% (109)	3.056	0.339	1.034	0.310	2.735	4.102
Sounds with meaning	54% (109)	0.621	0.708	1.343	1.455	1.895	3.789
Signs or natural gestures	68% (109)	1.483	1.349	1.191	0.859	4.870	5.478
≥5 signs	33% (109)	1.447	1.258	0.433	0.220	13.767*	35.400*
Photos	43% (109)	0.692	0.813	0.374	0.286	1.641	1.969
Pictures	33% (109)	1.001	1.369	0.122*	0.085*	0.595	3.125
Voice output device or iPad	15% (109)	1.008	1.267	0.463	0.324	IS (0%, 9)	1.292
Music extremely important	90% (108)	0.313	2.339	0.365	0.340	0.970	IS (100%, 9)

Age sub-groups compared with the 16–20y cohort. Genotype sub-groups compared with the Del cohort.

*statistically significant odds ratio ($\alpha = 0.05$).

[a]consistently does not wear a diaper or pull-up. IS: infinite solution (%, n). solution, AED: anti-epileptic drugs, Tx: treatment, y: years.

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TABLE VIII

Challenging behavior for individuals with Angelman syndrome, late-adolescence through adulthood

	Full Cohort % (n)	Female odds ratio	21–25y odds ratio	26–30y odds ratio	31–50y odds ratio	UBE3A odds ratio	UPD odds ratio
Challenging behavior							
Aggressive towards others [a]	72% (109)	1.302	0.377	0.222 *	0.284	1.387	1.585
Self-injurious	52% (109)	0.715	0.601	0.992	0.212 *	4.118	1.765
Obsessive or persistent	48% (109)	0.643	1.313	0.453	1.362	0.758	0.406
Identified emotional trigger							
Anxiety	20% (85)	0.465	0.985	1.173	0.678	0.762	3.200
Frustration	47% (85)	1.031	0.524	2.241	0.372	2.464	1.478
Behavior function							
Social attention	61% (109)	1.123	1.212	0.699	1.406	0.304	1.420
Tangible demand	61% (109)	1.507	0.587	3.080	0.634	1.364	0.682
Avoidant escape	57% (109)	1.452	0.992	1.631	0.317	0.952	1.143
Sensory stimulation	45% (109)	0.327 *	1.394	1.306	1.122	0.656	1.969
Behavior modification							
Consistent routine	93% (109)	0.290	0.344	0.159	0.172	IS (100%, 9)	0.794
Sensitive to change in routine	50% (109)	1.119	0.699	0.556	1.898	2.111	0.452
Motivation							
Immediate reward	55% (84)	2.185	0.824	0.326	0.169 *	3.222	7.519
Delayed reward	15% (84)	4.060	0.376	0.179	0.435	1.857	13.000 *
Psychiatric medications							
Anxyolytic/antidepressant							
Current	12% (109)	0.261	1.204	0.669	1.046	2.063	0.802
Past	6% (109)	1.356	1.450	IS (0%, 23)	0.841	2.187	4.375
SSRI							
Current	10% (109)	0.836	0.361	0.221	0.324	11.833 *	5.917
Past	11% (109)	1.032	1.066	1.948	0.616	IS (0%, 9)	1.806
Antipsychotic							

	Full Cohort % (n)	Female odds ratio	21–25y odds ratio	26–30y odds ratio	31–50y odds ratio	UBE3A odds ratio	UPD odds ratio
Current	10% (109)	0.838	0.835	1.078	IS (0%, 16)	1.196	IS (0%, 10)
Past	19% (109)	0.701	1.592	0.865	0.275	0.587	3.128
Stimulant/antihypnotic							
Current	5% (109)	4.456	0.666	IS (0%, 23)	2.835	IS (0%, 9)	IS (0%, 10)
Past	8% (109)	1.301	0.680	0.421	1.318	IS (100%, 9)	0.917

Age sub-groups compared with the 16–20y cohort. Genotype sub-groups compared with the Del cohort.

[b] behavior that has the potential to harm others.

[*] statistically significant odds ratio ($\alpha = 0.05$). IS: infinite solution (%, n), SSRI: selective serotonin reuptake inhibitor. Behavior medications: anxyolytic/anti-depressants (current: busparone-3, guanfacine-2, trazedone-2, clonidine-1, duloxetine-1, alprazolam-1, clobazam-1, clomipramine-1, clorazepate-1, diazepam-1, lorazepam-1, past: clonidine-3, guanfacine-2, clonazepam-2, diezepam-2, busarone-1); selective seratonin reuptake inhibitor (current: fluoxetine - 4, sertraline- 4, citalopram-3, escitalopram-1, past: sertraline-4, fluvoxetine-3, fluvoxamine-2, paroxetine-2, citalopram-1, escitalopram-1); antipsychotics (current: risperidone-6, quetiapine-2, aripiprazole-1, olazapine-1, paliperidone-1, past: risperdal-19, aripiprazol-5, olanzapine-4, quetiapine-2, promethazine-1, haloperidol (PRN)-1, ziprasidone-1); anxyolytic/anti-depressants (current: busparone-3, guanfacine-2, trazedone-2, clonidine-1, duloxetine-1, alprazolam-1, clobazam-1, clomipramine-1, clorazepate-1, diazepam-1, lorazepam-1, past: clonidine-3, guanfacine-2, clonazepam-2, diezepam-2, busarone-1); antihypnotic/stimulant (current: atomoxetine-2, buprobion-1, modafinil-1, dexmethamphetamine-1, past: methylphenidate-7, dexmethamphetamine-6); antiepileptics (current: oxcarbazepine-2, lamotrigine-1, topiramate-1, past: valproic acid-1, ethosuximide-1); Other: (current: vitamin B complex - 3, past: vitamin B complex-1, lithium-1).