Association between sleep disturbances and challenging behavior in children and adolescents with Angelman syndrome

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ARTICLE INFO

ABSTRACT

Angelman Syndrome (AS) is a neurodevelopmental disorder with severe symptoms and associated comorbidities. It is caused by the inactivity or lack of the UBE3a gene. Symptoms of the syndrome include intellectual disability and developmental delay.

The current study investigated sleep disturbances (SD) in children and adolescents with AS, associations between SD and possible predictors of SD. Variables examined included age, gender, newborn and infancy history, challenging behavior, type of therapy received, genetic type of AS, and seizures. The sample included data from 109 participants with a mean age of 8.21, accessed via the Global Angelman Syndrome Registry. Chi-square tests were carried out to assess the associations between the variables and a logistical regression was carried out to assess the possible predictors of SD. Associations were found between SD and certain repetitive behaviors: slapping walls, focal hand movements, and agitation at new situations. From these associations, a regression formed a predictive model for sleep disturbances. The findings of this research demonstrated the importance of investigating the relationship between sleep disturbances and challenging behavior in children and adolescents with AS and the need for further research in this area.

1. Introduction

1.1. Angelman syndrome

Angelman Syndrome (AS) is a rare neurodevelopmental disorder [1]. It is caused by the deletion or lack of expression of the maternally inherited UBE3A gene [2]. This genetic defect arises from one of several causes [3,4]. The most common cause of the disorder, accounting for around 70 % of cases, is the deletion of the UBE3A gene due to de novo mutation of the maternal chromosomal region 15q11.2-q13 [5]. Other causes include paternal point mutation, uniparental disomy, and imprinting defects [6]. The prevalence of AS is within the range of 1 in 12,000 to 1 in 20,000 [5,7,8].

The consistent symptoms that are experienced by individuals with AS include severe neurodevelopmental delay, lack of speech or communication, intellectual disability ranging from mild to profound, motor deficits, challenging behaviors, and sleep disturbances [9–13].

Symptoms identified as frequent include delayed or atypical physical development of the head and seizures [13]. Another common symptom of AS is an atypical behavioral phenotype that results in an overly happy affect and inappropriate laughter [14,15].

1.2. Comorbidity in angelman syndrome

Comorbidity is a term that refers to the phenomenon where an individual experiences multiple separate conditions at the same time [16]. Seizures or epilepsy, challenging behaviors, sleep disturbances, and gastrointestinal issues are all commonly comorbid with AS [17–19]. Gastrointestinal issues such as GERD (Gastroesophageal reflux disease), cyclical vomiting, and constipation are all commonly displayed by individuals with AS [20,21]. Another common comorbidity of AS is autism spectrum disorder (ASD) [22–24].

1.3. Sleep disturbances in angelman syndrome

Individuals with neurodevelopmental disorders, particularly those with intellectual disability, may have disturbed sleep habits [22,25,26]. The most common form of sleep disturbance is insomnia [27]. Insomnia is the inability to maintain sleep, the issues can be with falling asleep or staying asleep [28]. Difficulties with sleep, including problems getting to sleep or staying asleep, have a general comorbidity rate of 80 % in individuals with AS [29]. The types of sleep disturbance most commonly associated with AS are diminished need for sleep and abnormal sleep-wake cycles [30]. Other disturbances associated with AS include sleep-disordered breathing, sleep movement disorders, and excessive daytime sleeping [30,31].

Sleep disturbances are included in the criteria for diagnosis of AS [13]. The recorded rate of prevalence varies greatly from anywhere between 20 and 90 %. This has led some researchers to question if the variance may be due to methodological differences between studies [13, 26]. The incidence of sleep disturbances stays consistent across the genetic subtypes of AS [11].

A variety of sleep-related issues have been reported by caregivers of individuals with AS severely disruptive to the lives of both the individual and themselves [32]. The most common issues reported by caregivers were waking difficulties and an altered day/night cycle [32]. Sleep was listed second only behind communication as the area of AS study that caregivers would like to see expanded in future research [32].

1.4. Sleep disturbances and challenging behavior

Challenging behaviors in AS, and developmental disorders generally, are described as a set of behaviors including severe aggression, self-injury, antisocial, irritability, destructiveness, withdrawal, lethargy, uncooperativeness, hyperactivity as well as repetitive or stereotyped behaviors [33,34]. In the field of AS research, challenging behavior generally refers to either self-injurious behaviors or inappropriate aggression towards others [35–37].

In a recent cohort study of 42 children and adults aged between 2 and 57 years, Bakke et al. [38] identified a correlation between sleep disturbances and hyperactivity in individuals with AS. Hyperactivity is often cited as the most common and significant, but it is not the only behavioral symptom of the disorder [37].

1.5. Sleep disturbances and genetic type of AS, seizures and therapy received

The differing causes of AS constitute the 'genetic type'. Gentile et al. [39] found that those with AS caused by deletion had worse clinical and developmental outcomes. Walz et al. [40] found that there were distinctions in the sleep disturbance phenotype of individuals with AS based on their genetic type. Conant et al. [41] found similar findings on the association between genetic type and sleep disturbances.

Walz et al. [40] carried out a large-scale investigation of sleep disturbances in AS in a sample of 339 individuals and found that there was an association between sleep disturbances and seizures in AS. This finding is supported by Conant et al. [41] which specifically investigated the association between sleep disturbances and epilepsy in AS and found that 79 % of individuals with sleep disturbances also had epilepsy and 69 % had more than one type of seizure.

There are many treatments for AS that specifically seek to deal with sleep disturbances [42]. The type of therapy that an individual received can greatly affect many aspects of their experience of sleep disturbances, from improving to worsening it [42,43]. However, much of the existing research on this topic has focused on medication [43] and not on other therapies received alongside medication.

1.6. Current study

The purpose of the current study was to investigate sleep disturbances in children and adolescents who are enrolled in the Global Angelman Syndrome Registry (GASR). The study will: (1) examine the most common types of sleep disturbances in children and adolescents with AS enrolled in the GASR, (2) compare the differences between children and adolescents with AS with sleep disturbances to children and adolescents with AS without sleep disturbances with regard to the following variables: age, gender, newborn and infancy history, seizures, the genetic type of AS, type of therapy received, and challenging behavior, and (3) investigate predictors of sleep disturbances in children and adolescents with AS.

2. Methods

2.1. Sample

Inclusion criteria were participants in the GASR where their parents had completed the Sleep Disturbance Scale for Children [44]. Exclusion criteria were participants in the GASR whose parents did not complete the SDSC. The sample consisted of 109 children and adolescents with a mean age of 8.21 years ($SD = 4.09$) and an age range of 2.93 and 17.20 years. The sample was consisted of 53.2 % female participants ($n = 58$) and 46.8 % male participants ($n = 51$). This sample was divided into two groups based on whether or not the participant experienced sleep issues. Groups will be referred to as groups A (sleep issues present) and group B (sleep issues not present). The groups were determined based on if an individual reached a cut-off score of 40 on the SDSC [45,46]. There were 93 participants in Group A. with a mean age of 8.21 years ($SD = 4.11$). There were 16 participants in Group B with a mean age of 8.22 years ($SD = 4.12$). The cause of AS was due to chromosomal deletion in 56 % of participants ($n = 61$), 8.3 % was due to uniparental disomy ($n = 9$), 6.4 % was due to imprinting defects ($n = 7$), and 18.3 % was due to point mutation ($n = 20$), 2.8 % was due to 'other' causes ($n = 3$) and genetic cause was unavailable for 9 participants.

2.2. Procedure and informants

A secondary analysis was performed on data gathered by the GASR [47]. The GASR was launched in September of 2016 and, according to the official website for the registry, it has 1743 participants at the time of the study. It is an open-source, patient-centred, patient-generated, registry of information that allows those with AS and caregivers globally to add information via filling out surveys that are supplied by the various modules contained in the GASR [48]. Modules included demographics, newborn and infancy history, history of diagnosis and results, illnesses and medical problems, medical history, behavior and development, seizures, medications, sleep, the SDSC, and pathology and diagnostics [47]. The registry is web-based to allow ease of access for filling out surveys and for researchers accessing the data [48]. The informants included in the current study were voluntary informants. Researchers accessed the data by applying to the registry curator. The data was de-identified before being accessed for the current study. Ethical approval was obtained from the School of Psychology at (removed for peer review) before the data was accessed for analyses.

2.3. Measures

2.3.1. Demographic information

The basic demographic information that was collected from Modules 0 and 2 of the GASR included the sex of participants, their age at the time the information was filled out, and the age at which they were diagnosed.

2.3.2. Sleep Disturbance Scale for Children (SDSC)

The SDSC [45] consists of six sub-scales which each measure a different type of sleep disturbance from Module 9 of the GASR. The scales included are disorders of initiating and maintaining sleep, sleep breathing disorder, disorders of arousal, sleep-wake transition disorders, disorders of excessive somnolence and sleep hyperhidrosis. The scale includes 33 items that are answered using a Likert scale of one to six. The questions relate to the previous six months, and the cut off score for sleep problems is 40 according to Bruni et al. [45]. Saffari et al. [49] found that the SDSC was reliable when applied to a sample of one hundred children of school age, with a mean age of 9.36 years ($SD =$ 2.58). This demonstrates the scale's utility when applied to a sample very similar to that of the current study. Cronbach's α was calculated as .82 for the overall SDSC and ranged from .40 to .62 on the subscales. The inter-item and sub-scale total correlations were similarly acceptable ($r =$ .22 - .76, $r =$ .3 - .5). The scale as a whole was also found to be externally valid when compared to the Pediatric Quality of Life Inventory (PedsQL) ($r = -.20$ to $-.64$).

2.3.3. Newborn and infancy history

Newborn and infancy history was analysed from Module 1 of GASR. The newborn and infancy module covered information such as feedings during infancy, the general mood in the first year of life, and other health issues experienced during the same time frame. These sections consisted of questions that were answered using a Likert scale.

2.3.4. Seizures

The data collected from Module 6 described the history of seizures in a participant as well as their current status. This module consisted of 18 sub-sections that pertained to specific seizure types.

2.3.5. Therapy received

Data for the types of therapy received by participants was collected from Module 7 in the GASR on the type of therapy received which required a yes or no answer.

2.3.6. Challenging behavior

Data on challenging behavior was collected from Module 5 of the GASR. Data were collected concerning the type of challenging behavior: repetitive behaviors, unusual movements, fixations or fascinations, abnormal laughter, fear of new situations or people, willingness to socialise with anyone, anxious behaviors, aggressive behaviours and self-injurious behaviors. The answers to the questions were either coded via a rating scale of one to ten or using a Likert scale of one to five. An example of a possible answer would be a rating of frequency where 1 – Yes, all the time; 2 – Yes, most of the time; 3 – Yes, some of the time; 4 – Yes, rarely; 5 – No, never; 6 – Unknown.

3. Results

3.1. Analyses

Statistical analysis was carried out using the Statistical Package for Social Sciences, Version 27.0. The data provided via the GASR was analysed using a series of Chi-Squared tests for independence. These tests were used to investigate the associations between sleep disturbances and the following variables: newborn and infancy history, seizures, type of therapy received, genetic type of AS, and challenging behaviors. The assumption violated in all cases was the assumption that the expected value of any cell in the chi-square would be greater than 5. This was not possible with the current sample. However, the tests could still be run as all other assumptions were met [50]. A logistical regression was carried out to determine possible predictors for the presence of sleep disturbances.

3.2. Sleep disturbances

Using the criterion detailed above, it was found that 93 out of 109 participants had sleep disturbances. Table 1 displays the mean and standard deviation scores for the six subscales for participants with AS who had sleep difficulties and those who did not. As can be seen, the most common sleep disruptions in children and adolescents with AS appear to be sleep-wake transition disorders, disorders of excessive somnolence, sleep hyperhidrosis, and arousal disorders.

3.3. Sleep disturbances and demographic information

A Chi-Square test was used to test if sleep disturbances were associated with the gender of the individual with AS, with no significant association found ($p = .792$). The association between age, specifically the age at the time the registry was completed, and sleep disturbances, was also tested via the calculation of the Eta value, with no association found ($\eta 2 = .03$).

3.4. Sleep disturbances and newborn and infancy history

A series of Chi-Square tests were carried out to investigate the possible association between sleep disturbances and newborn and infancy history. No significant association was found between sleep disturbances and newborn and infancy history. The results of these tests are presented in Supplementary Material 1 and 2. Supplementary Material 1 includes the tests where no assumptions of chi-square tests were violated. Supplementary Material 2 shows the results from tests where the assumptions were violated.

3.5. Sleep disturbances and seizures

A series of Chi-Square tests were carried out to investigate the possible association between sleep disturbances and seizures, with no significant associations found between sleep disturbances and seizures. Supplementary Material 3 includes the tests where no assumptions of chi-square tests were violated. Supplementary Material 4 shows the results from tests where the assumptions were violated.

3.6. Sleep disturbances and genetic type of AS

A Chi-Square test was carried out to investigate the possible association between sleep disturbances and the genetic type of AS, with no significant association found between sleep disturbances and the genetic type of AS ($p = .164$).

3.7. Sleep disturbances and therapy received

A series of Chi-Square tests were carried out to investigate the possible association between sleep disturbances and therapy received with no significant association was found between sleep disturbances and therapy received. Supplementary Table 5 includes the tests where no assumptions of chi-square tests were violated. Supplementary Table 6

Table 1
Descriptive statistics for the Sleep Disturbance Scale for Children subscale scores of children and adolescents with AS with, and without, sleep disturbances.

Subscale	Sleep Disturbances		No Sleep Disturbances	
	M	SD	M	SD
Disorders of initiating sleep	2.86	.49	2.52	.63
Sleep breathing	1.65	.74	1.27	.43
Disorders of arousal	1.16	.33	1.04	.14
Disorders of excessive somnolence	1.94	.62	1.44	.41
Sleep Hyperhidrosis	1.62	1.03	1.43	.94
Sleep-wake transition disorders	2.24	.68	1.55	.54

shows the results from tests where the assumptions were violated.

3.8. Sleep disturbances and challenging behavior

A series of Chi-Square tests were carried out to investigate the possible association between sleep disturbances and challenging behaviors, with no significant association found between sleep disturbances and challenging behaviors. Table 2 shows the results of all tests that were not significant.

However, there were three cases in the analyses where a significant association was found between sleep disturbances and challenging behavior. In each of these cases, sleep disturbances were found to be associated with a specific kind of repetitive or abnormal behavior. Firstly, slapping or hitting walls was found to be associated with sleep disturbances ($\chi2$ (5) = 12.86, p = .025). The number of participants who displayed repetitive behaviours but did not experience sleep disturbances was greater than the statistical expectancy, an expected number of 5.7 with a real number of 10. Secondly, repetitive engagement in focal hand movements was found to be associated with sleep disturbances ($\chi2$ (5) = 12.22, p = .032). The number of participants that displayed focal hand movements and also experienced sleep disturbances was below the expected number, this 'expected value' was calculated as part of the chi-square statistical test. Finally, agitation in new scenarios or situations was found to be associated with sleep disturbances ($\chi2$ (5) = 11.34, p = .045). The number of participants that did not display agitation but did experience sleep disturbances was below the expected value, 15 versus an expected 18.8. Similarly, the expected value was calculated as part of the chi-square test.

3.9. Predictors of sleep disturbances

A logistic regression was conducted to examine if the presence of sleep disturbances in individuals with AS could be predicted by the variables found to be associated with sleep disturbances in the prior testing in the current study. These variables were the display of repetitive behaviors such as slapping walls or focal hand movements, as well

Table 2
Results of chi-square tests between sleep disturbances and challenging behavior (assumptions violated).

Variables	χ2 Value	Degrees of Freedom	Sig (p)
Whole-Body Movements	8.02	5	.155
Mouthing or Chewing	3.88	5	.566
Fear of Strangers	3.16	4	.531
Will Socialise with Anyone	5.56	5	.351
Fear of New Situations	9.07	5	.106
Anxious Behaviors	7.36	5	.195
Oppositional Behaviors	4.27	5	.511
Biting	4.47	4	.346
Hair Pulling	3.53	4	.473
Hitting	4.12	4	.390
Grabbing	1.58	5	.904
Hyperactivity	1.61	5	.901
Poor Attention	3.74	4	.443
Good concentration on things they enjoy	5.97	5	.309
Fascination with Water	1.96	4	.743
Impulsivity	6.47	5	.263
Frequent Smiling at Nothing Specific	.60	5	.988
Frequent Appropriate Smiling	2.27	4	.687
Spontaneous Laughter	2.19	4	.702
Night-time Laughter	1.53	5	.910
Appropriate Laughter	1.57	5	.905
Separation Anxiety	6.41	5	.269
Fear of being left at school or care	10.09	5	.073
Skin Picking	6.17	5	.290
Head Banging	7.31	3	.063
Self-Hitting	3.85	3	.278

as agitation in new situations. The dichotomous criterion variable was sleep disturbances (present/not present). The predictor variables were those that return significant effects in the chi-square tests.

The number of participants with sleep disturbances was 93 (85.32 %). The number who displayed repetitively slapping walls with any frequency was 44 (40.37 %). The number who displayed repetitive focal hand movements with any frequency was 65 (59.63 %). The number who displayed agitation in new situations with any frequency was 73 (66.97 %). There was no multicollinearity between the independent variables of wall slapping and hand movements, (r = .42, p = <.001), or wall slapping and agitation in new situations, (r = .07, p = .527), as the correlation coefficient was less than .7.

The logistical model for sleep disturbances was significant ($\chi2$ (15) = 34.39, p = .003). The model explained 62.5 % (Nagelkerke R^2) of the variance in sleep disturbances and correctly classified 92.5 % of participants. However, none of the included independent variables was found to significantly contribute to the model, as shown in Table 3.

4. Discussion

The first aim of the current study was to investigate the most common types of sleep disturbances in children and adolescents with AS. The second was to compare the differences between children and adolescents with AS with sleep disturbances to children and adolescents with AS without sleep disturbances with regard to the following variables: age, gender, newborn and infancy history, seizures, the genetic type of AS, type of therapy received, and challenging behavior. The third aim was to investigate the predictors of sleep disturbances in children and adolescents with AS.

The cut-off for sleep disturbance was a score of 40. With this criterion, it was found that 85.32 % of the sample experienced sleep disturbances. This strongly concurs with previous research, showing that sleep disturbances are an extremely common symptom of AS [13]. Among the sample, the analysis of the SDSC's six subscales showed that the most common types of sleep disturbance for children and adolescents were disorders of initiating sleep, sleep breathing, disorders of arousal, sleep-wake transition disorders, disorders of excessive somnolence and sleep hyperhidrosis. These findings are supported by the existing AS research [26]. This can be seen in the research conducted by Goldman et al. [51] which found that children with AS experienced sleep disturbances at a rate of 80 %. This incidence rate for sleep disturbances in AS is also supported by the work of Williams et al. (2005).

No significant association was found between the gender of a child or adolescent with AS and sleep disturbances. Similarly, no association was found between sleep disturbances and the age of participants. This finding contrasts with the general literature on AS and sleep disturbances which states that sleep disturbances are usually worse in younger individuals [31]. This contrast shows that further investigation of sleep disturbances in older adolescents with AS is needed in future.

Across all sub-items of the variables: newborn and infancy history, seizures, genetic type of AS, and therapy received, no statistically significant associations were found between the given variable and sleep disturbances. This trend also held for the majority of items contained within the variable of challenging behaviors. However, three types of challenging behavior were found to be significantly associated with sleep disturbances. These were 'slapping walls', 'focal hand movements', and 'agitation in new situations'. It can be hypothesised that some of these challenging behaviors could be considered repetitive

Table 3
Results of logistical regression to investigate the predictors of sleep disturbances.

	Wald	Degrees of Freedom	Sig (p)
Wall Slapping	>.001	5	.999
Hand Movements	2.10	5	.835
Agitation at new situations	.60	5	.988

behavior, such as 'slapping walls' and 'focal hand movements'. Relationships have been found between sleep disturbances and repetitive behavior in AS [22,52,53]. 'Agitation in new situations' would be categorised as a type of anxiety. Similarly, relationships have been found between sleep disturbances and anxiety in AS [53]. It can be hypothesised that children with ASD and sleep disturbances may have more difficulties in regulating their emotions and behavior due to poor sleep at night. This then may be evident in the relationship between sleep disturbances and daytime challenging behavior. This is demonstrated in previous research on the relationship between sleep disturbances and challenging behavior in adults with AS [52]. These findings are consistent with previous research into AS, as challenging behaviors have been associated with increased severity of other AS symptoms [35].

There are a number of limitations in the current study. The first is the skewed nature of the sample. The sample consisted of 93 individuals who experienced sleep disturbances and only 16 individuals who did not experience sleep disturbances. The second limitation is the large amount of missing data within the data of a high proportion of participants in the current study. This attrition rate of the number of participants who completed the study is significant. In such studies, families with AS who have sleep problems are more likely to participate in the hope of gaining some important information for their child. Therefore, individuals without sleep disturbances may be underrepresented in the data. The third limitation is the use of a subjective measure of sleep, instead of an objective measure of sleep such as actigraphy or polysomnography. Future research should investigate sleep quality and sleep disturbances using these measures. The fourth limitation is that when considering the types of therapy received, pharmacological treatment was not investigated. Pharmacological therapy should be included in future research as many drugs can interfere with sleep positively or negatively. With the limitations present, it can be strongly recommended that the area of sleep disturbances in AS, needs further investigation in a study with a larger sample that contains more balance between test and control groups. Another recommendation is that future studies in this area also mitigate the effect of missing data entries in the data set.

The current study found a clear connection between sleep disturbances and specific challenging behaviors. These findings show the need for future research in the area but also help to provide insight into the symptoms of AS which benefits both those with the condition and the clinicians that seek to treat AS. Sleep disturbances are a core aspect of AS and all research covering sleep disturbances, their effects, associations, and treatments allow clinicians globally to better understand and treat AS.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of (removed for peer review) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent

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

Source of funding

CRediT authorship contribution statement

Darragh S. O'Donohoe: Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. **Sally Whelan:** Conceptualization, Project administration, Supervision, Writing – original draft, Writing – review & editing. **Arlene Mannion:** Conceptualization, Investigation, Methodology, Supervision, Writing – original draft, Writing – review & editing. **Megan Tones:** Data curation, Writing – review & editing, Resources. **Helen Heussler:** Data curation, Writing – review & editing, Resources. **Matthew Bellgard:** Data curation, Resources, Writing – review & editing. **Geraldine Leader:** Conceptualization, Methodology, Project administration, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.sleep.2024.07.033.

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