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BRIEF COMMUNICATION

# Epilepsy and the sleep–wake patterns found in Angelman syndrome

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## Summary

**Sleep disturbances and epilepsy are common in Angelman syndrome (AS). This study examines seizure variables and sleep in a large AS cohort. Sleep disturbances and epilepsy were assessed in 290 individuals with AS using two questionnaires, including the Behavioral Evaluation of Disorders of Sleep (BEDS). Sensitivity to the sleeping environment, decreased nightly hours of sleep, and a difficulty initiating sleep were significantly correlated with the presence of epilepsy, particularly focal seizures. Use of multiple anticonvulsant drugs was shown to affect sleep. No significant associations were present between molecular subtypes of AS and individual sleep factors. Sleep problems appeared to be associated with epilepsy in individuals with AS, especially with focal and absence seizures and multiple seizure types. Results were consistent with those of prior studies assessing sleep in AS. Severity of epilepsy and use of anticonvulsant drugs may be related to a higher degree of sleep disturbance in this population.**

**KEY WORDS: Epilepsy, Angelman syndrome, Sleep patterns, Behavioral Evaluation of Disorders of Sleep.**

Epilepsy is one of the most common features of Angelman syndrome (AS), present in 80–90% of affected individuals. Another common feature is a severe disturbance of sleep, which is present in 20–80% of those with AS and is included in the diagnostic criteria as ''abnormal sleep-wake cycles and a diminished need for sleep'' (Williams et al., 2005).

The most common sleep problems in AS include abnormal patterns of sleep initiation, frequent night awakenings, and a ''decreased need for sleep'' in younger children (Clayton-Smith, 1993; Summers et al., 1995; Zhandova et al., 1999; Clarke & Marston, 2000; Williams et al., 2005; Pelc et al., 2008). Hyperkinesia, diurnal somnolescence, and bruxism have also been described (Bruni et al., 2004; Walz et al., 2005), as well as the persistence of sleep disorders into adulthood (Clayton-Smith, 1993; Smith et al., 1996). Previous smaller studies assessing sleep in AS have demonstrated an association between severe sleep problems and the presence of more than one seizure type (Didden et al., 2004) but no association between sleep issues and molecular subtypes (Bruni et al., 2004).

In the largest study to date assessing sleep in AS, Walz et al. (2005) studied 339 individuals, assessing sleep patterns using a standardized measure derived from the International Classification of Sleep Disorders. More than half of their sample displayed a variety of abnormal sleep patterns, with more than 40% of the respondents describing problems with sleep initiation and duration. Analysis of genetic subtypes revealed a few distinctive relationships, and medications were only anecdotally reported. Seizure disorders did not show an association with the existence of sleep disturbances or with sleep duration.

The purpose of this study was to not only validate the previously described sleep patterns in AS, but to further examine the association between epilepsy and sleep disturbance in AS, as well as examine the medications used to treat the abnormal sleep patterns described in this population and consider the effects of antiepileptic drugs (AED) on sleep patterns.

## Methods

As part of a larger study of epilepsy in AS, families of individuals with AS were asked to complete a questionnaire survey online relating to the presentation and

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treatment of epilepsy in AS, as well as the Behavioral Evaluation of Disorders of Sleep (BEDS) (Schreck, 1997, 1998) to assess the prevalence of abnormal sleep patterns in this population; the same sleep measure employed in the previous large cohort (Walz et al., 2005) assessing sleep in AS.

The BEDS questionnaire assesses sleep behaviors observed by parents or family members during the 6 months prior to the completion of the questionnaire. Frequencies of sleep behaviors are assessed by 107 questions on a five-point Likert scale, and four additional open-ended questions pertaining to general sleep patterns and hours of sleep. The standardized scale contains 28 items taken from the full questionnaire that comprises empirically derived scales in four distinct factors relating to sleep disturbances: expressive sleep disturbance, sensitivity to the environment, disoriented awakening, and apnea. Seven additional items from the larger questionnaire were included in our analysis (Table 1) because of their likelihood to occur within this population and in order to parallel the methods of the previous investigators adapting the BEDS measure for use in the AS population (Walz et al., 2005).

Correlations between presence of seizures and sleeping problems were tested by chi-square analysis. Associations between epilepsy variables (seizure types, frequency of seizures) and sleep factors were tested by multiple analyses of variance (MANOVAs). The effects of seizure type on each sleep factor were assessed by *z*-tests between the sleep factor mean statistics and sleep factor distributions

**Table 1. Items included from the Behavioral Evaluation of Disorders of Sleep (BEDS) with percentage of individuals who were rated 3 or 4, endorsing each behavior "frequently" or "always"**

| BEDS item | n = 290 | % |
|---|---|---|
| Factor 1: Expressive sleep disturbances | | |
| Wakes up screaming during the night for more than 1 min | 32 | 11 |
| Screams during the 2nd half of the night | 14 | 4.9 |
| Is not awake when screaming at night | 7 | 2.6 |
| Wakes up screaming in the second half of the night | 6 | 2.2 |
| Wakes up screaming during the night and cannot be calmed down | 6 | 2.1 |
| Wakes up screaming approximately 2 h after going to sleep | 5 | 1.7 |
| Doesn't remember crying or screaming at night | 4 | 0.16 |
| Acts out dreams | 1 | 0.4 |
| Walks in sleep | 0 | 0 |
| Factor 2: Sensitivity to environment | | |
| Is awakened by loud noises | 81 | 28.4 |
| Sleeps better in a place other than own bed | 32 | 11.2 |
| Needs a night light to fall asleep | 25 | 8.8 |
| Is afraid to fall asleep | 6 | 2.3 |
| Is afraid of noises at night | 3 | 1.1 |
| Complains that room is uncomfortable | 1 | 0.4 |
| Complains that bed is uncomfortable | 1 | 0.4 |
| Factor 3: Disoriented awakening | | |
| Is sluggish when awakened | 78 | 27.1 |
| Reacts slowly when awakened | 58 | 20.6 |
| Is disoriented when awakened | 23 | 7.9 |
| Speaks slowly when awakened | 4 | 1.6 |
| Factor 4: Apnea | | |
| Stops breathing during sleep | 9 | 3.1 |
| Has difficulty breathing during sleep | 7 | 2.6 |
| Additional items | | |
| Has trouble falling asleep | 149 | 50.5 |
| Sleeps less than other children his/her age | 138 | 49.1 |
| Gets less than 6 h sleep in a 24-h period | 68 | 23.4 |
| Is sleepy during the day | 35 | 12.2 |
| Sleeps more than other children his/her age | 23 | 10 |
| Takes frequent naps during the day | 22 | 7.6 |
| Takes medicine during the day that makes him/her sleep worse | 5 | 1.9 |
| | | |
| Supplementary questions | Total | Mean |
| How many hours does your child sleep per night? | 265 | 8 h |
| How many hours has your child slept in the last 24 h? | 258 | 8.5 h |
| How many hours does your child nap during the day? | 263 | <1 h |
| Do you think your child has a sleeping problem? (Yes) | 169 | 58% |

for the rest of the epilepsy population. Associations between genotype and sleep factors were tested by analysis of variance (ANOVA), as were analyses assessing the impact of current sleep medications and AEDs on sleep factors. Statistical tests were performed with SPSS v. 11.5 (SPSS, Chicago, IL, U.S.A.). All tests of significance were two-tailed, with $\alpha = 0.05$.

## Results

There were 290 respondents who completed both questionnaires, 82% reporting a family member with epilepsy. The percentage of respondents endorsing a sleeping problem for their child or family member with AS clustered around certain questions within each of the BEDS factor scales (Table 1), with more than half of the respondents having reported a difficulty with sleep initiation. From the standardized scale, the two most commonly described factors affecting sleep patterns were sensitivity to the environment, and disoriented awakening. Although there was a mild association between molecular subtype and sleep factor scores, particularly with greater expression of sleep disturbances in those with AS caused by deletion; this relationship was not significant by ANOVA.

Sleep disturbances were subjectively described by 58% of those who completed the BEDS. Of those indicating a sleep disorder was present, 79% had epilepsy, and 69% of those describing both epilepsy and sleep problems had multiple seizure types. Endorsement of sleep problems by parents or family members was significantly associated with the presence of a seizure disorder ($p = 0.005$) and was greater for those with multiple seizure types. The presence of epilepsy alone was not found to be significantly associated with a particular sleep factor on the BEDS scale; however, the presence of epilepsy did show a significant association with difficulty of sleep initiation ($p = 0.031$) as well as a decreased need for sleep ($p = 0.040$). Multiple seizure types showed a strong association with expressive sleep disturbances ($p = 0.019$), duration of sleep ($p = 0.029$), and diurnal somnolescence ($p = 0.027$).

Focal seizures, absence seizures, generalized tonic–clonic seizures, and atonic seizures were the most commonly reported seizure types among the 82% of individuals with epilepsy in this sample. The likelihood of a sleeping problem among those with each seizure type was notable within the focal seizure and absence seizure types (Table 2). There were insufficient data available to correlate the impact of seizure freedom on sleep.

Those with epilepsy who had tried and not responded to more than two AED were found to have a higher total score across all BEDS scales than those whose epilepsy had been treated with up to two AEDs ($p = 0.086$). This association was most directly related to expressive sleep disturbances ($p = 0.007$), as well as sleep apnea ($p = 0.042$). Mean scores across all BEDS scales were higher for those individuals currently taking greater numbers of sleep medications. Supplementary Table S1 reports the sleep medications and proportions used within this sample.

## Discussion

The aim of this study was to help validate descriptions of sleep problems previously reported in AS and to examine their relationship with epilepsy in a large sample. The

**Table 2. Associations between epilepsy variables and items on the BEDS questionnaire. p-Values of z-scores for mean score for each seizure type compared with mean score for the rest of individuals with epilepsy**

| Seizure type<br>Z-test | Atypical absence<br>p-value | Atonic<br>p-value | Complex partial<br>p-value | Generalized tonic somnolescence clonic<br>p-value |
|---|---|---|---|---|
| Expressive sleep disturbance | 0.11 | 0.07* | 0.46 | 0.36 |
| Sensitivity to environment | 0.57 | 0.98 | 0.0003* | 0.98 |
| Disoriented awakening | 0.80 | 0.57 | 0.51 | 0.15 |
| Apnea | 0.40 | 0.77 | 0.10 | 0.89 |
| BEDS total | 0.35 | 0.77 | 0.03* | 0.62 |
| Avg. hours of sleep per night | 0.89 | 0.25 | 0.74 | 0.29 |
| Sleep in last 24 h | 0.50 | 0.33 | 0.95 | 0.20 |
| Avg. hours of nap per day | 0.07* | 0.86 | 1.0 | 0.02* |
| Sleeps more than other children | 0.94 | 0.39 | 0.51 | 0.88 |
| Trouble falling asleep | 0.24 | 0.58 | 0.003* | 0.99 |
| <6 h sleep per 24 h | 0.02* | 0.42 | 0.001* | 0.73 |
| Frequent daily naps | 0.01* | 0.56 | 1.0 | 0.42 |
| Daytime sleepiness | 0.44 | 0.77 | 0.35 | 0.98 |
| Daytime meds worsen sleep | 0.73 | 0.54 | 0.44 | 0.87 |
| Sleeps less than other children | 0.18 | 0.75 | 0.67 | 0.03* |

*$p < 0.05$.
BEDS, Behavioral Evaluation of Disorders of Sleep.

largest limitation of this study is the questionnaire-based study design, which used parental reporting to obtain data as opposed to medical records or polysomnography. This, however, allowed us to assess these variables in a very large sample (n = 290). Another limitation was the retrospective design that assesses sleep problems over the preceding 6 months, making it difficult to determine a linear progression of symptoms, including age of onset of sleep problems.

The results of this survey with respect to overall sleep disturbances were similar to those of the previous study employing the BEDS (Walz et al., 2005). It is unclear how much overlap there is between the two populations given that both studies were supported by the Angelman Sydrome Foundation, although the previous study did not examine the relationship between sleep and epilepsy. In the prior study, difficulty with sleep initiation (48%) and a decreased need for sleep (42%) were the most frequently reported sleep abnormalities, and these were also the most frequently reported in our study with similar rates (sleep initiation, 48%; decreased need for sleep, 49%).

Among the most frequently described sleep problems, the presence of epilepsy and seizure type appeared to be significant, with 69% of those with epilepsy reporting a sleep problem. Sensitivity to the environment, difficulty with sleep initiation, and overall decreased nightly sleep hours were significantly related to the presence of focal seizures. The strong associations with particular sleep behaviors may be related to the combination of multiple seizure types, particularly for sleep behaviors that demonstrated at least a weak association with more than one type. More hours spent napping during the day was related to both absence and generalized tonic–clonic seizures, and decreased nightly hours of sleep (perhaps related to the increased napping) showed a strong association with both focal and absence seizures.

Frequent night awakenings in previous studies have been described in relation to night terrors and nightmares, and may be indicative of the expressive sleep disturbance endorsed by 11% of our sample. This factor was shown to have a weak association with atonic seizures. Multiple seizure types may have contributed to this relationship, as this also shows a weak association with absence seizures. ANOVA assessment of the relationship between multiple seizure types and expressive sleep disturbances was also significant.

Although there appear to be clear associations between the presence and relative severity of epilepsy and sleep disturbances in those with AS, it is still unclear as to whether more severe epilepsies are causing the sleep disturbances or if poor sleep hygiene is exacerbating the epilepsies. Similarly, it is also unclear if the relationship between multiple AEDs and sleep disturbances is due to the AEDs themselves or to the severity of the epilepsy, although more likely to be related to drug-resistant epilepsy. Further prospective studies that could better assess the linear progression of epilepsy and sleep problems and the effects of specific AED on sleep–wake cycles, ideally using polysomnography, are needed.

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We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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## Supporting Information

Additional Supporting Information may be found in the online version of this article:

**Table S1.** Sleep medications.

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