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Brief Communication

Sleep phenotypes in infants and toddlers with neurogenetic syndromes

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ABSTRACT

Background: Although sleep problems are well characterized in preschool- and school-age children with neurogenetic syndromes, little is known regarding the early emergence of these problems in infancy and toddlerhood. To inform syndrome-specific profiles and targets for intervention, we compared parent-reported sleep problems in infants and toddlers with Angelman syndrome (AS), Williams syndrome (WS), and Prader–Willi syndrome (PWS) with patterns observed among same-aged typically developing (TD) controls.

Methods: Mothers of 80 children (18 AS, 19 WS, 19 PWS, and 24 TD) completed the Brief Infant Sleep Questionnaire. Primary dependent variables included (1) sleep onset latency, (2) total sleep duration, (3) daytime and nighttime sleep duration, and (4) sleep problem severity, as measured by both maternal impression and National Sleep Foundation guidelines.

Results: Sleep problems are relatively common in children with neurogenetic syndromes, with 41% of mothers reporting problematic sleep and 29% of children exhibiting abnormal sleep durations as per national guidelines. Across genetic subgroups, problems are most severe in children with AS and WS, particularly in relation to nighttime sleep duration. Although atypical sleep is characteristically reported in each syndrome later in development, infants and toddlers with PWS exhibited largely typical patterns, potentially indicating delayed onset of sleep problems in concordance with other medical features of PWS.

Conclusions: Our findings suggest that sleep problems in neurogenetic syndromes emerge as early as infancy and toddlerhood, with variable profiles across genetic subgroups. This work underscores the importance of early sleep screenings as part of routine medical care of neurosyndromic populations and the need for targeted, syndrome-sensitive treatment.

1. Introduction

Children with neurogenetic syndromes are at high risk for comorbid sleep problems, including increased sleep latency, frequent and prolonged night waking, and short sleep duration [1]. Sleep problems in preschool- and school-age children with neurogenetic syndromes have been well documented, occurring in up to 86% of children [2], and are known to impact child behavior [3] and parental stress [4]. In healthy developing infants, sleep problems have been associated with a number of negative outcomes including impaired cognitive development [5], emotion dysregulation [6], and attention problems [7]. However, despite the pervasive rates of sleep problems and debilitating impact of sleep on child and family functioning, few studies have examined sleep problems in neurogenetic syndromes during infancy and early childhood. The paucity of research in this area substantially limits our knowledge of when and how sleep problems emerge, constraining targeted and effective early treatment options.

To address this need, the present study evaluated parent-reported sleep problems in infants and toddlers with three low-incidence neurogenetic syndromes, namely Angelman syndrome (AS; prevalence 1:10,000–20,000 [8]), Prader–Willi syndrome (PWS; 1:7500–10,000 [8]), and Williams syndrome (WS; 1:15,000–30,000 [8]), relative to typically developing (TD) controls. In later childhood and adulthood, sleep problems in AS

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include reduced total sleep time [9], increased sleep onset latency [10], and frequent and prolonged night waking [11]. In contrast, PWS is associated with excessive daytime sleepiness [2], sleep apnea, reduced sleep quality [1], and early waking [12]. Individuals with WS are generally reported to exhibit the mildest sleep concerns among the considered syndromes, with increased sleep onset latency, decreased sleep efficiency [13], daytime sleepiness [13,14], and more frequent night arousals and wakings [14]. Although sleep problems are expected across these syndromes, variations in topography and severity in childhood thus suggest that infant profiles may similarly vary across groups, requiring syndrome-specific plans of care.

The goals of this study were to (1) compare early childhood sleep profiles across infants and toddlers with and without neurogenetic syndromes, including sleep latency, duration, night waking, and global parent impressions, with those of same-aged typically developing (TD) controls and (2) examine the magnitude of sleep problems relative to established national guidelines.

2. Methods

2.1. Participants and procedure

Participants included 80 infants and toddlers with AS (n = 18), WS (n = 19), PWS (n = 19), and TD (n = 24). Data were drawn from the Early Phenotype Survey, an ongoing longitudinal study of early development in low-incidence neurogenetic syndromes. Families were recruited through web-based support groups and social networks, including the Angelman Syndrome Foundation and Registry (www.angelman.org) and Williams Syndrome Association and Registry (www.williams-syndrome.org/registry). All recruitment, consent, and procedures were approved by the Institutional Review Board at Purdue University. Families were required to primarily speak English for enrollment, and the TD group was excluded if they were born at <37 weeks; had significant surgeries that may impact sleep, or had a family history of developmental delay, intellectual disability, or other neurogenetic conditions. Groups were matched for age and sex (% male: AS = 53%, PWS = 42%, WS = 58%). Eighteen percent of syndromic participants were born preterm (AS: n = 3, PWS: n = 6, WS: n = 1), consistent with higher rates of preterm birth in these populations. Analyses repeated without preterm infants generally yielded similar effect sizes, and any inconsistencies are reported in-text. Groups did not differ across socio-economic variables, as detailed in Supplemental Table 1.

Parents reported child genetic status and completed syndrome-specific screening questions, with 74% of cases confirmed with genetic report (AS = 63%, PWS = 89%, WS = 68%). AS subtypes included maternal deletion (83%, n = 15), UBE3A mutation (11%, n = 2), and uniparental disomy (6%, n = 1). PWS subtypes included paternal deletion (68%; n = 13) and maternal uniparental disomy (32%, n = 6). Medications to target sleep and seizures were most common in the AS group (sleep = 3, seizure = 9; PWS sleep = 0, seizure = 1; WS sleep = 0, seizure = 0).

2.2. Measures

Biological mothers completed the Brief Infant Sleep Questionnaire (BISQ) [15], a 12-item parent-report measure of sleep-related behaviors previously validated against both actigraphy and parent-report sleep diaries [15]. Mothers were instructed to complete the BISQ on their child's sleep over the past week. Primary dependent variables included (1) nighttime sleep onset latency in minutes (Item 7), (2) total sleep duration per 24 h (Items 3 and 4), (3) daytime (Item 4) and nighttime sleep duration (Item 3), and (4) whether mothers rated sleep as a “very serious problem” rather than “a small problem” or “not a problem at all” when asked “Do you consider your child's sleep a problem?” (Item 10). We also determined whether total sleep duration fell outside of “recommended” sleep duration ranges set by the National Sleep Foundation [16] (4–11 months: 12–15 h; 1–2 years: 11–14 h; 3–5 years: 10–13 h).

2.3. Statistical analyses

Analyses were performed in SAS 9.4 (SAS Institute, Cary, NC) using nonparametric methods appropriate to small samples and outliers. We contrasted sleep in TD versus each syndromic group using Wilcoxon–Mann–Whitney tests (sleep latency, duration, and waking variables) and Fisher's exact tests (categorical parent impressions and national guidelines) using $\alpha < 0.05$. Effect sizes are reported using Cohen's d or odds ratios, as appropriate. We also calculated a Levene's homogeneity of variance statistic for each continuous pairwise comparison to determine whether variability in sleep parameters differed by group. Next, we conducted several supplemental analyses to contextualize our primary findings, including (1) pairwise syndromic comparisons, (2) post-hoc within-group analysis of AS-specific factors (eg, subtype, medication use) that may have contributed to group differences, and (3) within-group comparisons of age across participants with and without clinically indicated sleep concerns (Wilcoxon–Mann–Whitney tests). See Supplemental Tables 2–4.

3. Results

3.1. Sleep latency

Table 1 includes primary analyses contrasting each syndrome group to TD controls. Across syndromic groups, parents reported a median sleep latency of 15 min, relative to 30 min in controls. Relative to TD controls, sleep latency was significantly shorter in PWS ($d = 0.95$) and marginally shorter in AS ($d = 0.43$). Supplemental pairwise comparisons (Supplemental Table 2) indicated that the PWS and AS groups did not differ from each other. Variability in sleep latency did not differ by group (Supplemental Table 3).

3.2. Sleep duration

The median sleep duration was 720 min (12 h) per 24 h across syndromic groups, with both the AS ($d = 1.22$) and WS ($d = 0.62$) groups displaying atypically short total nighttime sleep and the AS group also exhibiting greater variability in sleep duration relative to TD controls. Pairwise contrasts indicated marginally less nighttime sleep in AS than WS. When preterm infants were excluded, the PWS group displayed atypically longer total sleep ($d = 0.75$), while the WS group difference approached significance in nighttime sleep ($d = -0.56$).

3.3. Night waking frequency and duration

Across syndromic groups, the median number of parent-reported night wakings was one, lasting approximately 5 min in total. The AS group exhibited atypically long night wakings ($d = 0.70$), with waking durations over three times as long as in controls. The AS group also exhibited greater variability in duration

Table 1
Sleep problems in children with neurogenetic syndromes compared to typical controls.

	Median (range)				Wilcoxon Z *p*		
	Angelman (AS)	Prader–Willi (PWS)	Williams (WS)	Control (TD)	AS vs. TD	PWS vs. TD	WS vs. TD
n	18	19	19	24			
Sex (% male)	52.63	42.11	58.33	57.89			
Age in months	18 (8–45)	22 (10–44)	20 (6–46)	24 (6–44)			
Night sleep latency	15 (0–120)	10 (0–60)	20 (0–120)	30 (2–90)	−1.94 (0.051)	−2.74 (0.006)	−0.58 (0.562)
Total sleep duration	660 (360–870)	765 (630–900)	720 (570–840)	728 (630–960)	−2.14 (0.031)	0.70 (0.482)	−1.81 (0.070)
Daytime	120 (0–480)	120 (60–330)	120 (0–240)	120 (0–300)	1.14 (0.256)	1.38 (0.167)	0.35 (0.725)
Nighttime	540 (240–660)	630 (480–720)	600 (480–720)	630 (390–840)	−3.46 (0.001)	−0.41 (0.681)	−2.07 (0.039)
Night waking frequency	1 (0–10)	1 (0–2)	1 (0–5)	1 (0–3)	0.32 (0.584)	−0.81 (0.420)	−0.69 (0.495)
Night waking duration	40 (0–300)	0 (0–60)	5 (0–60)	3 (0–150)	2.26 (0.029)	−0.49 (0.629)	−0.07 (0.948)
	% Endorsed (n)				Fisher's exact test *p*		
	AS	PWS	WS	TD	AS vs TD	PWS vs TD	WS vs TD
Any parent problem	50 (9)	16 (3)	61 (11)	38 (9)	0.533	0.174	0.212
Small problem	22 (4)	16 (3)	56 (10)	38 (9)	0.333	0.174	0.350
Very serious problem	28 (5)	0 (0)	5 (1)	0 (0)	0.010	n/a	0.429
NSF guidelines	50 (9)	16 (3)	26 (5)	17 (4)	0.020	0.320	0.220

Note. National Sleep Foundation guidelines were used to determine whether total sleep duration fell outside of "recommended" ranges based on participants' chronological ages.

of night wakings. Night waking frequency was not atypical across syndromic groups.

3.4. Overall impression

The parents of 41% of children with neurogenetic syndromes reported "small" or "very serious" sleep problems, with atypically high rates of "very serious" problems in the AS ($p = 0.010$) group. Although most parents of children with WS endorsed small sleep problems, this endorsement was relatively common among parents of control children (38%) and therefore not statistically atypical. A substantial minority of children with neurogenetic syndromes (29%) exhibited sleep durations outside of the NSF's "recommended" ranges, with nearly three times higher likelihood of AS relative to controls (OR = 2.94).

3.5. Variable profiles in AS

Three AS participants exhibited statistically atypical scores (outliers) within continuous analyses (Fig. 1). These participants were born full-term, and varied in age (8–41 months), medication use (sleep n = 1; seizure n = 1), and AS subtype (deletion n = 2; paternal uniparental disomy n = 1). Children with AS who took sleep-related medications (classified as medications to target sleep or seizures) slept significantly less during the day than children who did not take sleep-related medications.

3.6. Group-specific age effects

Severity of parent-reported sleep problems did not differ by age (AS: Wilcoxon Z = −0.88, $p = 0.377$; WS: Z = 0.05, $p = 0.964$; PWS: Z = −0.06, $p = 0.955$; TD: Z = 1.37, $p = 0.170$) or the NSF's "recommended" ranges (AS: Z = 1.02, $p = 0.307$; WS: Z = 0.32, $p = 0.746$; PWS: Z = −0.06, $p = 0.955$; TD: Z = −1.43, $p = 0.152$).

4. Discussion

Although sleep problems are common in neurogenetic syndromes, the onset and nature of sleep problems in infancy are poorly understood. The present study examined sleep profiles in three understudied neurogenetic syndromes to inform best practice clinical care and future directions for treatment. Our findings suggest that sleep problems in a subset of children with neurogenetic syndromes emerge in early developmental stages, particularly in AS and WS. As sleep is a modifiable risk factor for developmental progress, our findings support the importance of screening, diagnosing, and treating sleep problems in high-risk syndromic infants, laying the foundation for optimal developmental outcomes.

4.1. Angelman syndrome

We observed particularly atypical sleep patterns in AS, including shorter and more variable sleep duration and longer and more variable periods of night waking. However, infants and toddlers with AS did not display as much abnormal sleep onset latencies or frequent night waking as observed in older children [10,11]. These patterns suggest that problems initiating and maintaining sleep, which are present in 48–70% [17] of older children with AS [10], likely emerge in early infancy and may be targeted proactively. The variable nature of sleep and wake durations in children with AS may contribute to increased and more serious parent concerns. Indeed, 17% of our AS sample were reported to take sleep-related medications, suggesting that interventions are already underway at young ages, and the impairments we describe may underestimate the true rates of sleep problems in non-medicated samples. These findings suggest that sleep problems in AS are more extensive than those observed in several other neurogenetic syndromes, warranting further research to develop syndrome-specific screening and intervention protocols that may minimize the negative developmental implications for this population.

4.2. Williams syndrome

Sleep problems were also elevated in infants and toddlers with WS, consistent with evidence that 36–57% of older children with WS exhibit problems related to sleep initiation, night waking, and sleep duration [17]. Indeed, our results suggest that even in early childhood, parents report shorter nighttime sleep duration in WS, with the majority indicating that sleep is problematic for their child. Notably, previous studies report atypically long sleep onset latencies and frequent night waking [14] in older children with WS [18,19], whereas sleep onset latencies and waking frequency in our infant and toddler sample did not differ from that in TD controls.

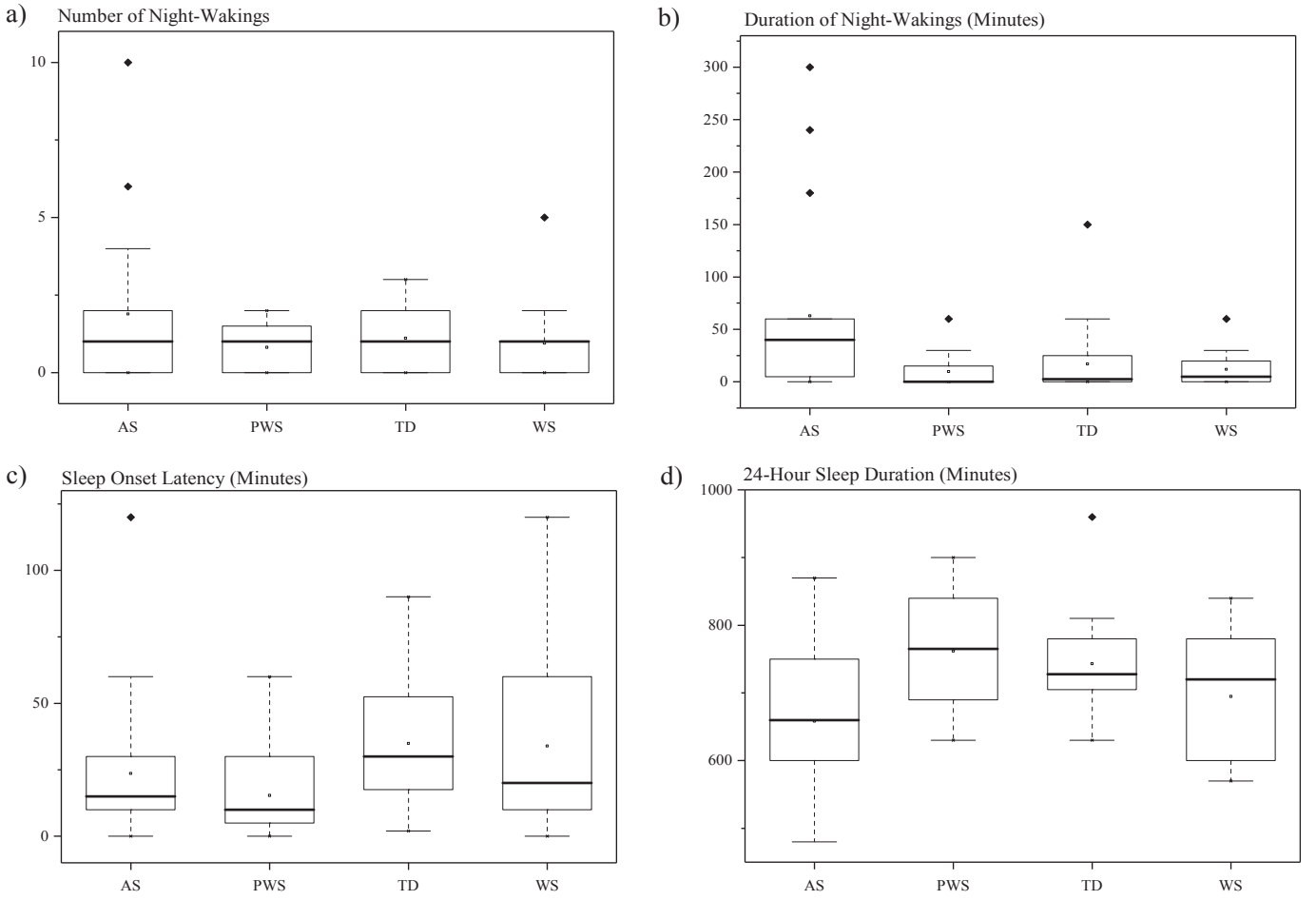

Fig. 1. Box-and-whisker plots detailing raw score variability and outliers for core continuous sleep variables.

This discrepancy may indicate that the topography of sleep problems changes across development in WS, with minor sleep problems emerging in infancy that may continue to intensify with age.

4.3. Prader–Willi syndrome

Although sleep problems are reported in 35–69% [2,12,20] of older children with PWS, parent-reported sleep problems were minimal in our infant and toddler sample. This discrepancy likely reflects that core PWS symptoms associated with sleep problems, such as hyperphagia and obesity [20], emerge later in development. The BISQ also does not capture many sleep concerns associated with PWS, such as excessive daytime sleepiness [12] and sleep-disordered breathing [20]. Our data suggest that infants and toddlers with PWS sleep more than children with other syndromes, which may indicate the early emergence of excessive sleepiness seen in older children [2]. Although the low rates of parent-reported sleep concerns we observed suggest that these sleep problems are likely minimal or absent in our PWS sample, future work is needed to characterize the emergence of these features in PWS across childhood.

4.4. Summary, limitations, and conclusions

Our findings overall suggest that sleep problems emerge as early as infancy and toddlerhood in a subset of children with neurogenetic syndromes, with different profiles emerging across genetic subgroups. Specifically, children with AS and WS exhibit reduced nighttime sleep durations that likely persist and intensify later in development, whereas children with PWS exhibit largely typical sleep patterns, potentially indicating delayed onset of problems in concordance with other medical features of PWS. This study provides novel information about the nature and severity of infant and toddler sleep profiles across AS, PWS, and WS—thus laying the foundation for the development of higher quality, targeted, and preventative treatment approaches. Despite these strengths, limitations include reliance on parent-reported sleep data and small sample sizes common to low-incidence infant neurogenetic studies. Future work is needed to replicate our findings in larger samples, assess the stability of sleep problems across childhood, and investigate the intersection of sleep with other problem behaviors and family functioning over time. This program of research will clarify the best practice for screening, diagnosing, and treating emergent sleep problems in neurogenetic syndromes, maximizing positive outcomes for affected children and families.

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Conflict of interest

The authors report no conflicts of interest.

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: http://dx.doi.org/10.1016/j.sleep.2017.07.014.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.sleep.2017.07.014.

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