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ORIGINAL PAPER

Composite Sleep Problems Observed Across Smith–Magenis Syndrome, MBD5-Associated Neurodevelopmental Disorder, Pitt–Hopkins Syndrome, and ASD

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Abstract

Caregivers of preschool and elementary school age children with Smith–Magenis syndrome (SMS), MBD5-associated neurodevelopmental disorder (MAND), and Pitt–Hopkins syndrome (PTHS) were surveyed to assess sleep disturbance and to identify disorder-specific sleep problems. Because of overlapping features of these rare genetic neurodevelopmental syndromes, data were compared to reports of sleep disturbance in children with autism spectrum disorder (ASD). While similarities were observed with ASD, specific concerns between disorders differed, including mean nighttime sleep duration, daytime sleepiness, night wakings, parasomnias, restless sleep, and bedwetting. Overall, sleep disturbance in PTHS is significant but less severe than in SMS and MAND. The complexity of these conditions and the challenges of underlying sleep disturbance indicate the need for more support, education, and ongoing management of sleep for these individuals.

Keywords Sleep disturbance · Autism spectrum disorder · Neurodevelopmental disorder · Smith–Magenis syndrome · Pitt–Hopkins syndrome · MBD5-associated neurodevelopmental disorder

Introduction

Sleep is a complex biological process that is mitigated by a wide range of internal and external cellular cues, and the primary genetic components governing the basic molecular mechanisms of this process have largely been elucidated (Ambrosius et al. 2008; Cirelli 2009; Crocker and Sehgal 2010; Gennaro et al. 2008; Tafti et al. 2005). Interestingly, with the advent of next generation sequencing and other genomic technologies, many single and contiguous gene neurodevelopmental disorders with sleep abnormalities have been identified and phenotypically characterized, implicating additional genetic components influencing sleep (Angriman et al. 2015; Blackmer and Feinstein 2016; Hoban 2000; Robinson-Shelton and Malow 2016). A recent study of a large autism spectrum disorder (ASD) cohort (n = 1859) aged 3 to 18 years indicated that children younger than 5 exhibited issues with bedtime resistance, sleep anxiety, and parasomnias, while adolescents over age 11 years had more significant problems with delayed sleep onset, shorter sleep duration, and daytime sleepiness (Goldman et al. 2012). While all children in this cohort had a clinical diagnosis of ASD, this cohort was likely heterogenous for the underlying cause of ASD, encompassing multiple genetic etiologies (Goldman et al. 2012). Thus, genetically distinct causes of ASD may have specific underlying concerns with regards to sleep disturbance. Other studies are consistent with these findings, with cohorts of ASD children reporting issues with sleep onset delay, sleep duration, and night wakings (Cortesi et al. 2010; Goodlin-Jones et al. 2008; Kotagal and Broomall 2012; Wiggs and Stores 2004). In order to develop better

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education and management of sleep concerns in genetically distinct neurodevelopmental syndromes with overlapping features with ASD, we must carefully define sleep abnormalities to determine the best approaches to sleep management toward improving quality of life for individuals with these disorders. Sleep disturbance is present in many rare neurodevelopmental disorders (NDD) such as Smith-Magenis syndrome (SMS; OMIM 182290), Pitt-Hopkins syndrome (PTHS; OMIM 610954), and *MBD5*-associated neurodevelopmental disorder (MAND; OMIM 156200); however, the specific sleep concerns have not been defined (Gropman et al. 2006; Mullegama and Elsea 2016; Smith et al. 1998, 2019; Spruyt et al. 2016; Trickett et al. 2018; Zollino et al. 2019). While there have been studies detailing the highly penetrant sleep features of SMS (Gropman et al. 2006; Smith et al. 1998, 2019; Spruyt et al. 2016; Trickett et al. 2018), sleep phenotypes are largely uncharacterized across other rare developmental disorders, including PTHS (Zollino et al. 2019) and MAND (Mullegama and Elsea 2016).

SMS is a rare, multisystem disorder in which individuals exhibit intellectual disability, developmental delays, and congenital anomalies due to haploinsufficiency of *RAI1* caused by either a chromosome 17p11.2 deletion or a pathogenic variant in *RAI1* (MIM 607642) (Smith et al. 1986; Santhosh Girirajan et al. 2008; Gropman et al. 2006; Slager et al. 2003). Individuals with SMS typically exhibit delayed language skills, characteristic behavioral anomalies, distinct craniofacial and skeletal features, and stereotypic and self-injurious behaviors (Shayota and Elsea 2019; Smith et al. 1986, 1998, 2019). One study found that 90% of their SMS cohort had Social Responsiveness Scale scores consistent with ASD, while the Social Communication Questionnaire suggested that a majority of individuals with SMS may meet criteria for ASD (Laje et al. 2010). Other neurodevelopmental characteristics include feeding difficulties and hypotonia in infancy and gross and fine motor delays in early childhood (Gropman et al. 2006; Smith et al. 1993). Individuals with SMS display a significant sleep disorder that is due to a disrupted circadian rhythm (De Leersnyder et al. 2001; Gropman et al. 2006; Smith et al. 2019; Spruyt et al. 2016; Trickett et al. 2018), which results in difficulties initiating sleep, shortened sleep cycles, prolonged and frequent night wakings, excessive daytime somnolence, snoring due to obstructive apnea, early awakenings, and bedwetting (Gropman et al. 2006; Shayota and Elsea 2019; Smith et al. 1998, 2019; Spruyt et al. 2016; Trickett et al. 2018, 2019). Sleep disturbance appears to escalate in degree of severity with age in childhood, suggesting that SMS sleep biology and sleep disturbance change with development from childhood to adolescence (Gropman et al. 2006; Smith et al. 2019).

MBD5-associated neurodevelopmental disorder (MAND) is due to haploinsufficiency of *MBD5* (MIM 611472) and caused by a deletion of chromosome 2q23.1, or a pathogenic variant in *MBD5* (Bonnet et al. 2013; Mullegama and Elsea 2016; Talkowski et al. 2011). MAND is characterized by intellectual disability and developmental delay, with significant speech impairment, and seizures (Hodge et al. 2014b). Roughly, 80% of individuals with MAND exhibit abnormal or autistic-like behaviors such as short attention span, gaze avoidance, and repetitive behaviors (Mullegama and Elsea 2016). Furthermore, 80% exhibit sleep disturbances, including recurrent nighttime waking, night terrors, and waking in the early hours of the morning, leading to excessive daytime sleepiness (Mullegama and Elsea 2016). *MBD5* regulates *RAI1* mRNA expression (Mullegama and Elsea 2016), and initial studies have indicated that MAND displays some sleep similarities to SMS (Mullegama et al. 2015). However; a larger, extended analysis of the MAND sleep phenotypic spectrum across a larger cohort to replicate initial findings is lacking.

Pitt-Hopkins syndrome (PTHS) is a rare neurodevelopmental disorder caused by heterozygous pathogenic variants in *TCF4* (MIM 602272) on chromosome 18q21.1 (Amiel et al. 2007). PTHS is characterized by moderate to severe intellectual disability and varying degrees of developmental delay, breathing problems, recurrent seizures, and distinctive facial features. Many individuals with PTHS exhibit characteristics consistent with ASD, such as impaired communication and social skills and stereotypic repeated hand movements (Peippo and Ignatius 2012; Pitt and Hopkins 1978; Watkins et al. 2019). The Social Communication Questionnaire Lifetime Version (SCQ) is a measure that is used to compare possible cases of ASD with previously diagnosed cases and controls (Berument et al. 1999), and while there has not been any similar work on using the SQC in groups with ASD-like behavior, this study found that 95.5% of their PTHS cohort met the clinical cut-off score for ASD, though the subscale profile did differ (Watkins et al. 2019). The characterization of sleep disturbances in individuals with PTHS is extremely limited, with reports characterizing some children as sleeping in excess (Peippo and Ignatius 2012) and experiencing insomnia and frequent nocturnal awakenings, as well as a lack of longer periods of sleep and problems sleeping through the night (de Winter et al. 2016; Goodspeed et al. 2018).

For children with ASD, sleep disturbance contributes to decreased quality of life both for them and their families (Delahaye et al. 2014; Mazurek and Sohl 2016). Existing research indicates that children with ASD are at a high risk of sleep disturbance (Mazurek and Sohl 2016) and exhibit significant sleep disturbance across all age levels, though the nature of the sleep disturbance differs with age (Goldman et al. 2012; Humphreys et al. 2014; Malow et al. 2016; Souders et al. 2009). Additional studies have replicated these findings and highlight that children with ASD experience more difficulty falling asleep than typical developed (TD) children

(Goldman et al. 2017; Richdale and Schreck 2009). Children with ASD also experience insomnia (Goldman et al. 2017; Richdale and Schreck 2009), which is similar to sleep disturbance reported in PTHS (de Winter et al. 2016; Goodspeed et al. 2018), and increased frequency and duration of night wakings (Goldman et al. 2017; Humphreys et al. 2014; Krakowiak et al. 2008; Richdale and Schreck 2009), similar to SMS (Gropman et al. 2006; Shayota and Elsea 2019; Smith et al. 1998; Spruyt et al. 2016; Trickett et al. 2018, 2019) and MAND (Mullegama and Elsea 2016). Younger children tend to experience more bedtime resistance, sleep anxiety, parasomnias, and night wakings, while older children and adolescents experience delayed sleep onset, shorter sleep duration, and daytime sleepiness (Goldman et al. 2012; Humphreys et al. 2014), along with associated anxiety (Mazurek and Sohl 2016; Richdale and Schreck 2009).

Taken together, previous research suggests that while SMS, MAND, PTHS, and ASD arise from different genetic etiologies and may have specific underlying sleep-related concerns, these disorders do display some overlapping sleep phenotypes. Sleep disturbance in children with these disorders can be disruptive to their own growth and development. This is partially due to not getting adequate sleep at night, but it also affects daytime activities such as worse performance in school and an inability to stay awake during educational and social activities. Sleep disturbance negatively impacts the child, but it also has consequences beyond the children themselves. A child's sleep habits can often affect the caregiver's sleep through instances such as frequent night wakings and monitoring parasomnias, so this degree of sleep disturbance can affect both the physical and mental health of the caregiver and other members of the household. Thus, it is important to identify specific features of sleep abnormalities present among children with these disorders so that they can be targeted for intervention and improvement of quality of life. In this study, we sought to investigate the phenotypic spectrum of sleep abnormalities in preschool and elementary school age children in each of these genetically distinct neurodevelopmental disorders using the Children's Sleep Health Questionnaire (CSHQ) to further delineate the nature and degree of severity of sleep abnormalities in rare disease.

Methods

Participants

Parents and/or primary caregivers of preschool and elementary school age children with SMS, MAND, or PTHS were recruited through the following Facebook support groups: Parents and Researchers Interested in Smith–Magenis Syndrome (PRISMS, Inc.), the 2q23.1 deletion syndrome group, and the Pitt-Hopkins syndrome support group and reaching out to families directly via our laboratory research enrollment database. Caregivers were contacted with a brief description of the study and time requirements and were provided a link to an online survey (www.surveymonkey.com) to which they responded anonymously.

Table 1 summarizes the demographics of each cohort, ranging from 21 to 31 children between 3–12 years of age. Levene's test for homogeneity of variances indicated no significant difference between the variances for age at the time of survey for the 3 groups ($p = 0.338$), and subsequently, a one way ANOVA revealed no significant differences between mean age at the time of the survey for SMS, MAND, and PTHS cohorts ($p = 0.735$).

We compared our data sets to previously published data regarding sleep disturbance in children with ASD and typically developing children (TD) (Hodge et al. 2014a). This dataset was chosen because the survey was caregiver reported, incorporated the Children's Sleep

Table 1 Study demographics

	SMS (n = 31)	MAND (n = 24)	PTHS (n = 21)
Gender (%)			
Male	32.3	54.2	47.6
Female	67.7	45.8	52.4
Age at time of survey (%)			
3–5 years	29	41.7	42.9
6–9 years	51.6	29.2	28.6
10–12 years	19.4	29.2	28.6
Caregiver's relationship to child (%)			
Mother	93.5	87.5	85.7
Father	3.2	12.5	9.5
Other	3.2	0	4.8
Age at diagnosis (%)			
Birth–5 months	19.4	4.2	9.5
6–11 months	16.1	12.5	9.5
1–3 years	45.2	50	42.9
4–6 years	16.1	16.7	14.3
> 6 years	3.2	16.7	23.8
Deletion or variant (%)			
Deletion	90.3	95.8	42.9
Gene variant	9.7	4.2	57.1
Method of diagnosis (%)			
FISH	48.4	0	9.5
Gene mutation testing	6.5	0	33.3
Chromosome microarray (CMA)	41.9	91.66	52.4
Whole exome sequencing (WES)	0	0	0
CMA and WES	0	4.17	0
Karyotype	9.7	0	0
Other/unsure	3.2	4.17	4.8

Health Questionnaire (CSHQ), and the ages assessed did not differ significantly from our cohorts for both the ASD and TD groups ($p = 0.8471$). The ASD data set consisted of 108 children (83.3% male) from 3 to 17 years of age (mean = 7.33 ± 3.18 years). The TD cohort, which was included for comparison to the norm, consisted of 108 children (83.3% male) with ages ranging from 3 to 17 y (mean = 7.71 ± 3.13 years). All respondents were mothers because the study was conducted with mother–child dyads, and the mothers were selected from a larger pool of families participating in a research program on parent and child functioning at a university in southern California.

Measures

The Children's Sleep Health Questionnaire (CSHQ) is a normed, caregiver reported survey used to determine the presence of sleep disturbance in preschool and elementary school aged children (Owens et al. 2000). The presence of sleep disturbance is determined from a total score generated from the sum of 8 subscales: Bedtime Resistance, Sleep Onset Delay, Sleep Duration, Sleep Anxiety, Night Wakings, Parasomnias, Sleep Disordered Breathing, and Daytime Sleepiness. A total CSHQ score > 41 indicates the presence of sleep disturbance. Although no questionnaire exists specifically for cognitively impaired populations, the CSHQ has been used extensively for children with ASD to assess sleep habits (Katz et al. 2018).

The CSHQ, along with additional questions regarding sleep problems, habits, and medications, was used to assess sleep disturbance in individuals ages 4–12 with PTHS, SMS, or MAND. Caregivers were also surveyed regarding diagnosis, family and medical history, and the use of medications to aid sleep and their effectiveness in helping initiate and maintain sleep. All 3 surveys were administered through SurveyMonkey (www.surveymonkey.com). The PTHS survey was open from 8/22/17 to 9/28/17 and collected 21 responses. The MAND survey was open from 9/19/16 to 5/27/18 and received 24 responses. The SMS survey was open from 1/29/17 to 9/26/17 and received 31 responses. Survey questions used in addition to the CSHQ are provided in the Supplemental Data.

Statistical Analysis

Results from each survey were analyzed independently and then aggregate data were compared across study populations. Individuals who provided incomplete data were excluded from analysis for that particular section of the study. Data were then compared to existing sleep data from Hodge et al. (2014a). Participants with incomplete survey sections were excluded from statistical analysis for that section. Survey data consisted of responses to the CSHQ, as well as additional questions about demographics, family history of sleep disturbance, sleep problems, and medications. Descriptive statistics were calculated for all major variables. Each set of survey data was analyzed individually by three different investigators to ensure objectivity when comparing data sets. The data sets were then compared using independent sample t-tests to identify similarities and differences between these defined genetic conditions and with published data regarding sleep in ASD. Correlation analyses using the Pearson method were conducted to determine any correlations between the features, characteristics and concerns identified in this study. One-Way Analysis of Variance (ANOVA) tests were conducted to identify statistically significant differences between mean values. Bonferroni and Tukey HSD adjusted post-hoc tests were used to identify specific differences between each population. A significance level of $p < 0.05$ was regarded as statistically significant. All analyses were performed using IBM SPSS Statistics 23 and StatPages.info. Figures were made with GraphPad Prism version 6.0 for Windows.

Results

In this study, sleep and characteristics associated with sleep disturbance across preschool and elementary school age children with SMS, MAND, or PTHS were investigated to identify common or unique patterns across these clinically similar but genetically distinct neurodevelopmental disorders. Results were also compared to reported sleep data in individuals with ASD to determine whether sleep problems in individuals with these three neurodevelopmental disorders mirror those described in individuals with ASD due to clinical and molecular overlaps between these conditions (de Winter et al. 2016; Goldman et al. 2017; Goodspeed et al. 2018; Gropman et al. 2006; Humphreys et al. 2014; Krakowiak et al. 2008; Mullegama and Elsea 2016; Richdale and Schreck 2009; Shayota and Elsea 2019; Smith et al. 1998; Spruyt et al. 2016; Trickett et al. 2018, 2019).

Sleep Duration is Altered in SMS, MAND, and PTHS

The questions presented to caregivers in this study attempted to investigate characteristics of sleep in SMS, MAND, and PTHS and to compare these findings to ASD and TD populations. Sleep disturbance was assessed across multiple factors known to impact sleep in preschool and elementary school aged children. Table 2 shows the mean duration of nighttime sleep of sleep survey respondents for each cohort. Mean nighttime sleep duration in PTHS did not differ from TD children, but all other groups reported significantly less sleep than TD. These data indicate that children with PTHS have similar sleep duration to TD children but significantly

Table 2 Mean duration of nighttime sleep in MAND resembles that in ASD

Mean Nighttime Sleep Duration (hrs ± SD)		Significance				
		SMS	MAND	PTHS	ASD	TD
SMS	7.84 ± 1.52		n.s.	**	*	**
MAND	8.41 ± 2.2			**	n.s.	*
PTHS	10.18 ± 1.52				**	n.s.
ASD	[a]8.78 ± 1.55					*
TD	[a]9.37 ± 1.27					

[a]Data from Hodge et al. (2014a)

*significance at $p < .05$

**significance at $p < .01$

n.s. not significant

Table 3 Mean duration of naps in SMS, MAND, and PTHS among those reporting napping

Age group	SMS (n = 31)	MAND (n = 24)	PTHS (n = 21)
3–5 years	1.5 ± 0.93 (n = 8/9, 88.89%)	1.5 ± 0.71 (n = 4/10, 40%)	1.62 ± 0.94 (n = 5/9, 55.55%)
6–9 years	1 ± 0.64 (n = 11/16, 68.75%)	0.5 ± 0 (n = 1/7, 14.29%)	1.5 ± 0 (n = 2/6, 33.33%)
10–12 years	1.28 ± 1.11 (n = 3/6, 50%)	1.5 ± 0 (n = 1/7, 14.29%)	n.r
All ages	1.22 ± 0.81 (n = 22/31, 70.97%)	1.33 ± 0.68 (n = 6/24, 25%)	1.58 ± 0.77 (n = 7/21, 33.33%)

Reported in h ± SD

n.r. No respondents

different than MAND ($p = 0.001$), SMS ($p < 0.001$) and ASD ($p = 0.0012$), who reported reduced mean duration of nighttime sleep. The SMS cohort reported significantly less nighttime sleep than ASD ($p = 0.0208$), PTHS ($p < 0.001$), and TD ($p < 0.001$) but did not differ significantly from MAND ($p = 0.6371$). The MAND cohort also reported significantly lower nighttime sleep duration than the TD group ($p = 0.042$) and PTHS group ($p = 0.001$) but did not differ from SMS or ASD.

While there were no significant changes in duration of nighttime sleep with age in the PTHS ($p = 0.727$) and SMS groups ($p = 0.870$), a linear regression analysis revealed that nighttime sleep duration decreased significantly with age in MAND ($p = 0.021$) (Fig. 1).

This analysis examined nighttime sleep and naps separately. While most TD preschool and elementary school age children beyond kindergarten age do not nap, napping is more common in individuals with neurodevelopmental disorders in our cohort. Table 3 shows the mean duration of naps reported by age cohort for all sleep survey respondents. A one-way ANOVA did not reveal significant differences between mean duration of naps between the three disorders; however, with the exception of SMS, few respondents reported napping (SMS, 71%; MAND, 25%; PTHS, 33%), possibly due to underlying differences in circadian rhythms, lack of need for nap, or the fact that most participants attend school and are above the age that typically allows napping at school. In SMS, more children from the 10–12 years cohort reported taking naps, indicating that this issue is prevalent in this population and that napping does contribute to total sleep time in this population.

Significant Sleep Disturbance in SMS, MAND, and PTHS Shown by CSHQ

This study utilized the CSHQ to assess the nature, frequency, and type of sleep disturbance experienced by individuals affected by these complex conditions. Table 4 shows the mean total CSHQ score for each cohort with comparison to the standard cutoff used for each subscale (Owens et al. 2000). A total score equal to or below the cutoff indicates only mild sleep disturbance, while a score above this cutoff indicates moderate to severe sleep disturbance. While significant differences were observed between the TD population and both SMS ($p < 0.001$) and MAND ($p < 0.001$), there were no significant differences in mean total CSHQ scores between the reported TD population and PTHS. However,

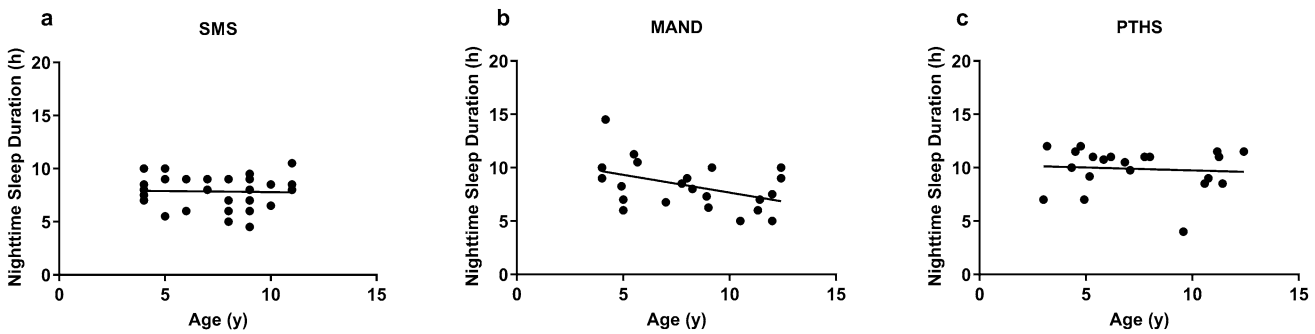

Fig. 1 Linear regression indicates that sleep duration is reduced in school-aged children with MAND. Age vs nighttime sleep duration in SMS (**a**), MAND (**b**), and PTHS (**c**)

Table 4 Mean CSHQ subscale scores

Subscale ([a]Cutoff for moderate sleep disturbance)		Mean Score	Significance				
			SMS	MAND	PTHS	ASD	TD
CSHQ Total (41)	SMS	51.81 ± 8.46		n.s.	*	n.s.	**
	MAND	55.33 ± 13.26			**	*	**
	PTHS	44.67 ± 7.91				n.s.	n.s.
	ASD	[b]48.83 ± 9.68					**
	TD	[b]42.80 ± 7.58					
Bedtime Resistance (9)	SMS	9.9 ± 3.02		n.s.	n.s.	n.s.	**
	MAND	10.67 ± 4.06			**	n.s.	**
	PTHS	7.76 ± 2.84				n.s.	n.s.
	ASD	[b]9.63 ± 3.05					**
	TD	[b]7.67 ± 2.21					
Sleep Onset Delay (1)	SMS	1.58 ± 0.76		n.s.	n.s.	n.s.	**
	MAND	1.71 ± 0.75			n.s.	n.s.	**
	PTHS	1.48 ± 0.68				n.s.	**
	ASD	[b]1.94 ± 0.74					**
	TD	[b]1.38 ± 0.60					
Sleep Duration (4)	SMS	5.71 ± 1.6		n.s.	n.s.	n.s.	**
	MAND	5.92 ± 2.06			*	n.s.	**
	PTHS	4.48 ± 1.89				n.s.	n.s.
	ASD	[b]4.96 ± 1.94					**
	TD	[b]3.87 ± 1.40					
Sleep Anxiety (6)	SMS	6.61 ± 2.03		n.s.	n.s.	n.s.	*
	MAND	7.29 ± 2.82			n.s.	n.s.	**
	PTHS	5.86 ± 1.85				n.s.	n.s.
	ASD	[b]6.67 ± 2.24					**
	TD	[b]5.38 ± 1.78					
Parasomnias (11)	SMS	11.23 ± 2.23		n.s.	n.s.	**	**
	MAND	11.29 ± 2.42			n.s.	**	**
	PTHS	11.33 ± 2.2				**	**
	ASD	[b]9.50 ± 2.48					n.s.
	TD	[b]8.86 ± 2.04					
Night Wakings (4)	SMS	5.84 ± 1.86		n.s	*	**	**
	MAND	6.5 ± 1.96			**	**	**
	PTHS	4.43 ± 1.43				n.s	n.s
	ASD	[b]4.72 ± 1.77					**
	TD	[b]3.77 ± 1.23					
Sleep Disordered Breathing (4)	SMS	4.06 ± 1.31		n.s.	n.s.	n.s.	n.s.
	MAND	4.17 ± 1.58			n.s.	n.s.	n.s.
	PTHS	3.57 ± 1.12				n.s.	n.s.
	ASD	[b]3.87 ± 1.42					n.s.
	TD	[b]3.42 ± 0.89					
Daytime Sleepiness (10)	SMS	10.32 ± 2.43		n.s.	n.s.	n.s.	n.s.
	MAND	11.54 ± 3.8			**	n.s.	n.s.
	PTHS	8.38 ± 1.86				**	**
	ASD	[b]10.88 ± 3.46					n.s.
	TD	[b]10.99 ± 2.81					

[a]Minimum score for moderate sleep disturbance from CSHQ (Owens et al. 2000)

[b]Data from Hodge et al. (2014a)

*Significance was met at the $p < .05$ level

**Significance was met at the $p < .01$ level

n.s. Not significant

significant differences between PTHS and SMS ($p = 0.0460$) and MAND ($p = 0.0010$) were observed, as well as differences between MAND and ASD ($p = 0.0147$). Further, no significant difference in total CSHQ score was observed between SMS and MAND, supporting less severe sleep disturbance in PTHS than with SMS and MAND.

Table 4 also shows the mean scores for each subscale of the CSHQ as well as significant differences for each subscale between cohorts. Overall, subscale scores indicate that sleep disturbance in PTHS is less severe than in SMS and MAND, with the exception of parasomnias (Table 4). Furthermore, sleep disturbance in PTHS does not differ significantly from TD in most subscales. The TD population did exceed the cut-off for sleep disturbance for the total CSHQ score (Table 4), but it is important to note that the cohort studied by Hodge et al. (2014a) included children between the ages of 3 and 17 years. This population does not exactly match our own, and teens have different sleeping patterns than preschool and elementary school age children, which could explain this discrepancy. The SMS and MAND cohorts scored very similarly on the CSHQ, with no significant differences on any subscale. For the bedtime resistance, sleep onset delay, sleep duration, sleep anxiety, and night awakenings subscales, the SMS and MAND groups differed significantly from TD but not from ASD (Table 4). For the parasomnias subscale, all three cohorts differed from both ASD and TD; however, no significant difference was observed between the ASD and TD groups (Table 4). No significant differences were observed between any of the 5 groups for sleep disordered breathing (Table 4). PTHS differed significantly from MAND, ASD, and TD for daytime sleepiness and there were no other differences identified between groups (Table 4).

Parasomnias, which include sleep talking, restless sleep, sleep walking, bedwetting, teeth grinding, awaking from a scary dream, and awaking screaming or sweating, were significant in all three cohorts evaluated (Fig. 2, Table 4), with 32–50% of the PTHS, MAND, and SMS respondents scoring in the moderate or severe range for the parasomnias subscale. Restless sleep and bedwetting were frequent issues across all three disorders. Bedwetting is common with developmental delay, so these findings are consistent with this indication (Touchette et al. 2005). Grinding teeth was a more prevalent issue in SMS, while sleep talking was more frequent in MAND, despite the observation of delayed speech in MAND (Mullegama and Elsea 2016).

Nighttime waking is a significant concern in many neurodevelopmental disorders (Esbensen and Schwichtenberg 2016; Hoban 2000; Robinson-Shelton and Malow 2016), consistent with findings in this study (Table 4, Fig. 3). The mean duration of a single waking among those who reported experiencing night wakings was 36.4 ± 31.1 min for SMS (range: 5–150 min), 33.6 ± 24.0 min for MAND (range: 2–90 min), and 30.5 ± 28.9 min for PTHS (range: 5–90 min), with no significant differences between mean number of night awakenings between the 3 groups. Hodge et al. (2014a) reported 23.06 ± 49.28 min of waking after sleep in the ASD cohort and 7.02 ± 9.24 min in the TD cohort. However, they reported total waking per night, while we report the duration of one waking (Hodge et al. 2014a), so the occurrence of multiple wakings per night in PTHS, SMS, and MAND individuals should be taken into account when discussing total waking duration after sleeping for the night.

Caregivers have Concerns About Sleep in their Child with SMS, MAND, and PTHS

Caregivers were assessed about sleep concerns in their child with a survey section asking whether their child experiences sleep problems and at what age they began, along with experiences with managing sleep problems with different treatments and interventions (Supplemental Data).

Caregivers across all three cohorts reported concerns about their child's sleep with various ages of onset (Fig. 4); however, not all parents of children with sleep disturbance as determined by the CSHQ indicated concern that their child had sleep problems. Only 43% of the PTHS cohort initially reported their children experience sleep problems, while 52% of SMS caregivers and 83% of MAND caregivers reported concerns related to sleep for their children (Fig. 5). In order to more fully assess the perspective of the caregiver responding to the survey about sleep disturbance in the child, we explored the possible discrepancy between caregivers reporting sleep problems and the CSHQ indicating sleep disturbance in their child (Fig. 5). In this analysis, 38.5% of caregivers in the PTHS cohort did not consider their child to experience sleep problems despite scoring greater than 41 on the CSHQ, indicating the presence of sleep disturbance. In contrast, the SMS group had almost no discrepancy between the caregiver reported sleep problems and a CSHQ score > 41. One-way ANOVAs on mean scores for each subscale suggested that PTHS children experienced significantly lower levels of bedtime resistance (Table 4), daytime sleepiness (Table 4), and night wakings (Table 4) than SMS and MAND children, all of which are notable aspects that contribute to caregivers reporting sleep problems, so this is one possible explanation for this pattern in the data.

To explore different approaches to treatment of sleep problems, we questioned whether caregivers perceived improvement with sleep problems in their child with different types of treatments or interventions (Fig. 6). Caregivers reported using at least one treatment or intervention in 57% of the PTHS cohort, 93% of the MAND cohort, and 100% of the SMS cohort. That said, some caregivers (10.71% SMS, 16.13% MAND, 23.81% PTHS) reported that their child did not have sleep problems but had used a treatment

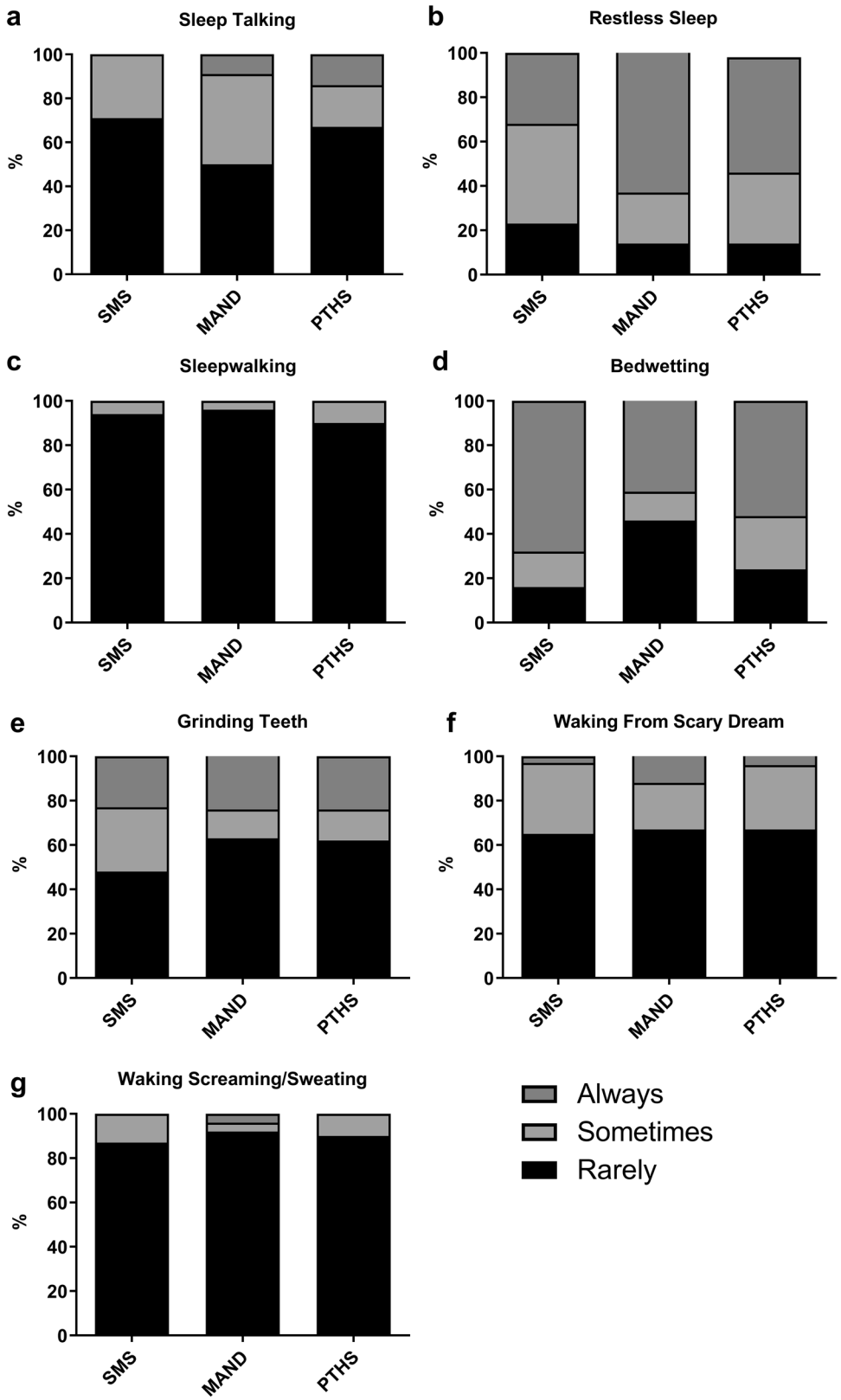

Fig. 2 Parasomnias are a major issue in SMS, MAND, and PTHS. Percent of caregivers reporting their child experiencing parasomnias "Always", "Sometimes", Or "Rarely" in the past week at time of survey

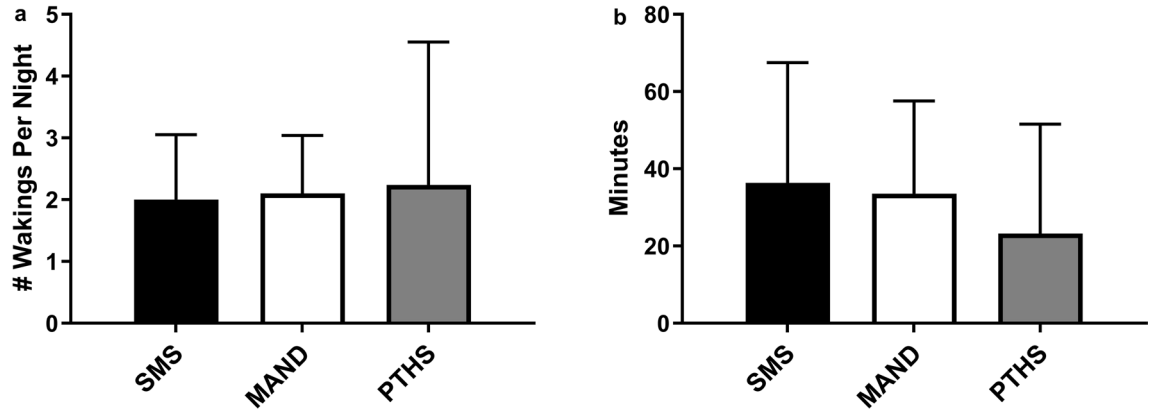

Fig. 3 Night wakings are similar in SMS, MAND, & PTHS. **a** Mean number of wakings per night as reported by caregivers in the past week at time of survey, **b** mean total duration of wakings per night as reported by caregivers in the past week at time of survey

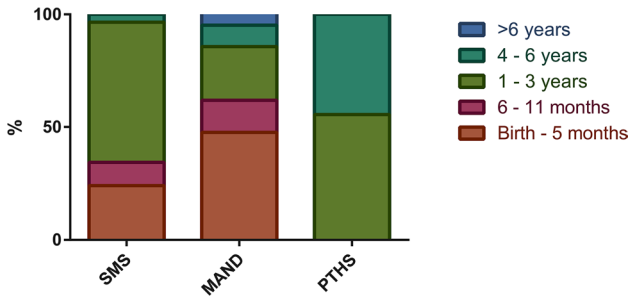

Fig. 4 Most sleep problems begin during toddler years. Percent of caregivers reporting first onset of sleep problems in each age group

or intervention. Figure 6 illustrates the percent of caregivers reporting improvement after each type of treatment or intervention. Among those that did report sleep problems, the PTHS group showed notable improvement after education sessions, other medications, and other therapies, and the SMS group showed overall notable improvement after melatonin.

Discussion

Specific aspects of sleep disturbance, as well as the differences between these sleep disturbances in SMS, MAND, and PTHS have not yet been well characterized. Several small scale studies of sleep in SMS patients have been reported (Gropman et al. 2006; Smith et al. 1998, 2019; Spruyt et al. 2016; Trickett et al. 2018, 2019), but comparable studies for PTHS and MAND have not been done. In order to fill in these gaps in the existing literature, we utilized a series of targeted questions plus the CSHQ to assess sleep concerns in preschool and elementary school age children and compared these findings to published data for both ASD and typically developing children (Hodge et al. 2014a). Some limitations

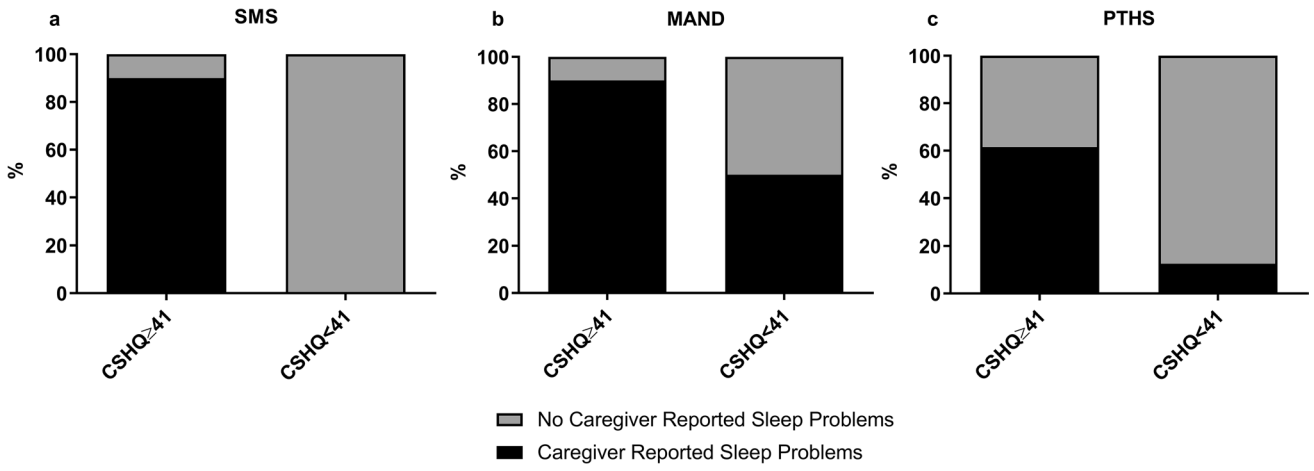

Fig. 5 Sleep problems are perceived as less of an issue in PTHS than in SMS/MAND. Percent of caregivers reporting sleep problems vs no sleep problems among those who scored ≥ 41 and < 41 on CSHQ

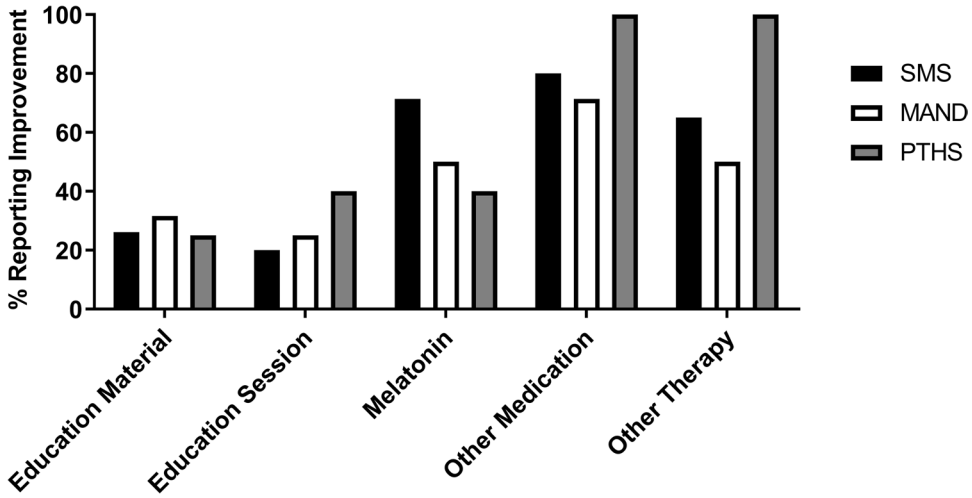

Fig. 6 Education sessions/other therapies in PTHS and melatonin in SMS are particularly effective interventions. Perceived improvement in symptoms and/or behavior as reported by caregivers having tried a treatment or intervention

in this study include small cohorts, though larger than previous studies, and since we reached out to families through email and social media, our inclusion criteria may have resulted in a non-representative sample. Our surveys were entirely caregiver reported due to the limitation of individuals who are unable to report for themselves, and caregivers were also asked to answer all questions with regard to the past week, so this could have introduced confounding data due to special circumstances. The data collected regarding interventions was also caregiver reported, so it is not possible to evaluate the consistency, dosage, or follow-through of interventions used, and it is unknown whether these interventions were directed by a healthcare professional. However, the patterns in sleep disturbance that we observed provide useful insight into potential therapies and therapeutic targets for these rare disease populations.

Shorter Sleep Duration in SMS/MAND

The SMS and MAND groups had shorter sleep duration than PTHS across all age groups, and MAND had the lowest mean duration of nighttime sleep for 10–12 year olds, suggesting that MAND and SMS patients experience deficient sleep. While the PTHS group reportedly slept for longer than the TD group, this difference was not significant and thus, we cannot confirm excessive sleep duration in this population. However, while individuals with PTHS have significantly longer mean nighttime sleep duration and exhibit less daytime sleepiness, they also scored lower on the sleep duration subscale, indicating that this is a complex issue. One possible explanation is that individuals with PTHS sleep more during the night and thus, do not experience as many issues with daytime sleepiness as the SMS and MAND groups, which sleep less during the night. All 3 groups had mean scores higher than the minimum required to be classified as moderate sleep disturbance for this subscale, but the concerns appear to be less severe in the PTHS population. With regards to naps, we note that no individuals with PTHS in the 10–12 years age cohort reported taking naps, while individuals in both the SMS and MAND groups do nap, an atypical behavior for children of this age, likely reflecting the underlying genetic etiologies for these latter two conditions. The current literature indicates that individuals with SMS typically exhibit significant daytime sleepiness (Carpizo et al. 2006; Gropman et al. 2006; Potocki et al. 2000; Smith et al. 1998), but this pattern was not evident in our cohorts, possibly due to both frequent napping and management of sleep problems using melatonin and other treatments among this group.

Sleep Disturbance is More Severe in SMS and MAND

A total score greater than 41 on the CSHQ is classified as the presence of overall sleep disturbance, and all 3 groups exceeded this cutoff, confirming what the existing literature reports about the presence of sleep disturbance in these populations (de Winter et al. 2016; Goodspeed et al. 2018; Gropman et al. 2006; Mullegama and Elsea 2016; Peippo and Ignatius 2012; Shayota and Elsea 2019; Smith et al. 1998, 2019; Spruyt et al. 2016; Trickett et al. 2018, 2019). Lower CSHQ scores suggest that overall sleep disturbance is less severe in PTHS than in SMS and MAND. However, it is important to examine specific subscales for issues that may be highlighted in certain disorders over others, as well as caregiver reports of sleep problems.

Bedtime resistance is less of an issue with PTHS than in SMS and MAND, as the mean did not meet the cutoff to qualify as moderate sleep disturbance. Furthermore, individuals with PTHS also exhibited fewer night wakings than SMS and MAND, though all 3 groups meet the cutoff for moderate sleep disturbance, and the durations of the wakings were not significantly different from each other. This observation is surprising given that other studies report

frequent night awakenings in individuals with SMS (Girirajan et al. 2005), with up to 75% experiencing awakenings in one study (De Leersnyder et al. 2001), and participants experiencing night awakenings even after melatonin use in another (Spruyt et al. 2016). Once again, this issue seems to be present in all 3 groups, though it appears less severe with PTHS than with SMS and MAND. Overall, the MAND group scored higher on the CSHQ than the SMS group. This could potentially be explained if sleep is being better addressed clinically in SMS than in MAND.

Regarding parasomnias, restless sleep was a major concern in all 3 groups, while grinding teeth was a moderate concern for only SMS, and sleep talking was a moderate concern for only MAND. Bedwetting was also a major issue in the PTHS and SMS groups but was only moderate in the MAND group. All PTHS and MAND children and all but 1 SMS child met the cutoff for moderate parasomnias, suggesting that this is a major and noticeable aspect of disturbance in patients' day to day lives.

Overall sleep patterns in the PTHS and TD cohorts did not differ significantly in many aspects. However, this is further complicated by the fact that the TD group also experienced sleep disturbance as per the CSHQ, so while they did not differ significantly from each other, neither seemed to express the normal phenotype for sleep. Additionally, while our cohorts were limited to ages 3 to 12, the TD group included individuals between the ages of 3 and 17, which is a wider age range that included teenagers who may have different sleep patterns and needs (Hodge et al. 2014a; Mercer et al. 1998). However, the SMS and MAND groups did exhibit significantly different sleep patterns from the TD group, which was expected based on what we know about the disruption of circadian pathways common to SMS and MAND (Mullegama et al. 2015). The SMS and MAND groups also resembled the ASD group in bedtime resistance, sleep onset delay, sleep duration, sleep anxiety, and night wakings, suggesting that these aspects of sleep disturbance mirror those in children with ASD, which has implications for potential success in using similar treatment and management strategies.

Discrepancy in Caregiver Reporting of Sleep Problems in Their Child

A greater percentage of SMS and MAND caregivers reported their children experiencing problems with sleep than PTHS respondents. MAND caregivers also tended to first report sleep problems at the youngest age, while SMS and PTHS were reported sleep problems at a later age, typically between 1–3 years for SMS and 1–6 years for PTHS. Very few MAND caregivers reported first experiencing sleep problems at later ages, suggesting that sleep problems in MAND may manifest earlier or may be noticeable to caregivers earlier than in SMS or PTHS. Infants with SMS often experience hypersomnolence during the first year of life, and difficulty falling asleep becomes noticeable in older children (Girirajan et al. 2008); further, sleep disturbance is a key concern in SMS so families are typically educated early on and often supported to treat any concern for sleep disturbance, so these issues may also explain some differences in reporting.

Furthermore, it is important to compare caregiver reports of sleep problems with the diagnosis of sleep problems based on the CSHQ. In PTHS, 38.5% of children showed sleep disturbance based on the CSHQ, but the caregivers did not consider it to be an issue (Fig. 5), further supporting our previous conclusion that disturbance in PTHS may be milder. However, PTHS also had the greatest number of cases where the CSHQ did not report sleep disturbance but the caregivers did report sleep problems (Fig. 5), highlighting the need to consider that sleep disturbance may differ based on a case by case basis with regards to what the caregiver considers to be a problem. Sleep disturbance and caregiver reporting are further complicated by medications taken by both the child and caregiver to moderate and manage sleep. Many caregivers reported that their child does not have sleep problems, but the child may in fact experience significant sleep disturbance that is ameliorated by one or more treatments/interventions, suggesting that a larger proportion of these cohorts may be sleep disturbed than previously thought. Earlier diagnosis of sleep disturbance also impacts this treatment and subsequent reporting. Some families that participated in this study reside outside of the United States, so the impact of cultural and societal differences on sleep and the manageability of PTHS, MAND, and SMS could not be adequately assessed and is an area for further research.

Comparison of SMS, MAND, and PTHS to ASD/TD

These data show that several aspects of sleep disturbance across these three neurodevelopmental conditions overlap with concerns in the ASD population (Hodge et al. 2014a), including sleep duration, daytime sleepiness, sleep anxiety, and bedtime resistance.

The fact that these genetically distinct disorders have overlapping aspects with ASD with regard to sleep disturbance support the fact that ASD is a clinical diagnosis that includes a wide range of etiologies, diagnoses, and severities of sleep disturbance, and and that features of PTHS, SMS, and MAND all overlap with some aspects of ASD.

The TD population (Hodge et al. 2014a) exceeded cutoffs for moderate sleep disturbance on the daytime sleepiness subscale, as well as the total CSHQ score, bringing into question the presence of already existing sleep disturbance in children without ASD or other neurodevelopmental disorders examined in this study. However, these authors concluded that significantly fewer TD children attained scores of

41 or higher and children with ASD were more likely to have overall sleep problems (Hodge et al. 2014a). Sleep problems in TD children were also more likely to diminish with age than in ASD children (Hodge et al. 2014a).

Effectiveness of Treatments and Interventions

The perceived effectiveness of different treatments/interventions for sleep problems (Fig. 6) varied across all three disorders. Overall, educational material and education sessions were less effective than medications and therapies; however, educational interventions appeared to be more effective in PTHS than in SMS or MAND. While melatonin was reportedly effective in the SMS group for improvement of sleep problems, a number of other medications were reportedly effective in all groups on a case-by-case basis, including guanfacine, clonidine, risperidone, trazodone, acebutolol, and antihistamines (diphenhydramine). Consideration of the effectiveness of melatonin vs some of the reported other medications for each disorder may be a key area for future research, with a particular focus on identifying altered physiological pathways that may be impacted in these conditions and developing targeted approaches to therapy (Elsea and Williams 2011; Mullegama and Elsea 2016; Peippo and Ignatius 2012). Other therapies caregivers reported as effective in showing improvement for the PTHS group, in particular, included homeopathic preparation, cherry juice, vitamins, strict and consistent bedtimes, lavender oil, Herbalife Sleep, therapeutic listening, visual therapies, ABA therapy, OT, and blue lights.

Conclusions

Overall, this study confirms and further defines sleep disturbance in SMS, MAND, and PTHS populations. These three neurodevelopmental disorders differed in aspects and extent of sleep disturbance, as well as the effectiveness of traditionally used interventions and treatments. PTHS has significantly less severe sleep disturbance than SMS and MAND, while SMS and MAND have relatively similar patterns of sleep disturbance despite different genetic causes; however, these findings are consistent with previously published data showing interconnecting molecular networks in circadian pathways in these two conditions (Mullegama and Elsea 2016; Mullegama et al 2015). All three disorders exhibit sleep disturbance similar to that found in comparable groups with ASD in different aspects, including bedtime resistance, sleep onset delay, sleep duration, sleep anxiety, and sleep disordered breathing. The problem aspects of sleep identified in this study are critical for developing treatments and therapies that alleviate the specific aspects of sleep disturbance experienced by each population and will support therapeutic approaches that may improve sleep across all populations.

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Author Contributions AG and SHE conceptualized and designed the study. SHE supervised data collection. MF and EC desigend and reviewed surveys and data. AG and DZ conducted the analyses, and AG analyzed the data and drafted the initial manuscript. JA and SHE critically reviewed and edited the manuscript, and all authors approved the final manuscript as submitted.

References

Ambrosius, U., Lietzenmaier, S., Wehrle, R., Wichniak, A., Kalus, S., Winkelmann, J., et al. (2008). Heritability of sleep electroencephalogram. *Biological Psychiatry, 64*(4), 344–348. https://doi.org/10.1016/j.biopsych.2008.03.002.

Amiel, J., Rio, M., de Pontual, L., Redon, R., Malan, V., Boddaert, N., et al. (2007). Mutations in TCF4, encoding a class I basic helix-loop-helix transcription factor, are responsible for Pitt-Hopkins syndrome, a severe epileptic encephalopathy associated with autonomic dysfunction. *American Journal of Human Genetics, 80*(5), 988–993. https://doi.org/10.1086/515582.

Angriman, M., Caravale, B., Novelli, L., Ferri, R., & Bruni, O. (2015). Sleep in children with neurodevelopmental disabilities. *Neuropediatrics, 46*(3), 199–210. https://doi.org/10.1055/s-0035-1550151.

Berument, S. K., Rutter, M., Lord, C., Pickles, A., & Bailey, A. (1999). Autism screening questionnaire: Diagnostic validity. *The British Journal of Psychiatry, 175*, 444–451. https://doi.org/10.1192/bjp.175.5.444.

Blackmer, A. B., & Feinstein, J. A. (2016). Management of sleep disorders in children with neurodevelopmental disorders: A review. *Pharmacotherapy, 36*(1), 84–98. https://doi.org/10.1002/phar.1686.

Bonnet, C., Ali Khan, A., Bresso, E., Vigouroux, C., Béri, M., Lejczak, S., et al. (2013). Extended spectrum of MBD5 mutations in neurodevelopmental disorders. *European Journal of Human Genetics EJHG, 21*(12), 1457–1461. https://doi.org/10.1038/ejhg.2013.22.

Carpizo, R., Martínez, Á., Mediavilla, D., González, M., Abad, A., & Sánchez-Barceló, E. J. (2006). Smith-Magenis syndrome: A case report of improved sleep after treatment with β1-adrenergic antagonists and melatonin. *The Journal of Pediatrics, 149*(3), 409–411. https://doi.org/10.1016/j.jpeds.2006.04.055.

Cirelli, C. (2009). The genetic and molecular regulation of sleep: From fruit flies to humans. *Nature Reviews Neuroscience, 10*(8), 549–560. https://doi.org/10.1038/nrn2683.

Cortesi, F., Giannotti, F., Ivanenko, A., & Johnson, K. (2010). Sleep in children with autistic spectrum disorder. *Sleep Medicine, 11*(7), 659–664. https://doi.org/10.1016/j.sleep.2010.01.010.

Crocker, A., & Sehgal, A. (2010). Genetic analysis of sleep. *Genes & Development, 24*(12), 1220–1235. https://doi.org/10.1101/gad.1913110.

De Leersnyder, H., de Blois, M.-C., Claustrat, B., Romana, S., Albrecht, U., von Kleist-Retzow, J.-C., et al. (2001). Inversion of the circadian rhythm of melatonin in the Smith-Magenis syndrome. *The Journal of Pediatrics, 139*(1), 111–116. https://doi.org/10.1067/mpd.2001.115018.

de Winter, C. F., Baas, M., Bijlsma, E. K., van Heukelingen, J., Routledge, S., & Hennekam, R. C. M. (2016). Phenotype and natural history in 101 individuals with Pitt-Hopkins syndrome through an internet questionnaire system. *Orphanet Journal of Rare Diseases, 11*, 37. https://doi.org/10.1186/s13023-016-0422-2.

Delahaye, J., Kovacs, E., Sikora, D., Hall, T. A., Orlich, F., Clemons, T. E., et al. (2014). The relationship between health-related quality of life and sleep problems in children with autism spectrum disorders. *Research in Autism Spectrum Disorders, 8*(3), 292–303. https://doi.org/10.1016/j.rasd.2013.12.015.

Elsea, S. H., & Williams, S. R. (2011). Smith-Magenis syndrome: Haploinsufficiency of RAI1 results in altered gene regulation in neurological and metabolic pathways. *Expert Reviews in Molecular Medicine*. https://doi.org/10.1017/S1462399411001827.

Esbensen, A. J., & Schwichtenberg, A. J. (2016). Sleep in neurodevelopmental disorders. *International Review of Research in Developmental Disabilities, 51*, 153–191. https://doi.org/10.1016/bs.irrdd.2016.07.005.

Gennaro, L. D., Marzano, C., Fratello, F., Moroni, F., Pellicciari, M. C., Ferlazzo, F., et al. (2008). The electroencephalographic fingerprint of sleep is genetically determined: A twin study. *Annals of Neurology, 64*(4), 455–460. https://doi.org/10.1002/ana.21434.

Girirajan, S., Elsas, L. J., Devriendt, K., & Elsea, S. H. (2005). RAI1 variations in Smith-Magenis syndrome patients without 17p11.2 deletions. *Journal of Medical Genetics, 42*(11), 820–828. https://doi.org/10.1136/jmg.2005.031211.

Girirajan, S., Patel, N., Slager, R. E., Tokarz, M. E., Bucan, M., Wiley, J. L., et al. (2008). How much is too much? Phenotypic consequences of Rai1 overexpression in mice. *European Journal of Human Genetics EJHG, 16*(8), 941–954. https://doi.org/10.1038/ejhg.2008.21.

Goldman, S. E., Alder, M. L., Burgess, H. J., Corbett, B. A., Hundley, R., Wofford, D., et al. (2017). Characterizing sleep in adolescents and adults with autism spectrum disorders. *Journal of Autism and Developmental Disorders, 47*(6), 1682–1695. https://doi.org/10.1007/s10803-017-3089-1.

Goldman, S. E., Richdale, A. L., Clemons, T., & Malow, B. A. (2012). Parental sleep concerns in autism spectrum disorders: Variations from childhood to adolescence. *Journal of Autism and Developmental Disorders, 42*(4), 531–538. https://doi.org/10.1007/s10803-011-1270-5.

Goodlin-Jones, B. L., Tang, K., Liu, J., & Anders, T. F. (2008). Sleep patterns in preschool-age children with autism, developmental delay, and typical development. *Journal of the American Academy of Child and Adolescent Psychiatry, 47*(8), 930–938. https://doi.org/10.1097/CHI.ObO13e3181799f7c.

Goodspeed, K., Newsom, C., Morris, M. A., Powell, C., Evans, P., & Golla, S. (2018). Pitt-Hopkins syndrome: A review of current literature, clinical approach, and 23-patient case series. *Journal of Child Neurology, 33*(3), 233–244. https://doi.org/10.1177/0883073817750490.

Gropman, A. L., Duncan, W. C., & Smith, A. C. M. (2006). Neurologic and developmental features of the Smith-Magenis syndrome (del 17p11.2). *Pediatric Neurology, 34*(5), 337–350. https://doi.org/10.1016/j.pediatrneurol.2005.08.018.

Hoban, T. F. (2000). Sleeplessness in children with neurodevelopmental disorders. *CNS Drugs, 14*(1), 11–22. https://doi.org/10.2165/00023210-200014010-00002.

Hodge, D., Carollo, T. M., Lewin, M., Hoffman, C. D., & Sweeney, D. P. (2014a). Sleep patterns in children with and without autism spectrum disorders: Developmental comparisons. *Research in Developmental Disabilities, 35*(7), 1631–1638. https://doi.org/10.1016/j.ridd.2014.03.037.

Hodge, J. C., Mitchell, E., Pillalamarri, V., Toler, T. L., Bartel, F., Kearney, H. M., et al. (2014b). Disruption of MBD5 contributes to a spectrum of psychopathology and neurodevelopmental abnormalities. *Molecular Psychiatry, 19*(3), 368–379. https://doi.org/10.1038/mp.2013.42.

Humphreys, J. S., Gringras, P., Blair, P. S., Scott, N., Henderson, J., Fleming, P. J., et al. (2014). Sleep patterns in children with autistic spectrum disorders: A prospective cohort study. *Archives of Disease in Childhood, 99*(2), 114–118. https://doi.org/10.1136/archdischild-2013-304083.

Katz, T., Shui, A. M., Johnson, C. R., Richdale, A. L., Reynolds, A. M., Scahill, L., et al. (2018). Modification of the children's sleep habits questionnaire for children with autism spectrum disorder. *Journal of Autism and Developmental Disorders, 48*(8), 2629–2641. https://doi.org/10.1007/s10803-018-3520-2.

Kotagal, S., & Broomall, E. (2012). Sleep in children with autism spectrum disorder. *Pediatric Neurology, 47*(4), 242–251. https://doi.org/10.1016/j.pediatrneurol.2012.05.007.

Krakowiak, P., Goodlin-Jones, B., Hertz-Picciotto, I., Croen, L. A., & Hansen, R. L. (2008). Sleep problems in children with autism spectrum disorders, developmental delays, and typical development: A population-based study. *Journal of Sleep Research, 17*(2), 197–206. https://doi.org/10.1111/j.1365-2869.2008.00650.x.

Laje, G., Morse, R., Richter, W., Ball, J., Pao, M., & Smith, A. C. M. (2010). Autism spectrum features in Smith-Magenis syndrome. *American Journal of Medical Genetics Part C, 154C*(4), 456–462. https://doi.org/10.1002/ajmg.c.30275.

Malow, B. A., Katz, T., Reynolds, A. M., Shui, A., Carno, M., Connolly, H. V., et al. (2016). Sleep difficulties and medications in children with autism spectrum disorders: A registry study. *Pediatrics, 137*(Suppl 2), S98–S104. https://doi.org/10.1542/peds.2015-2851H.

Mazurek, M. O., & Sohl, K. (2016). Sleep and behavioral problems in children with autism spectrum disorder. *Journal of Autism and Developmental Disorders, 46*(6), 1906–1915. https://doi.org/10.1007/s10803-016-2723-7.

Mercer, P. W., Merritt, S. L., & Cowell, J. M. (1998). Differences in reported sleep need among adolescents. *Journal of Adolescent Health, 23*(5), 259–263. https://doi.org/10.1016/S1054-139X(98)00037-8.

Mullegama, S. V., & Elsea, S. H. (2016). Clinical and molecular aspects of MBD5-associated neurodevelopmental disorder (MAND). *European Journal of Human Genetics, 24*(9), 1235–1243. https://doi.org/10.1038/ejhg.2016.35.

Mullegama, S. V., Pugliesi, L., Burns, B., Shah, Z., Tahir, R., Gu, Y., et al. (2015). MBD5 haploinsufficiency is associated with sleep disturbance and disrupts circadian pathways common to Smith-Magenis and fragile X syndromes. *European Journal of Human Genetics: EJHG, 23*(6), 781–789. https://doi.org/10.1038/ejhg.2014.200.

Owens, J. A., Spirito, A., & McGuinn, M. (2000). The children's sleep habits questionnaire (CSHQ): Psychometric properties of a survey instrument for school-aged children. *Sleep, 23*(8), 1043–1051.

Peippo, M., & Ignatius, J. (2012). Pitt-Hopkins syndrome. *Molecular Syndromology, 2*(3–5), 171–180. https://doi.org/10.1159/000335287.

Pitt, D., & Hopkins, I. (1978). A syndrome of mental retardation, wide mouth and intermittent overbreathing. *Journal of Paediatrics and Child Health, 14*(3), 182–184. https://doi.org/10.1111/jpc.1978.14.3.182.

Potocki, L., Glaze, D., Tan, D.-X., Park, S.-S., Kashork, C. D., Shaffer, L. G., et al. (2000). Circadian rhythm abnormalities of melatonin in Smith-Magenis syndrome. *Journal of Medical Genetics, 37*(6), 428–433. https://doi.org/10.1136/jmg.37.6.428.

Richdale, A. L., & Schreck, K. A. (2009). Sleep problems in autism spectrum disorders: Prevalence, nature, & possible biopsychosocial aetiologies. *Sleep Medicine Reviews, 13*(6), 403–411. https://doi.org/10.1016/j.smrv.2009.02.003.

Robinson-Shelton, A., & Malow, B. A. (2016). Sleep disturbances in neurodevelopmental disorders. *Current Psychiatry Reports, 18*(1), 6. https://doi.org/10.1007/s11920-015-0638-1.

Shayota, B. J., & Elsea, S. H. (2019). Behavior and sleep disturbance in Smith-Magenis syndrome. *Current Opinion in Psychiatry, 32*(2), 73–78. https://doi.org/10.1097/YCO.0000000000000474.

Slager, R. E., Newton, T. L., Vlangos, C. N., Finucane, B., & Elsea, S. H. (2003). Mutations in RAI1 associated with Smith-Magenis syndrome. *Nature Genetics, 33*(4), 466–468. https://doi.org/10.1038/ng1126.

Smith, A. C., Dykens, E., & Greenberg, F. (1998). Sleep disturbance in Smith-Magenis syndrome (del 17 p11.2). *American Journal of Medical Genetics, 81*(2), 186–191.

Smith, A. C. M., Morse, R. S., Introne, W., & Duncan, W. C. (2019). Twenty-four-hour motor activity and body temperature patterns suggest altered central circadian timekeeping in Smith-Magenis syndrome, a neurodevelopmental disorder. *American Journal of Medical Genetics. Part A, 179*(2), 224–236. https://doi.org/10.1002/ajmg.a.61003.

Smith, A. C., McGavran, L., Robinson, J., Waldstein, G., Macfarlane, J., Zonona, J., et al. (1986). Interstitial deletion of (17)(p11.2p11.2) in nine patients. *American Journal of Medical Genetics, 24*(3), 393–414. https://doi.org/10.1002/ajmg.1320240303.

Smith, Ann CM, Boyd, K. E., Brennan, C., Charles, J., Elsea, S. H., Finucane, B. M., Foster, R., Gropman, A., Girirajan, S., & Haas-Givler, B. (1993). Smith-Magenis syndrome. In M. P. Adam, H. H. Ardinger, R. A. Pagon, S. E. Wallace, L. J. Bean, K. Stephens, & A. Amemiya (Eds.), *GeneReviews®*. University of Washington, Seattle. https://www.ncbi.nlm.nih.gov/books/NBK1310/

Souders, M. C., Mason, T. B. A., Valladares, O., Bucan, M., Levy, S. E., Mandell, D. S., et al. (2009). Sleep behaviors and sleep quality in children with autism spectrum disorders. *Sleep, 32*(12), 1566–1578. https://doi.org/10.1093/sleep/32.12.1566.

Spruyt, K., Braam, W., Smits, M., & Curfs, L. M. (2016). Sleep complaints and the 24-h melatonin level in Individuals with Smith-Magenis syndrome: Assessment for effective intervention. *CNS Neuroscience & Therapeutics, 22*(11), 928–935. https://doi.org/10.1111/cns.12653.

Tafti, M., Maret, S., & Dauvilliers, Y. (2005). Genes for normal sleep and sleep disorders. *Annals of Medicine, 37*(8), 580–589. https://doi.org/10.1080/07853890500372047.

Talkowski, M. E., Mullegama, S. V., Rosenfeld, J. A., van Bon, B. W. M., Shen, Y., Repnikova, E. A., et al. (2011). Assessment of 2q23.1 microdeletion syndrome implicates MBD5 as a single causal locus of intellectual disability, epilepsy, and autism spectrum disorder. *American Journal of Human Genetics, 89*(4), 551–563. https://doi.org/10.1016/j.ajhg.2011.09.011.

Touchette, É., Petit, D., Paquet, J., Tremblay, R. E., Boivin, M., & Montplaisir, J. Y. (2005). Bed-wetting and its association with developmental milestones in early childhood. *Archives of Pediatrics & Adolescent Medicine, 159*(12), 1129–1134. https://doi.org/10.1001/archpedi.159.12.1129.

Trickett, J., Heald, M., Oliver, C., & Richards, C. (2018). A cross-syndrome cohort comparison of sleep disturbance in children with Smith-Magenis syndrome, Angelman syndrome, autism spectrum disorder and tuberous sclerosis complex. *Journal of Neurodevelopmental Disorders, 10*(1), 9. https://doi.org/10.1186/s11689-018-9226-0.

Trickett, J., Oliver, C., Heald, M., Denyer, H., Surtees, A., Clarkson, E., et al. (2019). Sleep in children with Smith-Magenis syndrome: A case-control actigraphy study. *Sleep*. https://doi.org/10.1093/sleep/zsz260.

Watkins, A., Bissell, S., Moss, J., Oliver, C., Clayton-Smith, J., Haye, L., et al. (2019). Behavioural and psychological characteristics in Pitt-Hopkins syndrome: A comparison with Angelman and Cornelia de Lange syndromes. *Journal of Neurodevelopmental Disorders, 11*(1), 24. https://doi.org/10.1186/s11689-019-9282-0.

Wiggs, L., & Stores, G. (2004). Sleep patterns and sleep disorders in children with autistic spectrum disorders: Insights using parent report and actigraphy. *Developmental Medicine and Child Neurology, 46*(6), 372–380. https://doi.org/10.1017/s0012162204000611.

Zollino, M., Zweier, C., Van Balkom, I. D., Sweetser, D. A., Alaimo, J., Bijlsma, E. K., et al. (2019). Diagnosis and management in Pitt-Hopkins syndrome: First international consensus statement. *Clinical Genetics, 95*(4), 462–478. https://doi.org/10.1111/cge.13506.