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ORIGINAL ARTICLE

Sleep and Phelan–McDermid Syndrome: Lessons from the International Registry and the scientific literature

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Abstract

Background: Sleep is essential to maintaining a healthy life. Sleep disturbances among individuals with neurodevelopmental disorders are not well studied, affecting their early detection and treatment. Sleep disturbances in individuals with Phelan–McDermid Syndrome (PMS) are among the primary concerns reported by parents. However, little research has been aimed at addressing their concern.

Methods: The purpose of this investigation was to identify and quantify specific sleep disturbances in people with PMS by analyzing data collected by the PMS Foundation International Registry.

Results: The registry shows that 284 out of 384 (73.4%) individuals with confirmed chromosome 22q13 deletions or *SHANK3* pathogenic variants have a sleep disturbance. The prevalence of sleep disturbances increases with age with 56% reporting a sleep disturbance in the 0–3 year age group and 90% reporting these disturbances in those over age 18 years old. The primary sleep disturbances were circadian rhythm sleep disorders that included difficulty falling asleep, frequent nighttime awakenings, difficulty returning to sleep after a nighttime awakening event, and hypersomnia and parasomnias including enuresis, night terrors, sleepwalking, and sleep apnea. Sleep disturbances were similarly frequent among individuals with *SHANK3* pathogenic variants (84.8%) and those with deletions (71.9%), supporting the role of haploinsufficiency of *SHANK3* in sleep.

Conclusion: Sleep disturbances are a common feature of PMS and should be considered in clinical evaluation and management because of the effect they have on the quality of life of the patients and their families.

KEYWORDS

Phelan-McDermid Syndrome, PMS, sleep disturbance, SHANK3, 22q13 deletion syndrome

1 | INTRODUCTION

1.1 | Sleep and sleep disturbances

Sleep is necessary for all people and animals to maintain proper metabolic homeostasis. In recent years, sleep has been found to have an essential role in the development, energy conservation, and maintaining a healthy brain and body via regulating immune responses (Eugene & Masiak, 2015; Zielinski et al., 2016). The exact molecules, genes, and molecular and physiological pathways that interact to regulate sleep are complex and are still being investigated. The importance of sleep can be seen through the effects of lack of sleep on individuals and their health. Short-term effects include an increased risk of accidents, the inability to focus or concentrate on tasks, and a negative influence on mood and behavior in healthy individuals (Chokroverty, 2010; Eugene & Masiak, 2015; Ramar & Olson, 2013). Many long-term observational studies have found that people receiving inadequate amounts of restful sleep have an increased risk of obesity, heart disease, depression, dementia, diabetes, and early death (Chokroverty, 2010; Xie et al., 2017). Sleep affects metabolic and neurologic processes and has a significant impact on the quality of life for individuals with PMS and their families (Bro et al., 2017).

Sleep abnormalities are described in the scientific literature as sleep disorders or disturbances. We could not find consistent criteria to differentiate the two categories; the terms are used as equivalent in many papers and, consequently, in this study as well. To align better with the data collected from the Phelan–McDermid Syndrome International Registry, we will refer to abnormalities in sleep as sleep disturbances. Disturbances that affect sleep typically involve the amount of sleep, the quality of the sleep, and the timing of sleep (Shanahan et al., 2019). The most common sleep disturbances fall into three categories: circadian rhythm sleep disorders (CRSDs), parasomnias, and sleep apnea. CRSDs are characterized as the inability to sleep during desired times (Glickman, 2010). Symptoms include difficulty getting to sleep, difficulty staying asleep, waking early in the morning, and daytime sleepiness (Carter et al., 2014; Glickman, 2010). Parasomnias are sleep disturbances that occur from an undesired event—behavioral or physiological—while sleeping (Carter et al., 2014; Chokroverty, 2010; Ophoff et al., 2018; Thorpy, 2012). These events are divided into nonrapid eye movement (NREM) and rapid eye movement (REM) related parasomnias based on when the event generally occurs during the sleep cycle (Ophoff et al., 2018). A distinct classification for parasomnias encompasses enuresis (bedwetting), sleep-related hallucinations, and sleep-related groaning (Chokroverty, 2010; Ophoff et al., 2018; Thorpy, 2012). Enuresis is considered a primary sleep disorder for a child over the age of 5 who has not been dry for 6 months or longer (Thorpy, 2012). However, children considered intellectually disabled should have reached a mental age of 4 years old before they are considered enuretic. According to the ICSD-3 (International Classification of Sleep Disorders-3rd edition), sleepwalking, sleep-talking, and sleep terrors, also known as night terrors, are NREM-related sleeping disorders (Ophoff et al., 2018; Thorpy, 2012). NREM-related parasomnias tend to occur during the deep sleep cycle and within the first third of the night, whereas REM-related parasomnias occur when an individual is in a lighter stage of sleep later in the night (Chokroverty, 2010; Ramar & Olson, 2013; Salkind & Sutcliffe, 2015). REM-related parasomnias include nightmare disorder, isolated sleep paralysis, bruxism, and REM sleep behavior disorder (RSBD) (Ophoff et al., 2018; Singh et al., 2018; Thorpy, 2012). Sleep apnea occurs due to the partial or complete closure of the upper airway (Carter et al., 2014; Ramar & Olson, 2013). This obstruction causes inadequate ventilation leading to inconsistent breathing patterns, difficulty taking a breath, and abnormal breathing sounds (Thorpy, 2012). Sleep apnea symptoms include loud snoring, choking during sleep, enuresis generally in children, insomnia, abnormal movements during sleep, breathing stops, and severe sleep disruptions (Carter et al., 2014; Chokroverty, 2010). Polysomnography is necessary to diagnose and treat sleep apnea so that severe complications such as cardiovascular disease, and developmental and behavioral disorders can be prevented (Salkind & Sutcliffe, 2015).

Sleep disturbances are typically classified as primary or secondary. Primary sleep disorders are not resulting from or are associated with a particular medical condition (Dikeos & Georgantopoulos, 2011). Secondary sleep disorders are caused by another medical problem such as depression, stroke, dementia, or by a condition such as Phelan–McDermid Syndrome, Parkinson's Disease, Fragile X syndrome, or Rett syndrome (Agar et al., 2021; Chokroverty, 2010; Smith-Hicks et al., 2021). Sleep disorders can be particularly problematic in people with developmental disabilities which encompasses intellectual disabilities, autism spectrum disorder (ASD), and certain genetic conditions (Moss et al., 2014). It is estimated that 85% of individuals with a developmental disability have a sleep disturbance (Moss et al., 2014; Spruyt & Curfs, 2015). In individuals with developmental disorders, a sleeping disturbance may manifest as having difficulties calming down at night, nighttime awakening, sleep-disordered breathing, and daytime sleepiness (Moss et al., 2014). Children with developmental disabilities and sleep disturbances are more likely to display behavioral problems such as aggressive behavior, hyperactivity,

and lack of emotional control leading to outbursts and noncompliance (Didden et al., 2002; Moss et al., 2014). Among neurodevelopmental disorders, ASD has been frequently associated with sleep disturbances. Sleep has been extensively characterized in individuals with ASD with a prevalence of 44%–83% (Kotagal & Broomall, 2012; Surtees et al., 2019). Currently, no drugs have been FDA approved to treat all symptoms of sleep disturbances experienced by individuals with developmental disabilities. Many nonpharmacological methods have been used to develop better bedtime routines. However, the variability of the disorders and conditions encompassed by a developmental disability diagnosis requires research and treatment to be specific to the condition.

1.2 | Phelan–McDermid Syndrome

Phelan–McDermid Syndrome (PMS) is a rare neurodevelopmental disorder, also known as 22q13.3 deletion syndrome (OMIM #606232). PMS can be caused by terminal deletions or other rearrangement affecting the distal region of chromosome 22 or pathogenic variants within the *SHANK3* (SH3 and multiple ankyrin repeat domains 3) gene, mapping to 22q13.33 (Costales & Kolevzon, 2015; Phelan et al., 2005). These deletions can range from as small as 29 kb to greater than 9 Mb and generally include the terminal end of the chromosome (Phelan et al., 2005; Ponson et al., 2018; Sarasua et al., 2011; Soorya et al., 2013). The exact prevalence of PMS is currently unknown. However, Bro et al. (2017) estimated the prevalence of individuals affected by PMS to range from 1 in every 10,000 to 20,000 people, and that about 1% of all individuals with autism also have PMS (Bro et al., 2017). PMS is an underdiagnosed neurodevelopmental disorder with approximately 2500 individuals enrolled within the PMSF registry worldwide (PMSF, 2020). Due to the extreme variation in PMS phenotype, establishing a clinical diagnosis is challenging and individuals require confirmatory genetic tests (Phelan et al., 2005; Sarasua et al., 2011). The *SHANK3* gene encodes for a critical scaffolding protein of the postsynaptic density playing an essential role in the function and maintenance of excitatory synapses (Bozdagi et al., 2010; Grabrucker et al., 2012; Kolevzon et al., 2014). Mutations and deletions that cause *SHANK3* haploinsufficiency are considered to be the major cause of the neurological phenotype of PMS.

Individuals with PMS can present with a wide variety of clinical characteristics, including neonatal hypotonia, global developmental delays, intellectual disability, absence or severely delayed speech, seizures, deficits in motor function and abilities, kidney malformations, brain abnormalities, and ASD (De Rubeis et al., 2018; Ricciardello et al., 2021; Sarasua et al., 2014). As these individuals age, they tend to exhibit regression of their motor skills starting as early as age four for an average of 50% of individuals (Phelan & McDermid, 2012; Zwanenburg et al., 2016). Many studies on PMS have observed that more than 40% of all patients with PMS experience seizures, sleep disturbances, and neuroanatomical abnormalities (Ricciardello et al., 2021). Genotype–phenotype correlation studies have reported that the deletion size is positively associated with the severity of behavioral problems, macrocephaly, and speech abilities (Oberman et al., 2015; Sarasua et al., 2014). The signs and symptoms of PMS vary significantly between patients; therefore, people with PMS require multiple specialists to manage the wide variety of clinical manifestations of the syndrome. Better characterization of the clinical features of PMS is needed to aid in the treatment and quality of life for these individuals and their families.

In order to better characterize the impact of sleep disturbances in PMS, the purpose of our investigation was to (1) determine the prevalence of the different types of sleep disturbances in PMS in a large cohort of subjects within the Phelan–McDermid Syndrome Foundation (PMSF) International Registry and relevant literature and (2) investigate the association of these disturbances with age, gender, and type of genetic anomalies (*SHANK3* pathogenic variant or 22q13 deletion).

2 | METHODS

2.1 | Assessment of sleep disturbances from participants in the PMS Foundation International Registry

Data used in the preparation of this article were obtained from the Phelan–McDermid Syndrome International Registry (PMSIR) version dated January 27, 2021. The Registry is now known as Phelan–McDermid Syndrome DataHub (https://pmsf.org/datahub/). The PMSIR is sponsored by the PMSF and collects clinical and genetic information from parents of affected children to conduct research (PMSF, 2020). The views expressed in this publication are held by the authors and do not necessarily reflect the opinions of the Phelan-McDermid Syndrome Foundation. This study used a deidentified subset of data from this Registry. Inclusion criteria for this analysis of sleep disturbances included a confirmed genetic diagnosis of PMS with either the presence of a *SHANK3* pathogenic variant or a 22q13 deletion of known size and chromosomal breakpoints. The sleep-related questions of the PMSIR must have been answered to be included in this study. Parents were able to select from eight different

sleep disturbances affecting their child with PMS: enuresis (bedwetting), difficulty falling asleep, frequent nighttime awakenings, difficulty going back to sleep after nighttime awakening, short nighttime sleep, night terrors, sleepwalking, and hypersomnia (excessive daytime sleepiness). Individuals were able to select all sleep disturbances they experienced (Figure 1). Responses of "Unsure" to experiencing a sleep disturbance were removed, and "Not applicable" responses were recorded and counted as a "No" response. Age was grouped (0–3, 4–10, 11–17, and 18 years and older) according to the same scale used by Bro et al. (2017). Chromosomal breakpoints were converted to hg19 using the UCSC Genome Browser Liftover tool. Genetic abnormalities were arranged into class 1 deletions, class 2 deletions, and *SHANK3* pathogenic variants, as per Levy et al. (2021). Class 1 deletions were small and encompassed only *SHANK3* or *SHANK3* with *ARSA*, *ACR*, and *RABL2B*. Class 2 deletions included all other deletions. Data were analyzed using Excel and statistical tests used were Chi-square and *t* tests. A *p* value of <.05 was considered significant.

3 | RESULTS

3.1 | Assessment of sleep disorders from participants in the PMS Foundation International Registry

PMSIR data included 1193 patients, 623 of which were excluded because they did not have a confirmed PMS genetic diagnosis. Of the remaining 570 individuals with a PMS diagnosis, 186 individuals were excluded due to missing sleep information or had a deletion of unknown size/genomic location. Thus, the final data set included 384 patients with complete genetic and sleep data. Female patients were more represented than males (53.6% vs. 46.4%) (Table 1). Participants ranged in age from 1 to 49 years old, with a mean age of 9.9 years old at the time of the survey. The study population contained 338 individuals (88%) with deletions encompassing *SHANK3* and 46 individuals (12%) with pathogenic variants within *SHANK3*. Of the individuals with deletions, 161 (41.9%) had chromosomal deletions of less than 3 Mb. Of the 384 individuals included in our study, 284 participants (73.4%) reported having at least one sleep disturbance, while 102 participants (26.6%) reported not experiencing a sleep disturbance (Table 1). The most commonly reported sleep disturbances were difficulty falling asleep (46.9%), difficulty going back to sleep after a nighttime awakening (49.5%), and frequent nighttime awakenings (53.1%) (Table 1).

The PMSIR data showed that the average age of individuals with sleep disturbances was about 11 years old compared to about 6.5 years old for individuals without sleep disturbances. The prevalence of sleep disturbances was similar for males and females. The prevalence of sleep disturbances increased steadily with age, with 53% of children 0–3 years having a sleep disturbance and 90% of those aged 18 years and over reporting a sleep disturbance, $p < .0001$ (Table 2). The prevalence of sleep disturbances was similar for those with *SHANK3* pathogenic variants (84.8%), or Class 1 (78.8%) or Class 2 (70.9%) deletions, $p = .0633$ (Table 2). People with the largest deletions (>6 Mb) reported the lowest prevalence of sleep

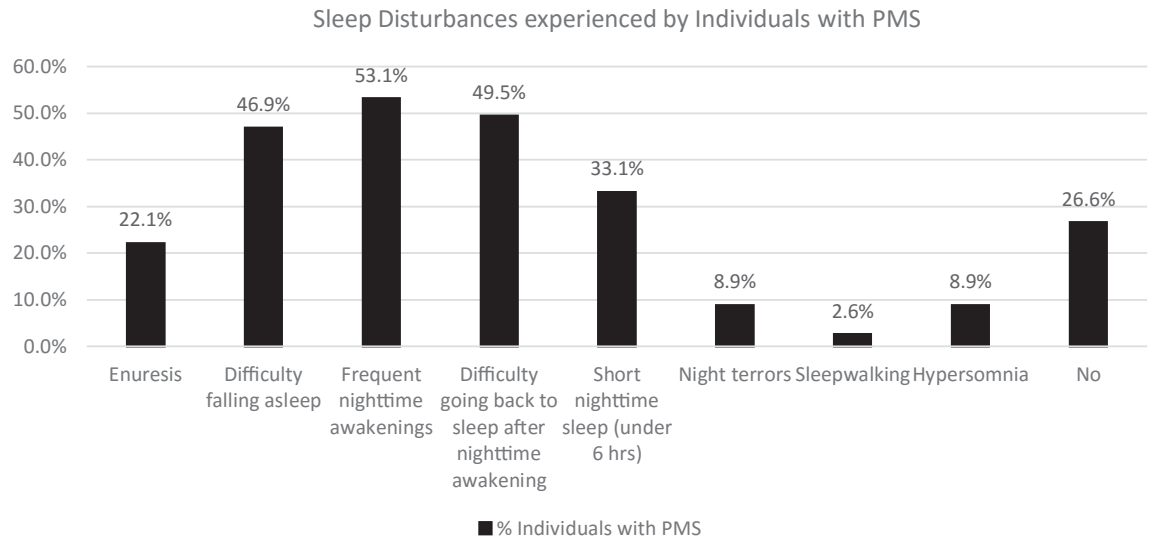

FIGURE 1 Prevalence of sleep disturbances reported by individuals with Phelan–McDermid Syndrome. The cohort from the Phelan–McDermid Syndrome International Registry reported that difficulty falling asleep, frequent nighttime awakenings, and difficulty returning to sleep were the most common sleep disturbances reported via parent-reported surveys.

TABLE 1 Demographic characteristics of individuals with Phelan–McDermid Syndrome within PMS Foundation International Registry assessed for sleep disturbance

	N	%
Total	384	100%
Sex		
Male	178	46.4%
Female	206	53.6%
Age (years)		
0–3	77	20.1%
4–10	179	46.6%
11–17	68	17.7%
≥18	60	15.6%
Genetic		
Deletion	338	88.0%
<3 Mb	161	41.9%
3–6 Mb	92	24.0%
>6 Mb	85	41.1%
SHANK3	46	12.0%
Sleep disturbance		
Yes	282	73.4%
Enuresis	85	22.1%
Difficulty falling asleep	180	46.9%
Frequent nighttime awakenings	204	53.1%
Difficulty going back to sleep after nighttime awakening	190	49.5%
Short nighttime sleep (under 6 h)	127	33.1%
Night terrors	34	8.9%
Sleepwalking	10	2.6%
Hypersomnia	34	8.9%
No	102	26.6%

disturbances (57.6%) compared to those with smaller deletions sizes ($p = .002$). Many people reported more than one type of sleep disturbance, with some having up to 7 disturbances, with a mean of 2 sleep disturbances experienced by individuals with PMS within the data set. Among those with any sleep disturbances, an average of 3 sleep disturbances were experienced (Figure 2).

3.2 | Sleep apnea

Forty-four individuals out of 384 (11.4%) reported suffering from sleep apnea, whereas 340 individuals did not suffer from sleep apnea (88.5%) (Table 3). Sleep apnea varied little by sex, age, or type of genetic diagnosis (Table 3). The individuals who reported having sleep apnea received treatment via bi-level positive air pressure (BiPAP) (6.8%), continuous positive airway pressure (CPAP) (11.4%), seizure medication (13.6%), or other medication (11.4%). However, 25 individuals (56.8%) reported not receiving treatment for their sleep apnea (Table 4).

3.3 | Literature review on sleep in PMS

Little is reported in the literature about sleep in PMS. Four studies investigated sleep disturbances within cohorts of individuals with PMS, and prevalence estimates ranged from 41% to 89.9% (Bro et al., 2017; Sarasua et al., 2014; Smith-Hicks et al., 2021; Soorya et al., 2013). Soorya et al. (2013) conducted a genotype–phenotype study with 32 individuals with PMS. Of the 32 individuals, 30 had deletions ranging from 101 kb to 8.45 Mb, while 2 presented with a *SHANK3* pathogenic variant (Soorya et al., 2013). Their study reported 13 individuals with sleep disturbances (44%) (Soorya et al., 2013). Sarasua et al. (2014) conducted a clinical and genetic evaluation of 201 individuals with PMS. Their study focused on determining the prevalence of 64 clinical features across ages and deletion sizes. Parent-reported data on sleep was only available for 26 individuals, and 12 of these (46%) had a sleep problem; however, specific types of such problems were not given (Sarasua et al., 2014). Bro et al. (2017) collected data on 162 individuals with PMS and 193 caregivers of individuals with PMS. They reported the most common sleep disturbances experienced were bedtime resistance, nighttime awakenings longer than 15 min, parasomnias, and difficulty returning to sleep (Bro et al., 2017). They implemented the use of the Children's Sleep Habits Questionnaire (CSHQ) and concluded that 173 out of 193 (89.9%) individuals with PMS scored above the clinical cutoff for a sleep disturbance (Bro et al., 2017). In a more recent study, Smith-Hicks et al. (2021), collected data on individuals with SYNGAP1-ID and individuals with PMS using the CSHQ. Forty-seven individuals with PMS were recruited along with unaffected siblings for comparison. They looked specifically at sleep abnormalities by implementing a structure sleep assessment tool with a sample size of 47 individuals with PMS (Smith-Hicks et al., 2021). Their study concluded that individuals with PMS have significant sleep disturbances related to nighttime awakenings, parasomnias, daytime sleepiness, and total CSHQ score among all ages of participants with PMS (Smith-Hicks et al., 2021).

4 | DISCUSSION

The large data set obtained from the PMSIR allowed for a representative assessment of sleep disturbances in PMS to be made. It was determined that 73.4% of individuals with

TABLE 2 Sleep disturbances in individuals with Phelan–McDermid Syndrome within the PMS Foundation International Registry

	Yes	%	No	%	*p* value
Sex					.5971
Male	133	74.7%	45	25.3%	
Female	149	72.3%	57	27.7%	
Age					**5.078×10^{-6}**
0–3	41	53.2%	36	46.8%	
4–10	131	73.2%	48	26.8%	
11–17	56	82.4%	12	17.6%	
≥18	54	90.0%	6	10.0%	
Genetic					.0633[a]
Deletion	243	71.9%	95	28.1%	
Class 1	41	78.8%	11	21.2%	
Class 2	202	70.9%	83	29.1%	
SHANK3	39	84.8%	7	15.2%	
Deletion size					**.002015**
<3 Mb	120	75.5%	41	25.5%	
3–6 Mb	74	80.4%	18	19.6%	
>6 Mb	49	57.6%	36	42.4%	

[a]Comparing those with any type of deletion compared to those with a *SHANK3* pathogenic variant.
Bold indicates the values that were significant with a p-value < 0.05.

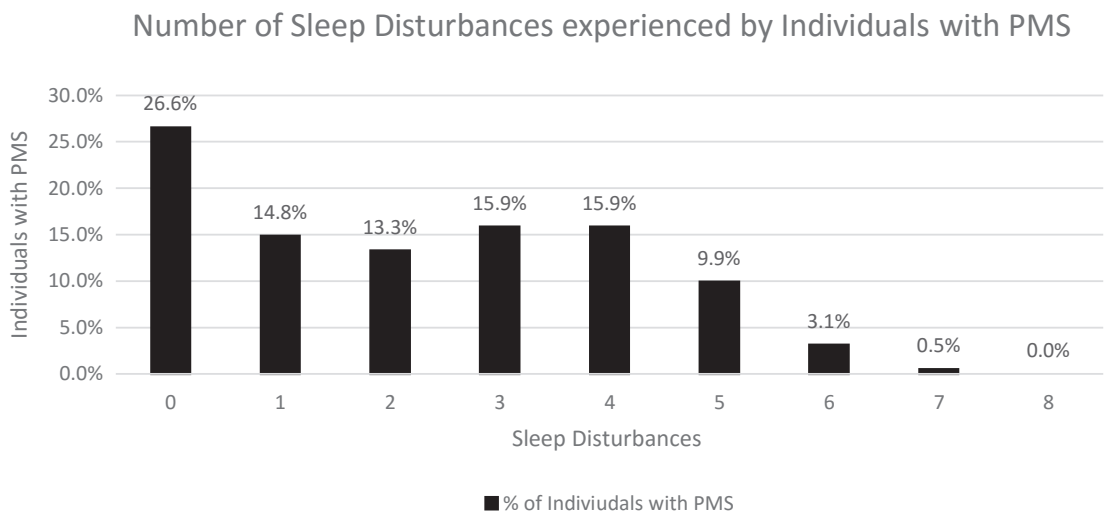

FIGURE 2 Prevalence of multiple sleep disturbances in people with Phelan–McDermid Syndrome ($N = 384$). The average number of sleep disturbances experienced by our total study population ($N = 384$) was 2. The mean increased to three sleep disturbances when only individuals who experience sleep disturbances are included.

PMS will experience at least one sleep disturbance with most experiencing more than one type of sleep disturbance. The prevalence of sleep disturbances was similar for males and females and increased with age (Table 1). There was no significant difference in the type of genetic abnormality between individuals that experienced sleep disturbances and those that did not, although those with deletions >6 Mb were somewhat less likely to have a sleep disturbance. This study's findings suggest that sleep disturbances are a prominent characteristic of PMS. Therefore, individuals diagnosed with PMS should be assessed for a sleeping disturbance just as they would be for seizures and other neurological problems.

This study is strengthened by the use of the PMSIR, which allowed for the collection of patient information across the world and is the largest study to date of systematically collected information on sleep disturbances in PMS. Future investigations may be strengthened by

TABLE 3 Sleep apnea in individuals with a PMS diagnosis and genetic data from the PMSF International Registry

	Yes	%	No	%	*p* value
Sex					.6600
Male	19	10.7%	159	89.3%	
Female	25	12.1%	181	87.9%	
Age					.6184
0–3	6	7.8%	71	92.2%	
4–10	24	13.4%	155	86.6%	
11–17	7	10.3%	61	89.7%	
≥18	7	11.7%	53	88.3%	
Genetic					.0965
Deletion	42	12.4%	296	87.6%	
SHANK3	2	4.3%	44	95.7%	

Abbreviations: PMFS, Phelan–McDermid Syndrome Foundation; PMS, Phelan–McDermid Syndrome.

TABLE 4 Treatment used for individuals with PMS with sleep apnea ($N = 44$)

	N	%
Seizure medication	6	13.6%
Other medication	5	11.4%
CPAP	5	11.4%
BiPAP	3	6.8%
None	25	56.8%

Abbreviations: BiPAP, bi-level positive air pressure; CAAP, continuous positive airway pressure; PMS, Phelan–McDermid Syndrome.

the use of standardized sleep assessments and clinical sleep studies to more precisely characterize sleep (Bonuck et al., 2017; Chokroverty, 2010).

4.1 | Sleep in PMS

The most commonly reported sleep disturbances reported across all studies were sleep apnea, sleepwalking, night terrors, parasomnias, sleep duration, and daytime sleepiness (Bro et al., 2017; Smith-Hicks et al., 2021). These specific sleep disturbances fall within the classification of CRSDs, parasomnias, and sleep apnea. We found a higher percentage of sleep disturbances (73%) than previously reported by Soorya or Sarasua et al. (44%–46%). Similar to Smith-Hicks et al. and Bro et al., difficulty falling asleep, frequent nighttime awakenings, and difficulty returning to sleep are common in people with PMS. Given the large impact of sleep disturbances on both people with PMS and their families, we are surprised at the paucity of research on this important topic and recommend additional research into identifying types of disturbances and therapeutic interventions.

Sleep disturbances in people with PMS affect not only the individual but also have huge impacts on caregivers and families. Caregivers of individuals with PMS report experiencing difficulty getting them to sleep, frequent awakenings during the night, and difficulty getting back to sleep once they have been awakened (Bro et al., 2017). Caregivers also reported getting 6 h or less sleep each night and being awakened by their child 5–7 times per week (Bro et al., 2017). Therefore, not only do the sleep habits negatively affect the individuals with PMS, but they also affect the caregivers and potentially other family members within their household.

4.2 | Sleep in PMS compared with ASD

More than 75% of individuals with PMS present with ASD or autistic traits, a percentage so high that PMS has been considered a syndromic form of autism (Costales & Kolevzon, 2015). Sleep disturbances are frequently reported in both PMS and isolated ASD, suggesting that the two conditions may share some pathogenic mechanisms. However, when data from the literature and the PMSIR were analyzed, the sleep disturbances experienced in PMS appeared more variable than those experienced by individuals diagnosed with isolated ASD. ASD has an estimated prevalence of 1 in 54 children and is generally diagnosed by age 3 (Kotagal & Broomall, 2012; Maenner et al., 2020). A parent-report sleep study concluded that about 56% of children with ASD experience at least one type of sleep problem (Kotagal & Broomall, 2012). However, Surtees et al. (2019) reported that the prevalence of sleep problems can vary from 44 to 83%. The most common sleep disturbance reported by parents of individuals with ASD was difficulty getting to sleep (73.9%), insomnia (56.3%), and daytime sleepiness (39.6%) (Kose et al., 2017; Kotagal & Broomall, 2012; Surtees et al., 2019). Several studies have reported no difference in the amount of sleep that individuals with ASD obtain each night compared with typically developing individuals of the same age (Surtees et al., 2019). In contrast, for individuals with PMS, total sleep duration is usually less than typically developing individuals. This reduction in sleep is due to the frequent nighttime awakenings and the time it takes to get the individuals back to sleep, which can take 15 to 60 min (Bro et al., 2017). Kose et al. (2017) reported insomnia as the most common sleep problem in ASD. In PMS, on the other hand, the most common sleep disturbances are sleep apneas, parasomnias including sleepwalking, night terrors and enuresis, and sleep duration (Bro et al., 2017; Saré et al., 2020).

4.3 | Shank3 model organisms and sleep

In recent years, studies have begun to focus on *SHANK3* and its role in the function of sleep and sleep disturbances. A *Shank3* knockout mouse model showed sleep difficulties even after sleep deprivation (Ingiosi et al., 2019). Mice, like humans, have a 24-h internal clock, and when *Shank3* is lost or disrupted, the clock genes are not correctly activated. It is proposed that this failure to regulate the clock genes affects the distribution and production of natural melatonin within the body (Alamilla et al., 2021; Ingiosi et al., 2019; Sarowar et al., 2016). The exact mechanisms that cause the parasomnias in people with PMS are not understood. However, the ERK/MAPK pathway, which is directly regulated by SHANK3 in neurons, has been shown to act as a mediator of sleep in *Drosophila* (Sehgal & Mignot, 2011). These neurons are closely located to the cells within the brain that mediate the wake-promoting effects caused by octopamine, a neurotransmitter that readies the body for action (Sehgal & Mignot, 2011). Ingiosi et al. (2019) demonstrated that MAPK signaling was downregulated in *Shank3*-deficient mice. It is believed that there is a substantial genetic susceptibility for certain parasomnias like sleepwalking, enuresis, bruxism, and night terrors that are related to errors within the SHANK3 gene (Ingiosi et al., 2019). Further studies need to be conducted to determine the specific genes involved within each of these parasomnias and how those genes are affected by individuals with PMS.

4.4 | Current therapies for sleep disturbances

Sleep disturbances are commonly experienced in many typically developing children and adults. A detailed sleep history of the individual allows medical professionals to correctly diagnose the specific sleep disturbance and make recommendations for polysomnography. Polysomnography, commonly referred to as a sleep study, can determine if the sleep disturbance is caused by obstructive sleep apnea (Chokroverty, 2010; Ophoff et al., 2018; Ramar & Olson, 2013). Children are at a greater risk for obstructive sleep apnea when the adenoids and tonsils are larger than the child's airway (Carter et al., 2014; Salkind & Sutcliffe, 2015). The first-line treatment for sleep apnea in children is to remove the tonsils and adenoids, if present, from the individual (Carter et al., 2014). Another option is CPAP, which provides constant pressure to prevent the airway from collapsing, or BiPAP, which delivers inhale and exhale pressure throughout the night (Salkind & Sutcliffe, 2015).

Treatments for other sleep disturbances such as CRSDs and parasomnias range from better habits leading up to bedtime or implementing the use of medications. Good sleep hygiene and relaxation techniques should be utilized to relax the mind and get the body ready for sleep (Ophoff et al., 2018; Salkind & Sutcliffe, 2015). Recommended sleep hygiene practices refer to avoiding daytime naps, going to sleep and waking up at a consistent time every day, avoiding caffeine and sugar late in the day, and not using electronic devices (tv, cellphone, computer, etc.) within the bedroom (Ophoff et al., 2018; Phelan & McDermid, 2012; Salkind & Sutcliffe, 2015; Xie et al., 2017). It has been proposed for typically developing children and those with autism that administering melatonin allows for the sleep–wake cycle to be reset, increasing the time spent sleeping and decreasing the amount of time it takes to fall asleep (Glickman, 2010; Ophoff et al., 2018). Individuals who experience sleepwalking and night terrors can use scheduled awakenings to prevent these parasomnias, but the true efficacy of this method is unknown (Ophoff et al., 2018; Salkind & Sutcliffe, 2015). There are pharmacological medications that can be used to treat parasomnias, such as diazepam and clonazepam for NREM-related parasomnias (Ophoff et al., 2018; Salkind & Sutcliffe, 2015). Antidepressants have been prescribed for both NREM- and REM-related parasomnias, but individuals must be monitored carefully as suicidal thoughts and behaviors are at an increased risk, especially in children and teens (Salkind & Sutcliffe, 2015). Generally, parasomnias in children resolve spontaneously with age; however, individuals with PMS report that as much as 70% over the age of 18 still experience parasomnias (Ingiosi et al., 2019). Treatment recommendations for these individuals may be of benefit to people with PMS, although research is needed into specific therapeutics.

5 | CONCLUSION

Sleep disturbances are common in people with PMS, with up to 90% of adults with PMS having at least one sleep disturbance. Identifying the biological pathways disrupted by the haploinsufficiency of *SHANK3* will be critical to establishing targeted therapies. This information will be useful for the treatment of sleep disturbances experienced by patients with other neurodevelopmental disorders who suffer from sleep disturbances. Particularly, early identification and characterization of

types and patterns of sleep disturbances will allow for earlier diagnosis, better clinical management, and more precise therapeutic approaches. Moreover, improving our knowledge of the clinical presentation of sleep disturbances in subjects with neurodevelopmental disorders may help the treatment of isolated sleep disturbances as well. Further research needs to be focused on identifying safe and effective therapies for people with PMS and sleep disturbances.

AUTHOR CONTRIBUTIONS

Bridgette Allen wrote the manuscript and submitted the paper. Bridgette Allen, Luigi Boccuto, and Sara Sarasua formulated the paper and created the research design. Luigi Boccuto, Curtis Rogers, and Katy Phelan selected the patients to be included from registry data. Bridgette Allen and Sara Sarasua conducted the data analysis. Luigi Boccuto, Sara Sarasua, Diana Ivankovic, Linda Ward, Kathleen Valentine, Curtis Rogers, and Katy Phelan reviewed the manuscript.

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CONFLICT OF INTEREST

The authors have declared that they have no conflict of interest.

ETHICAL COMPLIANCE

Our study was approved by the Clemson University Institutional Review Board for use of deidentified secondary data analysis (IRB2020-404).

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