

Prevalence, Nature, and Correlates of Sleep Problems Among Children with Fragile X Syndrome Based on a Large Scale Parent Survey

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Study Objectives: This study reports on current child sleep difficulties reported by parents of children with Fragile X syndrome (FXS). We address prevalence and type of sleep problems (e.g., difficulty falling asleep, frequent awakenings); type and effectiveness of medical and behavioral treatments (e.g., medication, surgery, environmental changes); and explore specific child and family characteristics (e.g., child age, child gender, co-occurring conditions) as possible predictors of child sleep difficulties.

Design/Participants: This study is part of a larger survey addressing needs of families with children with FXS. This article focuses on the families who responded to the survey sleep questions, had one or more children with the full mutation FXS, and who reside in the United States. The mean age for male and female children in this group was 15 years and 16 years respectively (N = 1,295).

Results: Parents reported that 32% of the children with FXS currently experience sleep difficulties; 84% of those children are reported to have ≥ 2 current sleep problems. Problems falling asleep and frequent night awakenings were the most frequently reported difficulties; 47% of males and 40% of females received ≥ 1 medication to help with sleep. Children with more problematic health or behavioral characteristics had a higher likelihood of having current sleep problems.

Conclusions: Our survey provides the most representative sample to date of sleep problems in children with FXS or any other neurodevelopmental disability. This large scale survey establishes a foundation for the prevalence of sleep disorders in children with FXS.

Keywords: Sleep, Fragile X syndrome, survey

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CHILDREN WITH INTELLECTUAL AND DEVELOPMENTAL DISABILITIES OFTEN EXPERIENCE MORE SLEEP PROBLEMS THAN THE GENERAL POPULATION.¹⁻³ IN children and adults with neurodevelopmental disabilities, there are variations in sleep architecture as well as frequently reported sleep disturbances including insomnia, multiple night awakenings, and early morning rising with prevalence rates ranging from 13% to 86%.^{4,5} Variability in the prevalence of sleep problems in children is partially explained by several factors, including study aims (e.g., physiological, behavioral), the type and severity of the neurodevelopmental disorder (e.g., Down syndrome, Angelman syndrome, autism spectrum disorders), and the type of sleep disturbance studied (e.g. dys-somnias, parasomnias, sleep disordered breathing).⁶⁻¹⁰ Sleep disturbances in children with disabilities likely represent a complex interaction of biological and environmental factors.

Fragile X syndrome (FXS) exemplifies this complexity. FXS belongs to a family of disorders characterized by disease pathogenesis via trinucleotide repeat expansion.^{11,12} FXS is the leading known inherited cause of intellectual disability, and within the US population it is estimated that 37,000 males (1 in 3,847) and 38,400 females (1 in 3,847) carry the fragile

X full mutation.¹³ Located on the X chromosome (Xq27.3), the fragile X mental retardation-1 (*FMR1*) gene is silenced with the expansion of the cytosine-guanine-guanine (CGG) sequence to full mutation (> 200 repeats). The outcome results in the suppression or absence of the fragile X mental retardation protein (FMRP), known to be important for synaptic functioning and plasticity.^{14,15} The extent of the FMRP deficit may be associated with the severity of characteristics associated with FXS.¹⁶⁻¹⁸

Basic research using FX-knockout animal models suggests that diminished FMRP expression promotes changes in sleep behavior and cognitive functioning. The ability of flies and mice to maintain a normal sleep-wake cycle is significantly blunted in the absence of FMRP.¹⁹⁻²² Interestingly, lack of FMRP does not appear to alter the activity of the central clock neurons in the suprachiasmatic nucleus of the hypothalamus, which is traditionally thought to regulate the circadian rhythm.^{20,22} Potential mechanisms driving sleep changes in FXS may include molecular interactions with clock output proteins, dysregulation of clock gene expression in the liver, changes in the management of oxidative stress, and/or physical alteration of axonal and dendritic pathfinding.²²⁻²⁵

Despite intriguing data on possible underlying mechanisms of sleep problems in FXS, human studies have been limited. Richdale surveyed parents of 13 children with FXS; 10 reported that their child experienced problematic sleep.²⁶ Kronk et al. reported on a convenience sample of 90 children with FXS (81% males) and found that parents of 47% reported clinically significant sleep problems in their child.²⁷ Gould et al. reported elevated levels of melatonin in 13 preadolescent boys with FXS when compared with 8 age-matched controls.²⁸ Musumeci et

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al. employed polysomnography to evaluate sleep patterns in 9 boys with FXS, compared to 6 typically developing boys.²⁹ The boys with FXS demonstrated significantly less REM sleep and total sleep times, an increase in the first REM latency and slow wave sleep, and a significant increase in twitch movements during REM. Miano et al. used cyclic alternating pattern (CAP) analysis in conjunction with polysomnography to examine sleep architecture and NREM sleep alterations in 14 boys with FXS, compared to 8 children with Down syndrome and 26 age-matched normal controls.³⁰ Analysis of sleep microstructure revealed more disruption in both groups with cognitive impairment. The authors suggested that alterations in NREM sleep microstructure and lower percentage of REM sleep may provide key evidence regarding the role of sleep in learning and memory consolidation, major areas already compromised in children with developmental disabilities.

Variations in methodologies and limited sample size make it impossible to determine whether functional sleep disturbance is a primary feature of FXS or a problem in a subset of individuals. Little is known about the specific difficulties experienced by those children with FXS who are reported to have sleep disturbance or the factors that might differentiate those with reported sleep problems from those without. To address the scarcity of data, we embedded questions about sleep disturbance in a large-scale national survey of families who have at least one child with FXS. In addition to descriptive data on caregiver and child characteristics, the survey aimed to explore current sleep problems, interventions, and their effectiveness. The data reported here address 4 questions: (1) What is the prevalence, age of onset, and age distribution of current sleep issues among children with FXS as reported by their parents? (2) What is the nature and frequency of parent reported sleep problems in children with FXS? (3) What medical and behavioral treatments have been implemented by families to treat sleep problems in their children and what is the perceived efficacy of each? (4) Are selected child and/or family characteristics (e.g., co-occurring conditions, child's ability to interact with others, caregiver education) associated with the presence or absence of sleep problems in children with FXS?

METHOD

Participants

This study was part of a large national survey assessing the needs of families with at least one child who is a carrier of FXS or has the full mutation. Families were recruited in partnership with 3 national foundations (National Fragile X Foundation, FRAXA Research Foundation, and Conquer Fragile X Foundation), researchers, and clinicians. A total of 1,250 families initially enrolled in the project, and 1,075 families (86%) completed the full survey. Families participating in the full survey had a total of 2,672 children: 1,394 with the full mutation FXS (1090 males, 304 females), 235 premutation carriers (55 males, 180 females), 525 without FXS (257 males, 268 females), and 518 who had not been tested for FXS (272 males, 246 females).

This article focuses on the 978 families who responded to the survey sleep questions, had one or more children with the full mutation FXS, and who reside in the United States. The

current study reports on a total of 1,295 children: 1,013 boys and 282 girls.

Instruments and Procedures

Families were given an option of enrolling on-line via a web-based questionnaire or on the telephone by calling a toll free number and speaking with an interviewer. The enrollment process asked for basic demographic information about the family and each child. Parents rated each child's overall quality of life and overall health using a 5-point scale (excellent, very good, good, fair, poor). Parents also rated certain characteristics of the child, including the child's ability to listen and pay attention to others, ability to interact appropriately with others his/her own age, ability to adapt to new situations, people or changes in routine, overall mood most of the time, and overall abilities to think, reason and learn on a 4-point scale (very good, good, fair, or poor). In regards to physical activity, parents were asked, "How many days a week does your child do some physical activity?" Parents were also asked if their child had ever been diagnosed with or treated by a medical professional for any of the following conditions: attention problems, hyper-activity, aggressiveness towards others, self-injurious behavior, autism, seizures, anxiety, depression, and general developmental delay/ cognitive impairment.¹⁶ Parents indicated yes or no to each condition.

For each child with the full mutation, parents were asked if their child currently experiences any sleep difficulties. If yes, 9 additional questions with coded responses were presented:

1. At what age did your child first start to experience difficulty sleeping? Parents were to choose one of the following: less than 1 year, 1 to 3 years, 4 to 10 years, or 11 years or older.
2. What is the nature of the sleep problem? Parents were instructed to check all items that applied (i.e. problems falling asleep, waking up frequently, waking up too early, difficulty waking up, restless sleep, daytime sleepiness, other).
3. How many nights per week does your child experience difficulty sleeping? Parents were to choose only one of the following: less than 1 night a week, 1 or 2 nights a week, 3 to 5 nights a week, or more than 5 nights a week.
4. How much of a problem are the child's sleeping difficulties? Parents were to choose one of the following: mild, moderate, or severe.
5. Have you used any medical treatments to help with sleep difficulties? Parents answered yes or no to the following: surgery, medication, and other.
6. How many medications is your child currently taking to help with sleep difficulties? Of the following three choices, parents were to choose one: none, 1, or 2 or more.
7. How effective have the medical treatments been in addressing your child's sleep difficulties? Parents were to choose one of the following: not at all, a little, somewhat, or a lot.
8. Which of the following have you tried to help with your child's sleep difficulties? Parents were instructed to choose all that applied: changing the time child goes to bed or wakes up, changing sleep environment, using different pajamas or bedding, changing bedtime routines, using rewards or consequences, and other.

Table 1—Numbers and percentages of children diagnosed with a full mutation of FXS with and without current sleep difficulties within age group for All, Males, and Females

Age group	All (N = 1295) No. (%)		Males* (N = 1013) No. (%)		Females* (N = 282) No. (%)	
	With sleep difficulty ^a	Without sleep difficulty	With sleep difficulty ^b	Without sleep difficulty	With sleep difficulty ^c	Without sleep difficulty
≤ 5 years	87 (45)	108 (55)	66 (46)	79 (54)	21 (42)	29 (58)
6 to 10 years	108 (35)	200 (65)	94 (37)	161 (63)	14 (26)	39 (74)
11 to 15 years	90 (35)	166 (65)	76 (38)	125 (62)	14 (25)	41 (75)
16 to 20 years	47 (25)	138 (75)	35 (24)	113 (76)	12 (32)	25 (68)
> 20 years	81 (23)	270 (77)	60 (23)	204 (77)	21 (24)	66 (76)
Total	413 (32)	882 (68)	331 (33)	682 (67)	82 (29)	200 (71)

*There is no significant association found between those with sleep difficulties and gender.

^a χ^2 test indicates an association between all those with sleep difficulties and age group ($P < 0.0001$).

^b χ^2 test indicates an association between males with sleep difficulties and age group ($P < 0.0001$).

^cThere is no significant association between females with sleep difficulties and age group

9. How effective have the above changes been in addressing your child's sleep difficulties? Parents were instructed to choose one of the following: not at all, a little, somewhat, or a lot.

Recoded Variables

Some variables were recoded for analysis: respondent education (1 = low, 2 = high: 2-year college degree or higher); overall quality of life (1 = fair-poor; 2 = excellent-good); overall health (1 = fair-poor; 2 = excellent-good); ability to listen and pay attention to others (1 = fair to poor; 2 = very good-good); ability to interact appropriately with other children his/her own age (1 = fair to poor; 2 = very good-good); ability to adapt to new situations, people, or changes in routine (1 = fair to poor; 2 = very good-good); mood most of time (1 = fair to poor; 2 = very good-good); overall ability to think, reason, and learn (1 = fair to poor; 2 = very good-good); level of physical activity (1 = twice/week; 2 = ≥ 3 times/week); and high or low number of coexisting conditions (1 = 5 to 9 problems; 2 = ≤ 4 problems).

Although exploratory, these variables were selected because they provided insight into the child's overall ability to adapt, function, and participate in daily activities. They also reflect several domains in the Activities and Participation component of the International Classification of Functioning, Disability and Health (ICF), which is a biopsychosocial model that can synthesize the biology of FXS within a functional framework.³¹

Statistical Analyses

For all analyses, the Statistical Analysis System (SAS, Version 9, Cary, NC) was used.

Chi-square and Mantel-Haenszel summary statistics were used to assess associations of age group and gender for those with sleep difficulties. Chi-square tests were used to assess associations between gender and types of sleep difficulties and associations between gender and interventions for sleep difficulties. Within genders, χ^2 analyses were also used to assess associations between age groups and types of sleep difficulties and treatments.

Table 2—Type and frequency of sleep difficulties among children with the full mutation of FXS as reported by parents and categorized by gender (N = 413)

Sleep difficulty	Male	Female
	(N = 331) %	(N = 82) %
Problems falling asleep	58	64
Frequent nighttime awakenings	63	59
Waking up too early^a	68	30
Difficulty waking in morning^b	8	21
Restless sleep	49	41
Daytime sleepiness	26	23
Other^c	13	19

^a χ^2 test indicates an association between gender and "waking up too early" ($P < 0.0001$).

^b χ^2 test indicates an association between gender and "difficulty waking in morning" ($P = 0.0012$).

^c"Night terrors," "night fears," "sleep apnea," "will not sleep alone" were the most frequent responses to the "Other" response of the nature of sleep difficulty question.

RESULTS

Demographics

Means and frequencies were calculated for descriptive analyses. Of the 978 respondents to the survey's sleep questions, 89% indicated Caucasian, 2% African American or Black, 1% Asian, < 1% Native Hawaiian or Pacific Islander, 5% Hispanic or Latino, and 2% multiple races. The majority of the respondents earned a 4-year college degree or higher (59%) and an annual income \geq \$75,000 (56%). Eighty-five percent of respondents were married, and 64% were employed. Of these respondents, their male children ($n = 1013$) had a mean age of 15 years (SD 10.5), and female children ($n = 282$) had a mean age of 16 years (SD 10.4)

Age of Onset and Frequency of Sleep Problems

The number and percentages of all children with and without sleep problems, by age group, is displayed in Table 1. Of the 978 families who had one or more children with the full mutation FXS, 413 children (32%) were reported as currently experiencing sleep difficulties, representing 331 males and 82 females. There was no significant difference in the frequency of sleep problems reported for males (33%) or females (29%).

As depicted in Table 1, χ^2 analysis yielded a significant association between sleep difficulties and age ($\chi^2 = 32.7$, $P < 0.0001$) for males, but not females. Younger males generally experienced more sleep problems than older males, with a gradual decrement across age groups.

Of the 331 males currently experiencing sleep problems, 71% of caregivers reported these difficulties began at age 3 years or younger, 19% between 4 and 10 years, and 10% after age 11. Of 82 females currently experiencing sleep problems, 64% of

caregivers reported these difficulties began at age 3 years or younger, 15% between 4 and 10 years, and 21% after age 11.

Frequency and Nature of Sleep Problems

Table 2 highlights type and frequency of sleep difficulties among children who were reported by their parents to have sleep difficulties and had a full mutation of FXS: 84% of these children had ≥ 2 current sleep difficulties. Problems falling asleep and frequent nighttime awakenings were reported for more than half of both males and females with sleep problems. A significant association occurred for males and waking up too early ($\chi^2 = 40.0$, $P < 0.0001$), whereas females were more likely to have difficulty waking in the morning ($\chi^2 = 10.5$, $P < 0.0012$).

In response to the third survey question, families reported similar frequencies of sleep problems for males and females: 37% of males and 36% of females have difficulties sleeping > 5 nights per week. Another 36% of males and 36% of females have difficulties 3-5 nights per week, and 23% of males and 28% of females have difficulties sleeping ≤ 2 nights per week. When sleep difficulties occurred in males, 41% of families considered the difficulties mild, 47% moderate, and 12% severe. When sleep difficulties occurred in females, 32% of families considered the difficulties mild, 47% moderate, and 21% severe.

Table 3 shows the type and frequency of sleep difficulties in boys stratified by age. Chi-square analysis revealed significant associations between age and frequent nighttime awakenings ($P = 0.0495$), waking up too early ($P = 0.0004$), and daytime sleepiness ($P = 0.0302$). Table 4 shows that frequent nighttime awakenings ($P = 0.0296$) are significantly associated with age for girls.

Treatments Used and Perceived Efficacy

Caregivers were asked if they had ever used any of the following medical interventions to help with their child's sleep: surgery, medications, or other. The results are displayed in Table 5 and 6. The most common interventions tried for both males and females were environmental interventions: changing bed or wake time, changing the sleep environment, and changing the bedtime routine. Examples of the "other interventions" listed by caregivers included melatonin, other herbal supplements, and breathing support machines such as continuous positive airway pressure (CPAP).

Nearly half (47%) of males were administered some form of medication as a sleep aid. Currently, 19% were receiving ≥ 2 medications, 57% were currently receiving one medication and 24% were not receiving any medication. Table 5 presents significant χ^2 associations between age group in boys and medication ($P = 0.0019$), changing bed or awake time ($P = 0.0001$), changing sleep environment ($P = 0.0055$), changing bedtime routine ($P = 0.0004$), and providing rewards or consequences ($P = 0.0008$).

Forty percent of females were administered medication as a sleep aid. Currently, 3% were receiving

Table 3—Type and frequency of sleep difficulties in males stratified by age as reported by parents (n = 331)

Sleep difficulty	≤ 5	5 to 10	11 to 15	16 to 20	> 20
	years (n = 66) %	years (n = 94) %	years (n = 76) %	years (n = 35) %	years (n = 60) %
Problems falling asleep	70	61	51	63	47
Frequent nighttime awakenings ^a	79	61	59	60	55
Waking up too early ^b	68	74	79	66	45
Difficulty waking in morning	9	4	8	17	10
Restless sleep	48	49	47	51	48
Daytime sleepiness ^c	26	22	17	37	38
Other	8	15	11	20	13

^a χ^2 test indicates an association between age and "frequent nighttime awakenings" ($P = 0.0495$).

^b χ^2 test indicates an association between age and "waking up too early" ($P = 0.0004$).

^c χ^2 test indicates an association between age and "daytime sleepiness" ($P = 0.0302$).

Table 4—Type and frequency of sleep difficulties in females stratified by age as reported by parents (n = 81^a)

Sleep difficulty	≤ 5	5 to 10	11 to 15	16 to 20	> 20
	years (n = 21) %	years (n = 14) %	years (n = 14) %	years (n = 12) %	years (n = 20) %
Problems falling asleep	71	64	57	50	70
Frequent nighttime awakenings ^b	76	71	57	67	30
Waking up too early	38	36	43	25	10
Difficulty waking in morning	24	14	21	42	10
Restless sleep	57	21	29	50	40
Daytime sleepiness	19	29	14	25	30
Other	19	29	7	8	25

^aOne female did not have an age and is not included in an age group.

^b χ^2 test indicates an association between age and "frequent nighttime awakenings" ($P = 0.0296$).

≥ 2 medications, 66% were receiving one medication, and 31% were not receiving any medication. Table 6 shows that among girls, the only significant association is between age group and changing bedtime routine (P = 0.0014).

Caregivers were then asked to rate perceived efficacy of these interventions. Forty percent of parents with male children felt that the medical interventions had “none” to “little” effect, and 60% felt that the medical interventions had “somewhat” to “a lot” of effect. Of the behavioral treatments listed in Table 5, 62% felt that the treatments were “not at all” helpful to “a little” helpful. The remaining 38% felt that the treatments were “somewhat” to “a lot” helpful. For parents of females, 38% felt that medical interventions had “none” to “little” effect, and 62% felt that the medical interventions had “somewhat” to “a lot” of effect. Of the behavioral treatments listed in Table 6, 50% felt that the treatments were “not at all” helpful to “a little” helpful. The remaining 50% felt that the treatments were “somewhat” to “a lot” helpful.

Predictors of Sleep Difficulty

A logistic regression model was used to determine if sleep difficulties were associated with selected health and behavioral characteristics of the child (e.g., thinking/reasoning/learning, adaptability, mood, co-occurring conditions) while controlling for the child’s age and respondent’s education. Following a Kleinbaum and Klein logistic regression model, we specified the binary dependent variable as those with sleep difficulty (1 = yes) and those without sleep difficulty (0 = no).³²

Previous analyses using the same data showed that respondent education and family income are highly correlated, so only respondent education was included in the analysis.¹⁶ For each model, education as a dichotomous variable and child age as a continuous variable were included as potential confounders. For gender, both within- and between-group analyses were completed.

The results for the logistic regression analysis with “sleep difficulty” as the outcome variable, indicated for males only, age was a significant interaction term for the independent variable quality of life but none of the other independent variables (e.g., adaptability, mood, co-occurring conditions). Caregiver education was not a significant interaction term for any of the independent variables.

Table 7 displays the odds ratio and confidence interval for each behavioral and health variable that differentiated males and females with sleep problems from those without. For males, 6 behavioral and health characteristics were significantly associated with higher odds for sleep difficulties: overall health (P = 0.000), ability to listen and pay attention (P = 0.013), ability to interact with others (P = 0.003), abil-

ity to adapt to new situations, people, or changes in routine (P = 0.042), quality of mood (P = 0.001), and number of co-occurring conditions (P = 0.001). For females, 5 behavioral and health characteristics were significantly associated with higher odds for sleep difficulties: overall health (P = 0.004), ability to listen and pay attention (P = 0.008), ability to adapt to new situations, people, or changes in routine (P = 0.004), quality of mood (P = 0.006), and number of co-occurring conditions (P = 0.001). Among the significant behavioral and

Table 5—Type and frequency of treatments in males stratified by age as reported by parents

	Males					
	All age groups (n = 331)	≤ 5 years (n = 66)	5 to 10 years (n = 94)	11 to 15 years (n = 76)	16 to 20 years (n = 35)	> 20 years (n = 60)
Sleep treatment^a						
Medical Treatments	%	%	%	%	%	%
Surgery	10	12	8	12	16	4
Medication [*]	47	30	49	64	53	41
Other ^b	25	22	29	20	36	24
Behavioral Interventions						
Changing bed or wake time [*]	70	84	72	75	67	39
Changing sleep environment [*]	73	84	70	80	67	54
Changing pajamas or bedding	43	49	44	44	45	27
Changing bedtime routine [*]	58	71	64	55	55	29
Rewards or consequences [*]	26	11	26	42	30	17

^aχ² tests did not show any significant associations between gender and interventions for sleep difficulties.

^b“melatonin” was the most frequent response to the “Other” response of medical interventions for sleep treatment.

^{*}χ² test indicates an association between age and the indicated medical treat or behavioral intervention (P ≤ 0.005).

Table 6—Type and frequency of treatments in females stratified by age as reported by parents

	Females					
	All age groups (n = 81)	≤ 5 years (n = 21)	5 to 10 years (n = 14)	11 to 15 years (n = 14)	16 to 20 years (n = 12)	> 20 years (n = 20)
Sleep Treatment^a						
Medical Interventions	%	%	%	%	%	%
Surgery	4	5	8	7	0	0
Medication	40	24	54	43	33	50
Other ^b	19	12	20	20	25	23
Behavioral Intervention						
Changing bed or wake time	69	65	79	69	75	56
Changing sleep environment	67	70	71	69	63	56
Changing pajamas or bedding	33	50	36	31	0	22
Changing bedtime routine [*]	55	65	71	77	13	11
Rewards or consequences	34	50	43	38	13	0

^aχ² tests did not show any significant associations between gender and interventions for sleep difficulties.

^b“melatonin” was the most frequent response to the “Other” response of medical interventions for sleep treatment.

^{*}χ² test indicates an association between age and the indicated medical treat or behavioral intervention (P ≤ 0.005).

Table 7—Odds ratios and 95% confidence intervals for behavior and health variables among those with sleep difficulties compared to those with no sleep difficulties (N = 1295)

Independent variable ¹	Male (N = 1013)	Female (N = 282)
	Odds ratio (confidence interval) and P-values	Odds ratio (confidence interval) and P-values
Overall quality of life	NS	NS
Overall health	3.72 (2.13-6.49) P = 0.000	4.79 (1.67-13.69) P = 0.004
Ability to listen	1.48 (1.09-2.02) P = 0.013	2.09 (1.21-3.58) P = 0.008
Ability to interact	1.78 (1.21-2.62) P = 0.003	NS
Ability to adapt	1.41 (1.01-1.95) P = 0.042	2.34 (1.32-4.13) P = 0.004
Mood most of time	1.86 (1.31-2.64) P = 0.001	2.37 (1.37-4.10) P = 0.006
Ability to think, reason, learn	NS	NS
Level of physical activity	NS	NS
Co-occurring conditions	1.61 (1.22-2.11) P = 0.001	2.77 (1.50-5.12) P = 0.001

NS, not significant; ¹Adjusted for child age and respondent education

health characteristics for males and females, individuals with more problematic health or behavior characteristics (e.g., poor health, more coexisting conditions) were more likely to experience sleep problems.

A logistic regression model was also used to determine if taking medication for sleep difficulties was associated with the health and behavioral characteristics of the child. For both males ($P < 0.001$) and females ($P = 0.014$), only the number of coexisting conditions was associated with medication use. Both groups were more likely to receive medication if they had a higher number of coexisting diagnoses, i.e., more than 4 conditions (males OR, 2.78; 95% CI, 1.72-4.48; females OR, 3.49; 95% CI, 1.29-9.44).

DISCUSSION

This is the first large scale study to report sleep difficulties in children with FXS based on an extensive parent survey. Four main questions addressed prevalence and type of sleep problems, age of onset and age distribution of sleep difficulties, medical and behavioral treatments and their efficacy, and child functional and behavioral characteristics as predictors of sleep problems. Thirty-two percent of parents reported that their children with FXS exhibited current sleep problems; 84% of those children had two or more existing sleep problems. Age of onset for current sleep problems was 4 years of age or older in one-third of all children. Problems falling asleep and frequent night awakenings were the most frequently reported difficulties. For males, stratification of sleep difficulties by age revealed a significant negative association for frequent nighttime awakenings and waking up too early and a significantly positive association with daytime sleepiness. In females, frequent nighttime awakenings had a significant negative association with age. Of the children whose parents reported current sleep problems, 47% of males and 40% of females had received at least one medication to help with sleep. Children with more than 4 coexisting conditions were more likely than others to receive medication to aid sleep. Children with more problematic health or behavioral characteristics had a higher likelihood of having current sleep problems.

Frequency, Onset, and Nature of Sleep Problems

The overall prevalence of sleep difficulties reported here is generally lower than reported in several previous studies of individuals with FXS.^{26,27} Our sample is much larger than any previous study, and so our findings likely provide more confidence in the general conclusions. However, differences also exist in study aims, data collection protocols, and the focus on current versus lifetime history of sleep problems. For example, Richdale et al. reported on current as well as previous problematic sleep behaviors and Kronk and colleagues incorporated standardized sleep questionnaires that quantified parent reports on current sleep problems in their children.^{26,27} Varied design and sample sizes may account for frequency differences in these studies as compared to the present study. Additionally, it should be noted that this survey reflects caregiver report of their child's sleep difficulties. If a child's sleep difficulties are

not causing functional challenges to other family members, they may not be considered problematic and therefore may not be reported as current sleep issues. Similarly, a parent may view a particular behavior as problematic when that behavior is actually within normal developmental range. For instance, this study found that 68% of males experience early awakening. Is the child, despite awakening at an early time, actually getting an adequate amount of sleep? Is the child who is awakening early having difficulty staying awake during the day? Is it just that an early awake time is disruptive to the rest of the family member's schedules? To monitor sleep quality and quantity, objective data collection (i.e., actigraphy) would be very useful in future studies.

The age of onset of sleep difficulties found in this study of children with FXS is most noteworthy when contrasted to typically developing children. While developmentally it can be expected that infants and toddlers have a certain tolerated level of sleep difficulty, this survey discovered that many parents of children with FXS do not begin to perceive and/or report sleep difficulties until their children are significantly older. While difficulty with bedtime settling and night awakenings are frequently reported by parents of typically developing infants and toddlers,³³⁻³⁵ we found similar rates of sleep difficulties reported by parents of children whose mean ages were 13 and 14 years, depending on gender. Many parents may be more accepting of sleep issues in their younger children with FXS because this is a typical developmental expectation; therefore, parents may not begin to report their concerns until sleep issues have become chronic. Several co-occurring conditions (e.g., ADHD, anxiety) become more prominent in older children with FXS introducing additional variables (e.g., medications, externalizing behaviors) that could play a significant role in parent reporting of sleep problems.¹⁶ Future studies will need to further explore why parents of older children with FXS report high rates of sleep difficulties.

The reported types and frequency of sleep disturbances in this study are comparable to other studies of parent reports on sleep in children with neurodevelopmental disabilities.^{1-3,5,8-10,36} For example, Quine also found higher rates of sleep problems

in children with special needs, including settling and night waking problems, with prevalence rates of 41% and 45% respectively.³ Sleep questionnaires provided to families of children with Angelman syndrome identified 40% of children as having a severe sleep problem.³⁶ Richdale and colleagues discovered that the children with intellectual disability had significantly higher frequencies of both past (67%) and current (58%) sleep problems, more frequent night awakenings (69%), and yelling at night (35%) than the comparison group.⁹ Surveys have been an initial, accessible method of data collection to identify the magnitude and types of sleep problems in children with neurodevelopmental disabilities. No other survey of this size has been completed within a FX cohort of families; by comparison, we find very similar rates and types of sleep difficulties reported by parents among children who have other special health care needs. Comparison of findings can lay the groundwork to begin investigations to improve functioning and treatments across a spectrum of disorders.

Treatments Used and Perceived Efficacy

This survey was also the first to gather information regarding use and parental satisfaction with medical and behavioral interventions to improve sleep. Approximately two-thirds of families indicated medical interventions had “somewhat” to “a lot” of effect. The OR indicated the probability for taking medication for sleep difficulties was less likely for those males and females who had a lesser number of co-occurring conditions. Strikingly, 44% of children with sleep difficulties were receiving medications; however, they continued to have current sleep issues. Chi-square analyses did not find significant differences between males or females with current sleep difficulties and the type and frequency of interventions. However, males were currently prescribed two or more medications to help with sleep almost six times as frequently as females. A possible explanation may be that females, with a full mutation of FMR1 gene, usually have a milder phenotype due to the X-inactivation factor.³⁷ Co-occurring conditions are usually less in number and intensity for females.¹⁶

In this survey, melatonin was the most frequent response to the “other” option under medical interventions for sleep treatments. This may indicate that many parents may not consider this hormonal supplement as a “medication” since a prescription is not required. In studies pertaining to pharmaceutical interventions, melatonin appears to be the most widely investigated supplement to enhance sleep in children with intellectual disabilities.³⁸⁻⁴² Wirojatan et al. determined that 10 of 12 children with autism and/or FXS experienced significant improvement in sleep duration in a two-week crossover trial of melatonin compared to placebo.⁴³ Also, sporadic attention has been given to clonidine and its success in treating sleep problems in children with neurodevelopmental disabilities.^{44,45}

Sixty-two percent of parents who had a male child with a full mutation reported behavioral treatments to be “a little” to “not at all” helpful. Parents of female children were almost evenly split as to the effectiveness of behavioral treatments. These data should stimulate more research to investigate specific types of behavioral interventions and their effectiveness. Currently, Weiskop et al. are the only investigators who have studied the implementation of a behavioral intervention

to address sleep issues in children with special needs.⁴⁶ They investigated a parent training program using the behavioral technique of extinction and were able to improve four out of six sleep problems, including pre-sleep disturbances, falling asleep alone, night awakenings, and cosleeping in children with FXS and/or autism.

Further well-designed investigations are warranted for both behavioral and pharmaceutical interventions to treat sleep disturbances of children with FXS. This information is essential to evidence-based practice. The data from this survey provide a foundation on which to build future investigations.

Child and Family Characteristics Associated with Sleep Difficulties

Regression analyses indicated that for both males and females, the probability of sleep difficulties was higher for individuals with fair to poor health, fair to poor ability to listen, fair to poor ability to adapt, fair to poor overall mood, and a higher number of co-occurring conditions. Although, we cannot distinguish a unilateral cause and effect between sleep and specific areas of functioning, many studies in typically developing children have identified an underlying link between neurobehavioral and cognitive functioning and sleep.⁴⁷⁻⁴⁹ Therefore, it seems implicit that such a link exists for children with neurodevelopmental disabilities and underscores the need for research in this area, especially in subjects with developmental impairments such as FXS. As stated in the Method Section, the specific child characteristics analyzed provided further insight into the child’s overall ability to adapt, function, and participate in daily activities. The ICF and ICF-CY (children and youth version) can move the focus away from specific diagnoses and towards the unique functional capabilities of each child within his or her environment. The ICF recognizes that a disability is not one-dimensional but is woven within multiple layers of child and family experiences.⁵⁰ Our data suggest that sleep disturbance is not a primary characteristic of FXS, but rather occurs in a subset of children. Therefore, it is important to consider the unique characteristics of the child, environment, and the dynamic interplay between these variables and the health condition, particularly when targeting interventions for sleep problems. Since the ICF was designed with the life span in mind, it provides a continuous framework for assessment and reassessment of the effectiveness of specific interventions targeted at promoting abilities to listen, adapt, improve mood, and improve health outcomes, including sleep.^{51,52}

Limitations and Conclusions

There are several limitations to the current study. First, the survey was conducted on a convenience sample of families and may represent only those families connected to a FXS specialty clinic or FXS association. Families who do not have access to such care may have been excluded. In addition, there are many children in the general population who remain undiagnosed and therefore, data may not be reflective of the entire population of children with FXS and should not be interpreted as such. It is important to note the imbalance between the number of male and female participants in this study, as well as in most studies involving FXS. This may be part of a larger diagnostic issue. It is important to recall that although females

have similar prevalence rates, they are usually milder in their presentation and may only be suspected of having FXS once their proband male sibling is diagnosed. Therefore, many females may go undiagnosed and underrepresented in these studies. Secondly, the survey did not employ the use of a validated sleep questionnaire. The use of individual validated questionnaires to collect data on each domain of the survey (e.g., nutrition, sleep, functional skills, speech and language) was beyond the scope of this study. However, the 10 sleep items utilized in the survey were based on key sleep screening questions typically asked during a health encounter.⁵³ Thirdly, the questions regarding sleep were answered by families whose children have a “current” sleep difficulty and are not representative of children with a sleep difficulty that resolved or families who have learned to tolerate the sleep behaviors and no longer view them as current or difficult. There is information to be gained from families whose children have been treated successfully or who have outgrown their sleep problems. With that said however, cross-sectional designs are typical in sleep research when collecting descriptive data, and longitudinal designs lend themselves more to intervention studies. Fourth, information collected on medication use needs to be interpreted with caution because of what families may have considered a sleep medication. For example, some families may not have considered melatonin or other supplements as medication and placed this intervention under “other.” Some families may not know why certain medications were prescribed and therefore did or did not include them when asked to list medications their child takes for sleep. Also, medications to treat various behaviors (e.g., Risperdal) can also enhance sleep, although it may not be prescribed for that purpose. Finally, information collected in surveys is limited by parent report.

In summary, the large scale survey described in this paper establishes a foundation for the prevalence of sleep disorders in children with FXS. Parents report that current sleep difficulties are frequent and begin when children are a very young age. Frequency of sleep difficulties diminish with age, most notably with males. However, caregivers continue to report sleep difficulties at considerable levels even in their adolescent and adult children.

Additional research questions may address why gender differences were not as apparent as expected in the frequency and type of sleep difficulties. Also, why do males with sleep difficulties appear to improve somewhat with age and females do not? Is anxiety a significant confounder in older females contributing to their sustained level of sleep difficulties? To answer these and other questions, future research should utilize objective data collection through the use of actigraphy, polysomnography, and possibly MRI scanning. Double-blind randomized studies should evaluate the effectiveness of medication on specific target symptoms and utilize objective measures of assessment. Furthermore, those children with FXS who do not have sleep difficulties may provide additional insights to understand sleep in this syndrome. Conjointly, molecular research on the underlying gene effects of FMR1 will continue to expand our knowledge of neuronal morphology and its influence on circadian rhythm. Most importantly, we must apply what we learn to assist families and individuals to gain greater functional capabilities in their everyday lives.

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