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Sleep patterns and daytime sleepiness in adolescents and young adults with Williams syndrome

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Abstract

Background—Sleep disorders are common in individuals with neurodevelopmental disorders and may adversely affect daytime functioning. Children with Williams syndrome have been reported to have disturbed sleep; however, no studies have been performed to determine if these problems continue into adolescence and adulthood.

Methods—This study examined overnight sleep patterns and daytime sleepiness in 23 adolescents and adults with Williams syndrome age 25.5 (8.0) years [mean (SD)]. Interviewer-administered sleep questionnaires were used to evaluate nighttime sleep behaviours and daytime sleepiness. Wrist actigraphy was used to evaluate sleep patterns.

Results—Although individuals in our sample averaged 9 h in bed at night, daytime sleepiness and measures of sleep disruption were common and comparable to those of other populations with neurodevelopmental disorders. These measures included reduced sleep efficiency [74.4 (7.0)%] with prolonged sleep latency [37.7 (37.3) min], increased wake time after sleep onset [56.1 (17.6) min], and an elevated movement and fragmentation index [14.3 (4.6)].

Conclusion—Adolescents and young adults with Williams syndrome were found to be sleepy despite averaging 9 h in bed at night. Implications are discussed for associated causes of sleep disruption and future polysomnographic evaluation.

Keywords

adolescents and young adults; daytime sleepiness; sleep patterns; Williams syndrome

Introduction

Williams syndrome, a developmental disorder resulting from a microdeletion of several genes on chromosome 7q11.23, results in cardiovascular, endocrine and neurological problems (Poher & Morris 2007). Williams syndrome is associated with a distinctive cognitive-linguistic profile, marked by visual-spatial deficits and relative strengths in expressive language. Individuals with Williams syndrome also have high levels of non-social

anxiety, worries and fears, as compared with others with intellectual disabilities (ID) (Einfeld *et al.* 1997; Davies *et al.* 1998; Dykens 2003), even though they show marked sociability and interests in interacting with others. In addition, children with Williams syndrome may exhibit over activity and short attention spans. Approximately 65% are diagnosed with attention-deficit hyperactivity disorder (ADHD) or other behavioural disorders (Einfeld *et al.* 1997; Dykens 2003; Leyfer *et al.* 2006; Pober & Morris 2007). Both mental health and medical problems persist into adulthood, and may reduce adult quality of life (Davies *et al.* 1998; Howlin & Udwin 2006).

Sleep is one aspect of the Williams syndrome phenotype that has yet to be adequately characterized. Sleep disorders are common in individuals with developmental disorders, and persist if not treated (Lancioni *et al.* 1999). Prevalence rates range from 13% to 86% dependent on age, physical and mental impairment, and genetic syndrome (Didden & Sigafoos 2001). To date, only one study has specifically looked at sleep in Williams syndrome. Parents of 28 children [mean age (SD) = 4.7 (2.3) years] participated in a telephone survey to examine possible sleep problems (Arens *et al.* 1998). The authors reported, based on parental response, that 16 children (57%) had symptoms consistent with a possible sleep disorder. In particular, restless sleep, awakening and sleep initiation were reported. Polysomnography was performed on seven of these children and the authors reported a periodic limb movement index that was fivefold greater in these children than in control subjects. These children also had a greater amount of sleep time spent awake than control subjects. Based on this study, and extrapolating from the literature on sleep in normal children, it was suggested that children with Williams syndrome may be at risk for sleep disruption because of limb movements, restless leg syndrome or sleep disordered breathing (Mason & Arens 2006). These authors further suggest that a sleep history should be included in the clinical evaluation of children with Williams syndrome. Clinically, sleep complaints are believed to persist into adulthood (Pober & Morris 2007), although studies have yet to examine the nighttime sleep patterns and associated daytime sleepiness in adolescents or adults with Williams syndrome.

Disturbed sleep in neurodevelopmental disorders is associated with poorer daytime function and behaviour (Malow & McGrew 2008). Given their high levels of fears and anticipatory anxiety, we wished to explore whether disturbed nighttime sleep might be present in our adolescents and adults with Williams syndrome. If present our work would then provide a basis for future interventional studies aimed at improving sleep in Williams syndrome, with the goal of improving anxiety and other daytime behaviours. The primary objective of this study is to describe the sleep patterns of adolescents and adults with Williams syndrome using sleep questionnaires and wrist actigraphy.

Method

Participants

We examined nighttime sleep patterns and daytime sleepiness in 23 adolescents and adults with Williams syndrome (12 males, 11 females) using structured interviews and wrist actigraphy. Participants were recruited during a residential summer music camp offered through the Vanderbilt Kennedy Center for Human Development. Participants ranged in age

from 17 to 35 years, with a mean age of 25.5 (8.0) years. As identified by the Kaufman Brief Intelligence Test-2 (K-BIT-2) (Kaufman & Kaufman 2004), participants' overall mean IQ was 66.1 (14.5). Consistent with the cognitive profile often seen in Williams syndrome, participants showed, on average, better developed verbal skills [K-BIT-2 verbal IQ = 79.3 (15.8)] than non-verbal skills [K-BIT-2 non-verbal IQ = 60.6 (17.7)]. All participants but two lived at home with their parents; two individuals resided with a roommate in a supervised, supported living apartment in close proximity to their families. Prior to arrival at the summer music camp, parents of all participants were asked if they felt their child would be able to independently participate in this study and all felt they would be able to. This study was approved by the Vanderbilt University Medical Center Institutional Review Board and all participants provided informed consent.

Procedure and instruments

Participants completed an interviewer-administered sleep habits questionnaire which included the Epworth Sleepiness Scale (ESS), a validated questionnaire to measure excessive daytime sleepiness in adults. The ESS is widely used in sleep medicine to evaluate daytime sleepiness. The ESS consists of eight questions designed to evaluate an individual's propensity to fall asleep during routine daytime situations. The ESS has a test-retest reliability with a Pearson correlation coefficient of 0.822 in circumstances where daytime sleepiness was expected to be stable, and a Cronbach's alpha = 0.88 for internal consistency (Johns 1991; Johns 1992). A score of >10, out of a possible 24, on the ESS is indicative of increased daytime sleepiness (Johns 1994). Participants were also asked how often they awoke during the night, and for what reason; if they felt they had problems sleeping at night (yes/no); if they snored (yes/no); and if they were tired during the day (yes/no). Finally, participants were also asked about feelings in their legs. If they acknowledged leg symptoms, they were queried further as to the time of day and the character of these sensations.

Three to 4 weeks after the camp ended, participants were contacted to see if they would be willing to wear a wrist actigraph and complete a sleep-wake diary to measure nighttime sleep. A total of 17 individuals assented and they were sent wrist actigraphs (MiniMitter® AW 64 Mini-Mitter, Respironics, Bend, OR, USA). These 17 individuals did not differ from the larger group of 23 participants in demographic variables, sleep or behavioural features. The actiwatch is a small computerized wristwatch-like device that is used to detect movement (Sadeh & Acebo 2002) and is used as a surrogate measure of sleep and wake. It was worn on the non-dominant wrist over seven consecutive 24-h periods. The actiwatch has been validated as a highly reliable method to differentiate sleep from wake (Sadeh *et al.* 1995; Jean-Louis *et al.* 2001; Sadeh & Acebo 2002; Ancoli-Israel 2005). It is widely used in sleep research and sleep medicine. The actigraph was set to record in 1-min epochs at a medium sensitivity level for scoring sleep and wake times (40 activity counts/min) (Oakley 1997); Mini-Mitter Co. Inc 2004). Participants were sent a sleep-wake diary to complete concurrent with wearing the watch. Each day, participants recorded the time they went to bed, woke up in the morning and the number of times they awoke during the night. All participants were instructed in the use of the actigraph and how to complete the sleep diary. Telephone support was available throughout the monitoring period.

Data from the actigraphs were downloaded to a personal computer where all sleep intervals were manually placed on the actogram based on the time recorded in the participants' diary. Time in bed was defined as the time elapsed from lights out (the set sleep start) to lights on (the set sleep end). The total nighttime sleep duration was the sum of all sleep epochs within the interval between the time set on the actogram for nighttime sleep and morning wake time. Sleep efficiency was calculated as the ratio of total nighttime sleep duration to the total time in bed. Sleep latency was calculated as the time required for sleep onset after attempting to get to sleep. Wake after sleep onset (WASO) was measured as the sum of all wake epochs during the sleep period and reflects the number of minutes scored as wake that exceeded the sensitivity threshold. The movement and fragmentation index (MFI), often referred to as an index of restlessness, was calculated by the software as the sum of the per cent of mobile minutes plus the per cent of immobile bouts less than 1-min duration to the number of immobile bouts, for a given interval. The MFI captures all movement regardless of the intensity of the movement. All sleep variables were calculated using Actiware Version 5 software (Mini-Mitter Co., Bend, OR, USA).

Statistical analyses

Descriptive statistics were conducted on all major variables. Associations were measured with Spearman correlation. Nonparametric Wilcoxon-Rank Sum Tests were used to test differences in means between dichotomous variables, and chi-squared analyses were used for categorical variables between individuals. Results are presented as mean (SD) and significance is at $P < 0.05$. Analyses were run using sas Version 9 software (SAS Institute, Cary, NC, USA).

Results

Demographics

No significant differences were found between males and females on any sleep variable. Similarly, no significant differences were found by age for any sleep variable.

Subjective sleep perception

Ninety-five per cent of the participants indicated that they felt tired during the day, with over 1/3 (34.8%) having excessive daytime sleepiness as measured by an ESS score ≥ 10 .

Ninety-one per cent of participants reported awakening at least one time per night to use the bathroom, with over 65% of participants reporting awakening two or more times per night. Other symptoms included snoring in 22.7%, and urge to move their legs in 13.6% (see Table 1). The majority of our participants responded that they were tired during the day, felt that they had sleep problems and stated that, if possible, they would like to sleep more.

Actigraphy-measured sleep

Time in bed, documented with wrist actigraphy, averaged 9.0 (1.1) h and the average nighttime sleep duration was 7.6 (1.2) h. The average sleep latency was 37.7 (37.3) min. Sleep efficiency was 74.4% (7.0) and the measures of disruptive sleep in the sample overall were high, including 56.1 (17.6) min of WASO and an MFI of 14.3 (4.6).

Discussion

To our knowledge, this study is the first to specifically examine sleep patterns in adolescents and adults with Williams syndrome. Through the use of actigraphy, an objective measure of sleep patterns, and subjective questionnaires, we were able to describe the sleep concerns and patterns in this group of individuals. The majority of our participants acknowledged sleep problems and daytime tiredness. We documented that these individuals were sleepy even though they are spending an average of 9 h in bed at night, and averaging 7.5 h of sleep.

We postulate that the daytime sleepiness that our patients reported is due to sleep disruption. Sleep disruption in the population may be caused by multiple factors including nocturia, restless legs syndrome/periodic limb movements of sleep, obstructive sleep apnoea or factors intrinsic to Williams syndrome. Children with Williams syndrome have been reported to have periodic limb movements in sleep with associated arousals and awakenings (Arens *et al.* 1998), and these symptoms have also been reported in adults (Davies *et al.* 1998; Mason & Arens 2006). Individuals in our study reported unpleasant sensations in their legs when lying down at night symptoms suggestive of possible restless legs syndrome. While most individuals with restless leg syndrome have periodic limb movements of sleep, periodic limb movements of sleep can occur independently of restless legs syndrome and are diagnosed by polysomnography. Therefore, we cannot exclude periodic limb movements of sleep as a potential cause of perceived sleepiness in these individuals.

Nocturia is another potential cause of sleep disruption in our population. The majority of our participants reported the need to urinate at least once during the evening with a large per cent reporting this need multiple times. A high prevalence of urinary frequency, and incontinence, has been reported in children and adults with Williams syndrome (Schulman *et al.* 1996; Cherniske *et al.* 2004) and some adults complain of night wakings because of a full bladder (Pober & Morris 2007). In one study ($n = 20$), urinary frequency was found to affect half of all participants; however, renal function was normal in all (Cherniske *et al.* 2004). Ultrasound has shown bladder diverticula in individuals with Williams syndrome (Schulman *et al.* 1996; Cherniske *et al.* 2004); however, an association with increased urinary frequency has not been established. Nocturia is not expected in this age group in the general population. The prevalence by self-report in these Williams syndrome individuals suggests need for further quantification with more detailed objective measurement. Furthermore, treatment of such disorder with vasopressors may help minimize some of the daytime sleepiness.

While nocturia and periodic limb movements of sleep might explain a portion of the sleepiness in these individuals, the possibility of obstructive sleep apnoea also merits consideration. We found that more than a fifth of our participants reported they had been told they snored. Although snoring is not diagnostic of sleep apnoea, it is common in sleep apnoea. Furthermore, this population has a high prevalence of cardiovascular anomalies, hypertension, abnormal glucose tolerance and diabetes (Cherniske *et al.* 2004), all symptomatic of sleep apnoea. In the overall population, these diseases all are associated with

a high prevalence and risk of obstructive sleep apnoea, and they may also be associated with obstructive sleep apnoea in Williams syndrome as well.

An underlying sleep disorder may be a contributing factor to the higher prevalence of anxiety and behavioural disorders in Williams syndrome. Sleep behaviours may play a role in the broader phenotypical presentation of Williams syndrome (Mason & Arens 2006). Individuals with Williams syndrome often have coexistent psychiatric disorders, such as ADHD, stress and anxiety, that may be complicated by disturbed sleep (Stores 2001). Existing research shows significant overlap between anxiety and sleep in children (Chorney *et al.* 2008). Adults with ADHD are more than likely to have a variety of sleep problems (Gau *et al.* 2007). Similar to our population of adults with Williams syndrome, an actigraphy study of adults with ADHD showed these individuals to have lower sleep efficiency, longer sleep onset latency and shorter sleep duration than a matched control group of normal adults (Boonstra *et al.* 2007).

Behaviour problems occur in association with poorer sleep and higher levels of daytime sleepiness. Sleep problems have been implicated in poor daytime learning and occupational performance, as well as with higher probabilities of daytime behavioural disorders in individuals with ID (Lancioni *et al.* 1999). Problematic behaviours have been found to be associated with sleep disorders in a group of 205 adults with mental handicaps; these individuals scored significantly higher on a majority of the subscales of the Aberrant Behavior Checklist (Didden & Sigafos 2001). Although we can not ascertain whether behavioural disturbances are associated with sleep disturbances in the current study, future research is warranted to define this association.

Other neurodevelopmental disorders such as Prader-Willi syndrome, Angelman syndrome, Fragile X syndrome, autism, Asperger syndrome, Rett syndrome and Smith-Magenis syndrome list sleep disturbances as associated features (Stores 2001; Walz *et al.* 2005). However, there has been little work performed on adolescents and adults, with most of the reported studies focusing on childhood. Sleep parameters measured with actigraphy in adolescents and young adults with autistic disorder, Asperger syndrome and an unspecified intellectual disorder (Oyane & Bjorvatn 2005; Hare *et al.* 2006) suggest individuals with Williams syndrome share similar sleep patterns with these disorders. These patterns differ from the sleep patterns of adolescents and young adults without a neurodevelopmental disorder. In general, the individuals with neurodevelopmental disorders took longer to fall asleep, had poorer sleep efficiency and spent more time awake after sleep onset. Potential reasons for these differences are speculative. Many developmental disabilities have clear genetic etiologies, and evidence suggests the potential for different polysomnographic phenotypes in children with developmental disabilities (Harvey & Kennedy 2002). Further, developmental disorders are often associated with psychiatric disturbances, sensory deficits and immobility issues, as well as with medication side effects (Stores 2001).

This study has several strengths and weaknesses. Strengths include that this is the first study to look at sleep in a population of adolescents and adults with Williams syndrome. We employed both objective and subjective measures to obtain this information. With actigraphy, we were able to characterize sleep-wake patterns over several nights in the

participants' own environment. This allowed us to document the prevalence of insomnia and disrupted sleep in these individuals. Shortcomings of this research were the lack of polysomnography as a mechanism to evaluate sleep in this population, the lack of a control group, potential bias associated with self-report data. Additionally, individuals with Williams syndrome have a strong desire to please others and give the answer that they think others want to hear, which may have biased results. However, the presence of documented sleep disruption with actigraphy supports the validity of self-report of sleep in Williams syndrome even though the subjective sleep data were collected 3–4 weeks prior to the wrist actigraph data.

These findings suggest avenues for future research. First, the high prevalence of sleep disruption found indicates the need for polysomnography evaluation. Use of polysomnography would provide additional information on sleep in Williams syndrome, including measurement of EEG activity, respiratory parameters and leg movements. Second, the use of control subjects with and without developmental disabilities would further provide information as to the extent that Williams syndrome individuals have sleep disruption that is similar or dissimilar to other individuals of matched age and gender. Third, future studies could measure behavioural correlates and relate these to disordered sleep in Williams syndrome. Finally, defining the sleep characteristics of these individuals will provide direction for future studies to improve nighttime sleep and subsequent daytime function in this syndrome and other related disorders of neurodevelopment.

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Table 1

Sleep and behaviour characteristics of Williams syndrome adolescents and adults

	Total n = 23
	Mean (SD)
Age (years)	25.5 (8.0)
Epworth Sleepiness Scale	8.7 (4.4)
Subjective sleep perception *	% yes
Have problems with sleep	36.4
Want to change their sleep	76.7
Sleepy during the day	77.3
Tired during the day	95.2
Nocturia	90.5
Snoring	22.7
Restless leg symptoms	13.6
Actigraphy-measured sleep (n = 17) †	Mean (SD)
Time in bed (h)	9.0 (1.1)
Sleep duration (h)	7.6 (1.2)
Sleep onset latency (min)	37.7 (37.3)
Sleep efficiency (%)	74.4 (7.0)
Wake after sleep onset (min)	56.1 (17.6)
Movement and fragmentation index	14.3 (4.6)

* Responses to sleep interview questions asked were based on a yes/no scale.

† Variables calculated by Actiware V5 software (Mini-Mitter Co., Bend, OR, USA).