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Characterisation of sleep problems in children with Williams syndrome

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ABSTRACT

Sleep is critical to optimal daytime functioning, learning and general health. In children with established developmental disorders sleep difficulties may compound existing learning difficulties. The purpose of the present study was to evaluate the prevalence and syndrome specificity of sleep problems in Williams syndrome (WS), a neurodevelopmental disorder affecting around 1 in 20,000 live births.

Parents of 64 children with WS, aged 6–12 years, and 92 age matched healthy controls were surveyed about their child's sleep habits. The Child Sleep Habits Questionnaire, general health and background information were collected from the parents. Ninety seven percent of parents reported that their children had sleep problems and reported a high prevalence of sleep difficulties: greater bedtime resistance, sleep anxiety, night waking and daytime sleepiness. This is the first study to our knowledge to survey sleep problems in a large cohort of school age children with WS. Sleep problems in children with learning difficulties are often amendable to treatment if diagnosed early. Furthermore the negative impact of sleep disturbances on daytime behaviour and learning should be measured before diagnoses of behaviourally defined disorders are considered.

1. Introduction

There is now a substantial body of evidence indicating that sleep is important for the healthy development of children and contributes to optimal social and neuropsychological function (Hill, Hogan, Karmiloff-Smith, 2007). Sleep requirements alter through life as a function of biological and environmental changes with age, and there are distinct differences between adult and child sleep patterns. The prevalence of sleep problems in typically developing school-aged children is relatively low (around 6–10%). However, in direct contrast, the existence of a high rate of sleep disturbances (34% to 86%) has been reported in children with developmental disorders such as Autism (Richdale, 1999; Richdale & Schreck, 2009; Stores & Wiggs, 2001), Angelman syndrome (Pelc, Cheron, Boyd & Dan, 2008), Attention Deficit Hyperactivity Disorder (Paavonen et al., 2009) and Down syndrome (Carter, McCaughey, Annaz, & Hill, 2009). Although the existence of sleep disorders in developmental disability is well established, their causes and syndrome specificity are yet to be identified and quantified.

There is abundant evidence to suggest that good night-time sleep leads to improved daytime behaviour in typically developing children and in children with developmental disorders (e.g., Maas et al., 2010; Scher, Hall, Zaidman-Zait, & Weinberg, 2010). Sleep disturbances can give rise to severe behavioural difficulties during the day, such as aggression,

Abbreviations: CSHQ, Child Sleep Habits Questionnaire; SRE, sleep-related enuresis; TD, typically developing children; WS, Williams syndrome.

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screaming, tantrums, non-compliance, and impulsivity (Stein, Mendelsohn, Obermeyer, Amromin & Benca, 2001) and predict maternal mood, stress, and fatigue family functioning, including maternal depression and familial stress (Meltzer & Mindell, 2007). Persistent sleep problems have been also linked to immune-system dysfunction (Franck et al., 1999), impairments in cognitive functioning resulting in a possible lack of understanding of the differences between wakefulness and sleep, inability to self soothe between sleep phases, and general anxiety (Sheldon, Ferber & Kryger, 2005).

Williams syndrome is a rare genetic disorder caused by a hemizygous microdeletion of some 28 genes on chromosome 7q11.23, with an approximate incidence of 1 in 20,000 live births (Schubert, 2009; Tassabehji, 2003). It results in a complex physical, cognitive and behavioural phenotype that includes an uneven cognitive profile, with relatively proficient face recognition and language skills alongside poor numerical and visuo-spatial skills compared to overall mental age, and overall IQs in the 50s to 60s range (Donnai & Karmiloff-Smith, 2000; Searcy, Lincoln, Rose, Klima & Bavar, 2004). Physically, the WS phenotype includes a dysmorphic face, growth retardation, congenital heart disease (typically supravalvular aortic stenosis occurring in 75% of cases), premature ageing, weakness of connective tissue, renal anomalies and reported infantile hypercalcaemia. Facial symptoms include a wide mouth with full cheeks and full lips and periorbital fullness with a broad forehead.

Although parents of children with WS informally report that their children suffer from sleep disturbances, research into the specific sleep problems in WS is scarce, however, there are now several research groups investigating the issue. Early studies described settling problems and night waking (Einfeld, Tonge, & Florio, 1997; Udwin, Yule & Martin, 1987), as well as bed wetting and sleep anxiety (Sarimski, 1996). In another study, Arens et al. (1998) undertook an eight-question telephone survey of 28 families of children with WS (age range: 1.5–10 years olds) and reported sleep problems such as night awakenings, restless sleep and difficulty initiating sleep. Polysomnography was performed on seven of these children with WS and compared to 10 typically developing controls. Periodic limb movement index was fivefold greater in children with Williams syndrome. However, the small sample size and wide age range make the results difficult to generalise to WS as a whole. A more recent study focused on a group of adolescents and adults with WS, using a sleep questionnaire and wrist actigraphy (Goldman, Malow, Newman, Roof & Dykens, 2009). The authors reported reduced sleep efficiency, prolonged sleep latency, increased number of night wakings and elevated movements during the night. However, no direct comparisons to controls or previously normative values were performed.

The aims of the current study were to (1) determine the prevalence of sleep problems in school-aged children with Williams syndrome and compare with TD children; (2) investigate the association between different types of sleep problems and (3) explore the relationship between sleep problems and child characteristics, including medication use, age, gender, ethnicity, child's health history and socioeconomic status. This was carried out by targeting a large population of children with WS within a narrow age range and primary school-aged children in the UK, by means of widely used sleep questionnaires.

2. Methods

2.1. Participants

Parents of primary school-aged children with WS were identified from the full database provided by the UK Williams Syndrome Foundation. Of the 82 invited parents, 64 completed and returned both questionnaires, yielding an overall response rate of 82%. Reasons for non-participation included: nine families unobtainable despite repeated contact attempts, seven changed addresses, with only two declining to participate. This cohort represents over half of all school-aged children with WS in the United Kingdom. All children with WS had been diagnosed clinically, as well as by means of the *fluorescence in situ hybridisation* (FISH) genetic test for deletion of one copy of the Elastin gene. The control group comprised 92 TD children sourced from Hampshire schools, UK. Background data from schools and parents were collected to ensure that the control group did not have any clinical diagnoses or learning difficulties before they were included in the study. Prior to recruitment of the participants, ethical approval was granted by the Middlesex University London Ethics Committee, the University of Southampton, School of Psychology Ethics Committee and the Williams Syndrome Foundation, UK.

2.2. Measures

The *Child Sleep Habits Questionnaire*: Parents completed the Child Sleep Habits Questionnaire (CSHQ) (Owens, Spirito & McGuinn, 2000), a screening instrument for school-aged children based on common clinical symptom presentations of prevalent sleep disorders. The CSHQ consists of 33 items rated on a 3-point Likert scale (never/rarely, sometimes, and usually). It yields scores on 8 sub-scales: sleep anxiety (e.g., "afraid of sleeping in the dark"), sleep duration, bedtime resistance, sleep onset delay, night waking, parasomnias, sleep disordered breathing and daytime sleepiness. It provides a total sleep disturbance score, as well as a problem-specific breakdown. Psychometric properties indicate that the CSHQ can identify sleep problems in a clinical sample and can distinguish between clinical and community samples (Waumans et al., 2010).

In addition, parents of children with WS completed developmental history and health habits sections of *The Pediatric Sleep Clinic Questionnaire* (Owens, http://www.kidzzzsleep.org). Demographic data were obtained from both groups.

3. Results

Data analysis consisted of three distinct strategies: (1) comparison of CSHQ subscale scores and the CSHQ Total score for the WS and TD groups, (2) evaluation of specific sleep problems for the WS group and health factors and (3) investigation of sleep disturbance scores with variables such as age, medication use, gender, ethnicity and SES.

Both ANOVA and multivariate ANCOVA comparisons were used in the current study. Data were checked for homogeneity of variance (Levene's test) and for the covariance structure (Box's M test). In addition, the absence of outliers was assured before analyses were performed (see, Thomas, Annaz, Ansari, Scerif, Jarrold, & Karmiloff-Smith, 2009, for details on analysis). The significance of differences in categorical variables was also calculated using Chi-square analyses.

3.1. Group characteristics

Demographic data were obtained for each individual (see Table 1). There was no difference between the groups on chronological age ($t(155) = 2.61$, $p = .32$). Next, in order to assess differences between groups on categorical variables of gender and ethnicity, *a priori* Chi-square analyses were conducted. The two groups did not differ on gender, $\chi^2(2) = 1.70$, $p = .424$ nor ethnicity, $\chi^2(3) = 4.11$, $p = .381$ nor parent occupation (professional, managerial and other occupation) $\chi^2(3) = 4.46$, $p = .487$.

3.2. Comparison of WS and TD controls on CSHQ scores

ANOVA analyses of group comparison were performed to investigate if there were any differences between the WS and TD control group on total sleep scores and subscales of CSHQ scores. As shown in Table 2, compared to TD controls, children with WS are significantly affected by several types of sleep disturbances, namely, sleep anxiety, bedtime resistance, sleep onset delay, frequent night waking and excessive daytime sleepiness.

Table 1
Group characteristic: TD = typically developing, WS = Williams syndrome, CA = chronological age and SD = standard deviation.

	Williams syndrome ($N = 64$)	Typically developing controls ($N = 93$)
Age, years (SD)	8:3 (2:07)	8:5 (1:08)
Age range	6:02–12:06	6:5–12:08
Gender (M/F %)	44/56	49/51
Ethnicity (% White)	92	99
Ethnicity (% Black)	1	0
Ethnicity (% Other)	7	1
Parent occupation	–	–
Professional (%)	54	57
Managerial (%)	24	20
Other (%)	21	23

Table 2
Group statistics on CSHQ subscales: TD = typically developing and WS = Williams syndrome.

Group statistics					
	Groups	Mean	Std. deviation	*F* value	*p* value
Total score	TD ($N = 93$)	40.54	5.83	64.73	<**.001**
	WS ($N = 64$)	47.88	8.12		
Bedtime resistance	TD ($N = 93$)	6.80	1.10	5.84	<**.001**
	WS ($N = 64$)	8.87	2.72		
Sleep onset delay	TD ($N = 93$)	1.49	.70	18.79	<**.001**
	WS ($N = 64$)	2.03	.85		
Sleep duration	TD ($N = 93$)	4.11	1.56	.34	.560
	WS ($N = 64$)	4.25	1.94		
Sleep anxiety	TD ($N = 93$)	4.57	.90	14.57	<**.001**
	WS ($N = 64$)	5.50	2.05		
Night waking	TD ($N = 93$)	3.45	.83	37.96	<**.001**
	WS ($N = 64$)	4.94	2.10		
Parasomnias	TD ($N = 93$)	8.99	1.93	.11	.740
	WS ($N = 64$)	8.86	2.93		
Sleep disordered breathing	TD ($N = 64$)	3.47	.90	0.49	.825
	WS ($N = 64$)	3.50	1.54		
Daytime sleepiness	TD ($N = 93$)	9.83	2.76	4.44	**.037**
	WS ($N = 64$)	10.80	3.32		

Table 3
Medical history variables of the WS group as predictor of CSHQ scores.

	% of children reported with problems	Impact on CSHQ sleep scores
Speech delay	33	ns
ADHD	17	ns
Allergies	20	Sleep onset delay
Asthma	12	Sleep onset delay
Sinus infections	6	ns
Had operations	62	ns
Hernias	32	ns
Kidney problems	6	ns
Cardiac problems	37	Sleep duration
Gastrointestinal problems	14	ns
Lungs	6	ns
Squint repair	8	ns
Other significant health problems	34	ns

Additionally, ANCOVA model using chronological age and gender as covariates was constructed to compare groups on the total CSHQ scores. It revealed a no significant group difference [$F(1,155) = 2.16$, $p = 0.12$] and a significant group by CSHQ interaction [$F(1,155) = 29.57$, $p < 0.001$], indicating that the WS group decreased in sleep problems with age at a much slower rate in comparison to the TD group.

3.3. Characteristics of sleep disturbances in children with WS

Particular sleep problems were notable: 45% usually resisted going to bed and 40% of children usually move to someone else's bed during the night and 43% have trouble falling asleep when away from home. Sleep talking was reported in 15% of children with WS. Almost all parents (97%) reported frequently interrupted sleep with more than two awakenings per night and 60% of parents reported their children to be restless during sleep. There were no gender differences in the reported sleep problems except for sleep onset delay with girls having greater reported difficulty in this area ($F(1,63) = 5.58$; $p = .008$).

Other frequently reported sleep problems included: enuresis in 51% of the WS sample, this was irrespective of the age of the child ($p > .05$). A relatively large number of parents reported their children to snore loudly (29%- to snore sometimes; 7%- to snore often). Importantly, 61% of WS children were tired during the day and 27% reported sleep problems and body pains during the night. Interestingly, 55% of parents reported that their children do not have enough sleep overall. The mean amount of reported sleep for the WS children was 9.9 h (SD = 1.2), however, in contrast to TD children, the amount of sleep hours varied substantially, from 7 h to 12.5 h per night. Chronological age did not influence sleep duration ($F(1,63) = 2.94$; $p = .092$). Finally, in line with TD children, 11% of WS parents reported bruxism. Moreover, despite appearing tired, only 2% of children were reported to nap during the day and none were reported to fall asleep spontaneously during daytime actives.

3.4. Health and medication of the WS group

Data gathered from the medical history section of the Pediatric Sleep Clinic Questionnaire were used to examine the relationship between sleep problems and child characteristics, including medication use, child's health history and disorder comorbidity. It should be noted that none of the children had secondary diagnosis of autism. Table 3 shows the percentage of children who were reported with specific problems. A fully factorial repeated-measures Analysis of Covariance (ANCOVA) was conducted on the CSHQ scores with variables from Table 3 as covariates to examine if any of these variables had a significant impact on the total CSHQ scores and its sub-scales. None of the most frequently reported medical conditions associated with sleep disorders, such as recurrent ear infections, constipation, tonsillitis and epilepsy, were reported in this survey (all $p > .50$; $\eta^2 = .04$). However, asthma (12%) and allergies (20%) showed to be strong predictors of sleep onset delay and cardiac problems (37%) had a significant effect on sleep duration.

4. Discussion

This study indicates that school-aged children with Williams syndrome suffer from significant sleep disturbance characterized by high levels of sleep anxiety, bedtime resistance, increased sleep latency and frequent night waking compared to age and gender similar TD controls. Daytime sleepiness and night waking, a common complaint in several neuro-developmental disorders, was also significantly noted in the current study. Unlike previous studies of children with development disorders, our findings pointed to improvement in sleep problems with increasing chronological age, albeit at a slower rate than in typically developing peers. This result needs further validation using a longitudinal developmental trajectories method (see, Thomas et al., 2009, for further details on method).

Atypical sleep duration or disturbed sleep is known to impact on neurocognition, particularly attention, learning and behaviour in childhood (Blunden & Beebe, 2006). Children with pre-existing learning difficulties lack the cognitive reserve to compensate for such impairments/delays and hence are likely to be more disadvantaged than typically developing peers.

Parental reports on sleep disturbances such as daytime sleepiness in Williams syndrome children is of concern. Unlike in adulthood, daytime sleepiness is often a late symptom of sleep impairment in children. The nature of the sleep problems reported in this study indicate that behavioural factors may be present. Sleep onset delay and bedtime resistance are commonly seen in external sleep disorders such as limit setting sleep disorder where a parent struggles to set clear limits to bedtime. Behavioural factors are important to identify as they are commonly seen in children with learning disabilities and eminently amenable to improvement with good sleep hygiene and parental education (Wiggs, 2009). A further indicator that psychosocial factors may have a bearing is the tendency for reported sleep problems to improve with the age of the child. Clements et al. reported that sleep in individuals with severe mental retardation, did not improve spontaneously over developmental ages. In a longitudinal survey of 200 children with severe mental retardation, sleep disorders were represented by difficulties of initiating and maintaining sleep, with a frequency of 51 and 67%, respectively. These sleep problems still persisted after 3 years follow-up (Clements, Wing & Dunn, 1986). More recently, Richdale and colleagues reported that prevalence of sleep disorders persisted over time in a sample of 52 children with mental retardation (Richdale, Gavidia-Payne, Francis & Cotton, 2000). Contrary to these studies, our results indicate that sleep problems are age-related and improve with increased age in both the WS and control group, although at a much slower rate for the WS children. Due to the cross-section nature of our study, this finding needs to be interpreted with caution and followed up by means of longitudinal data to have a firm conclusion. The observed age related reduction in sleep problems may represent a genuine regression of sleep difficulties with age, reporting differences in parents of older children who perhaps have adapted to their child's difficulties or have successfully responded to sleep interventions, or due to improved health issues in older children. These are important issues for future research.

Interestingly, reported total sleep time, which is often shorter in developmental disorders, appears to be within normal range in children with WS, at just under 10 h. However, examination of individual scores reveals a large variability in total sleep duration in the WS group which needs further investigation. Intrinsic sleep disorders such as sleep apnea and periodic limb movement disorder have the potential to disrupt sleep and promote night waking. While the WS children in this study did not differ from the typically developing children with respect to the sleep disordered breathing sub-scale, nonetheless a high rate of habitual snoring was reported (36%) and was significantly higher than in a general population of this age range (3–7%) (Ersu et al., 2004; Sahin, Ozturk, Ozturk, Songur, Bircan, & Akkaya, 2009) Similarly, Goldman et al. (2009) reported lower rates of snoring (27%) in adolescents and young adults while only one of the seven children in Arens's polysomnographic study had measurable mild upper airway obstruction. Further objective population based respiratory studies would be illuminating as craniofacial dysmorphic features may predispose to sleep disordered breathing.

Furthermore, none of the most frequently reported medical conditions associated with sleep disorders such as recurrent ear infections, constipation, tonsillitis and epilepsy were reported in this survey. Also, in contrast to the previous study, periodic limb movement disorder was only reported in a very small number of children. However, it should be noted that The Child Sleep Habits Questionnaire includes questions only about restless sleep, a non-specific marker of this disorder. Objective measures would be required to further explore this finding. A significant number of parents reported nocturnal enuresis (51%) compared to rates ranging from 10% in 6 years olds to 3% in 12 years olds typically developing children. Potential contributory factors include abnormalities of the urinary tract and chronic urinary tract infections (Pober, Lacro, Rice, Mandell & Teele, 1993; Sforzini et al., 2002), although reduced bladder capacity and detrusor overactivity observed in 60% is likely to have a significant bearing on maturation of nocturnal continence (Sammour, Gomes, Duarte, Trigo-Rocha & Srougi, 2006).

Evaluation of sleep in specific subgroups and types of learning difficulties/mental retardation is of great importance rather than attempting generalisations that risk being limited in meaning and clinical usefulness. Parental report of sleep problems is potentially subject to reporter bias. However, several studies have yielded strong correlations between parental questionnaire and more direct measures of sleep such as filmed observational studies and actigraphy to examine sleep disorders and their detailed patterns (Holley, Hill & Stevenson, 2010; Stein et al., 2001). Integration of different approaches using parental reports, actigraphy, polysomography, genetic and endocrine examination to determine causality of sleep disturbances and disorder specificity should be considered in future studies (Annaz, Karmiloff-Smith & Thomas, 2008).

The findings of the current study have direct implications for neurocognitive research and clinical practice. We have shown that cognitive studies of individuals with developmental disorders such as WS must in future consider sleep patterns and disturbances of an individual during their investigation as these may have a direct impact on performance scores. Lastly, health professionals should be aware of the high rate of sleep problems in children with Williams syndrome, should actively evaluate sleep in these children, and where appropriate, offer therapeutic approaches.

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