Published in final edited form as:

Sleep Med. 2011 October ; 12(9): 892–897. doi:10.1016/j.sleep.2011.05.003.

Sleep in Children with Williams Syndrome

Thornton B.A. Mason, MD, PhD, MSCE^{1,*}, Raanan Arens, MD², Jaclyn Sharman, MS³, Brooke Bintliff-Janisak, BA⁴, Brian Schultz, RPSGT⁵, Arthur S. Walters, MD⁶, Jacqueline R. Cater, PhD⁷, Paige Kaplan, MBBCh⁸, and Allan I. Pack, MBChB, PhD⁹

¹Sleep Center, The Children's Hospital of Philadelphia, Philadelphia, PA

²Division of Respiratory and Sleep Medicine, The Children's Hospital at Montefiore, Bronx, NY

³Clinical Trials Office, The Children's Hospital of Philadelphia, Philadelphia, PA

⁴Clinical Trials Office, The Children's Hospital of Philadelphia, Philadelphia, PA

⁵Sleep Center, The Children's Hospital of Philadelphia, Philadelphia, PA

⁶Department of Neurology, Vanderbilt University, Nashville, TN

⁷Biomedical and Statistical Consulting, Wynnewood, PA

⁸Section of Metabolic Diseases, The Children's Hospital of Philadelphia, Philadelphia, PA

⁹Division of Sleep Medicine/Department of Medicine and Center for Sleep and Circadian Neurobiology, University of Pennsylvania School of Medicine, Philadelphia, PA

Abstract

Objective—To analyze sleep in children with Williams Syndrome (WS) compared to normal healthy controls in order to determine whether particular sleep features are characteristic of WS, and to explore associations between disturbed sleep and behavior.

Methods—35 children with genetically-confirmed WS and 35 matched controls underwent overnight polysomnography and performance testing in the Sleep Center at the Children's Hospital of Philadelphia. Parents completed questionnaires regarding the subjects' sleep and behavior.

Results—WS subjects had significantly different sleep than controls, with decreased sleep efficiency, increased respiratory-related arousals, and increased slow wave sleep on overnight polysomnography. WS subjects were also noted to have more difficulty falling asleep, with greater restlessness and more arousals from sleep than controls. 52% of WS subjects had features of attention deficit-hyperactivity disorder.

Conclusions—Children with WS had significantly different sleep than controls in our sample. These differences demonstrated in our study may reflect genetic influences on sleep.

© 2011 Elsevier B.V. All rights reserved.

*Address correspondence to: Thornton B.A. Mason MD, PhD, MSCE, Sleep Center and Division of Neurology, 10th Floor, CTRB, CHOP, 3501 Civic Center Blvd. Philadelphia, PA 19104, Tel: (215) 590-1718, Fax: (215) 590-1771, masont@email.chop.edu.

Financial disclosure: Dr. Walters has received support from Boehringer-Ingelheim, GlaxoSmithKline, XenoPort, UCB Pharma, and Kyowa. Dr. Pack is the John L. Miclot Professor of Medicine; funds for this endowed professorship have been provided by Phillips Respironics. The other authors have indicated that they have no financial relationships relevant to this article to disclose.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Keywords

Williams Syndrome; polysomnography; attention deficit disorder; pediatrics; sleep architecture; sleep efficiency

INTRODUCTION

Williams Syndrome (WS) is a developmental disorder caused by a microdeletion in a distinct region of chromosome 7 (7q11.23), with a common deletion size of 1.5-1.7 megabases spanning 25-30 genes.[1] The prevalence of WS is estimated at 1 in 7,500.[2] Patients with WS manifest a variety of major phenotypic features, including neurological, neurocognitive, cardiovascular, musculoskeletal, and endocrine abnormalities.[3] Most patients with WS have mild-to-moderate intellectual disability, with a mean composite IQ ranging from 58-68, depending on the assessments used[4]. Neurocognitive deficits include poor visual-motor integration and attention-deficit hyperactivity disorder (ADHD), while relative strengths include short-term memory and language skills.[1, 5]

Parents often report that their children with WS have sleep difficulties.[6, 7] A prior study of 7 subjects with WS and sleep disturbances supported an association between WS and periodic limb movements in sleep, as well as increased wake time and more time in sleep stages 3 and 4 than control subjects.[8] We wanted to expand the polysomnographic analysis of sleep in children with a larger sample size, not selected for a history of sleep disturbance, to determine whether particular sleep features may be characteristic of WS. We also explored associations between disturbed sleep and daytime behaviors, including aspects of attention deficit-hyperactivity disorder (ADHD). To assess for ADHD features, a validated screening instrument was selected that was suitable for use in the age range of study subjects. We also selected a continuous performance task for evaluation of WS subjects and controls. Together, these testing components provided subjective and objective assessments of ADHD features that could be compared to subjective and objective sleep data.

PATIENTS AND METHODS

The study protocol was reviewed and approved by the Institutional Review Board of the Children's Hospital of Philadelphia. Informed consent was obtained from patients' and controls' parents/guardians; assent was obtained from children over 7 years.

Our goal was to enroll 35 WS subjects, ages 2-18 years who met clinical criteria for WS and had cytogenetically confirmed deletions of 7q11.23. WS patients were recruited primarily from the Children's Hospital of Philadelphia Multispecialty Center for WS. An equal number of healthy control subjects from the greater Philadelphia area were enrolled, who were matched in age, gender, and ethnicity to WS subjects. Controls had no history of sleep-related issues and took no medication on a regular basis. The data from all subjects (both WS and controls) were de-identified, and studies were scored and interpreted without knowledge of the subject's identity.

Overnight Polysomnography

Standard overnight polysomnography was performed in the Sleep Laboratory at the Children's Hospital of Philadelphia. All data were digitalized using a polysomnographic system (Somnostar, SensorMedics Corp., Yorba Linda, CA, or REMbrandt, Embla Corp., Denver, CO). Both systems are fully digital, record the same multiple parameters, and are reviewed similarly. The following parameters were recorded: electroencephalogram (C3/A2, C4/A1, O1/A2, and O2/A1); bilateral electrooculograms; submental electromyogram; tibial

electromyogram; electrocardiogram; chest and abdominal wall motion via respiratory inductance plethysmography (Respitrace Systems, Ambulatory Monitoring, Inc., Ardsley, NY); airflow via nasal pressure (Pro-Tech Services, Inc., Mukilteo, WA); 3-pronged thermistor (Pro-Tech Services, Inc.); end-tidal carbon dioxide partial pressure via capnography (Novamatrix 7000, Novamatrix, Wallingford, CT); arterial oxygen saturation (Novamatrix 7000, or Masimo, Irvine, CA); oximeter pulse waveform; and digital video.

Sleep architecture and arousals from sleep were analyzed using standard criteria.[9, 10] Respiratory parameters were scored using standard pediatric criteria.[11, 12] Periodic limb movements of sleep (PLMS) were scored if part of a series of 4 or more consecutive leg movements lasting 0.5 to 5 seconds, with an inter-movement interval of 5 to 90 seconds.[13] A periodic limb movement index >5/hour is considered pathologic.[14] In addition, the number of PLMS leading to an arousal were scored (PLMS arousal index). All studies were reviewed and interpreted by a Children's Hospital of Philadelphia sleep medicine physician (TM). As recommended by the American Academy of Sleep Medicine, inter-scorer reliability is assessed routinely and exceeds guidelines (>85% agreement).

Sleep Questionnaire

The parental sleep questionnaire included 13 items to evaluate respiratory status, body and limb movements, and arousal/awakenings during sleep, as well as restless legs syndrome symptoms while awake (modified from Arens et al. 1998[8]). For each item, the parent indicated whether the feature occurred in their child "never", "sometimes" (once per week or less), "often" (2-5 times per week), or "very often" (6-7 times per week).

ADHD Symptom Checklist-4 (ADHD-SC4)

The ADHD-SC4 is a screening instrument for the behavioral symptoms of attention deficit-hyperactivity disorder (ADHD) and oppositional defiant disorder (ODD) based on DSM-IV criteria.[15, 16] The ADHD-SC4 is a reliable, validated instrument that is designed for assessment in children ages 3-18 years.[15] A parent/guardian of each subject studied completed a questionnaire prior to the overnight polysomnogram.

Gordon Diagnostic System

The Gordon Diagnostic System is a continuous performance test that has been shown to have significant agreement with other indicators of ADHD, including other performance tests, behavior rating scales, clinical diagnoses, and behavioral observations[17]; it has been used in children with WS.[18] Subjects performed two tasks: a delay task and a vigilance task.[19] All tests were performed between 3-6 p.m., in the afternoons just prior to overnight polysomnography. For control children, an age-appropriate version of the delay and vigilance tasks was administered, while WS subjects completed the tasks based on their age if feasible; because of significant developmental issues, some WS subjects completed the tasks at a lower level or not at all. Children under age 4 did not perform these tasks, as no normative data are available for this age group.

Statistical Considerations and Data Analysis

There were 35 WS patients and 35 controls that were matched on gender and ethnicity, and were similar in age. All statistical analyses were based on paired data. The analysis of discrete variables (e.g. parental sleep items and ADHD classification) used McNemar's test for paired data.[20] Odds ratios were computed using conditional logistic regressions[21, 22] implemented in SAS PROC.LOGISTIC, which are computationally synonymous with McNemar's test, and have the advantage of yielding a point estimate for an odds ratio even when there is a zero cell in the table.

Differences between groups for continuous data (e.g. age) used a paired t-test. Spearman correlation coefficients were computed to assess the relationship between each of the items on the parental sleep questionnaire and the polysomnography limb movement variables. This was done for all subjects, as well as separately for WS subjects. Correlation analyses also assessed the relationships between polysomnography measures and scores on the delay and vigilance tasks of the Gordon Diagnostic System.

We wanted to explore further how sleep disturbance (specifically, decreased sleep efficiency determined by overnight polysomnography) might be related to ADHD features. We acknowledge several possible scenarios (see Discussion) in the interaction between sleep efficiency and ADHD features, including that decreased sleep efficiency could occur as a result of ADHD features (i.e., children with ADHD symptoms have greater difficulty initiating and maintaining sleep); alternatively, decreased sleep efficiency could cause ADHD features (i.e., compromised sleep could interfere with sustained attention and concentration during the day). Given these potentially reciprocal relationships, we chose sleep efficiency as the single dependent variable, allowing a sequential assessment of ADHD-related variables. A series of single variable regression analyses was used to assess which parental sleep ratings and ADHD measures were predictive of sleep efficiency. In the initial model building step, any variable which was significant at $p < 0.10$ was considered a candidate predictor for entry into the final multivariable model [21, 23] predicting sleep efficiency on the overnight sleep study. A stepwise regression procedure was used to guide the selection of variables for the final multivariable model (which used a cutoff p-value of 0.05 for retention in the final model).

RESULTS

Subjects and Demographics

35 WS subjects and 35 matched control children were included in the analysis. Two subjects were recruited who were not included in the analyses: one was a patient recruited as a WS subject but confirmation of *ELN* haplo-insufficiency could not be obtained. The other was a control subject who did not complete overnight polysomnography.

Demographic data are summarized in Table 1. Of the 35 pairs, 15 were male (43%), and 33 (94%) were non-Hispanic; WS subjects and controls were exactly matched by gender and ethnicity. Although the mean age was statistically different between the WS and control groups, this was not clinically meaningful, as the WS subjects were on average only several months younger than controls (mean age 9.34 ± 4.89 years for WS subjects, compared to 9.52 ± 4.87 years for control subjects; $p = 0.012$). There was not a significant difference in BMI z-scores between the two groups ($p = 0.158$).

Parental Sleep Data

The results of the analysis of each of the individual items in the parental sleep data questionnaire are summarized in Table 2. For McNemar's statistic, only the discordant pairs contribute to the computation of the p-value. Parents rated WS subjects as significantly more likely than controls to have difficulty falling asleep, repetitive leg movements, general restlessness, frequent and prolonged nighttime arousals, and an inability to keep still before sleep.

Symptoms of ADHD

Results for the ADHD-SC4 symptom count scores are summarized in Table 3. The number of "often" and "very often" responses to each item on a subscale were summed, and subjects were designated as meeting criteria for the scale if they were at or above the normative

threshold (greater than or equal to 6 for the ADHD Inattentive Type and the ADHD Hyperactive Impulsive Type). A subject had to meet the criteria for both of the ADHD Inattentive and Hyperactive/Impulsive subscales to meet the criteria for the ADHD Combined Type. Note that there were 33 matched pairs for this analysis, as there were 2 matched pairs of subjects who were less than 3 years old (and so the ADHD-SC4 could not be administered).

Results for the symptom counts indicated that WS subjects were significantly more likely to be classified as being in the ADHD Inattentive Type, ADHD Hyperactive/Impulsive Type, and ADHD Combined Type relative to controls. The prevalence of any ADHD for WS subjects in the present study was 52%. In contrast, only 1 of 33 controls was considered to have features of ADHD. The prevalence of ADHD features was 62% for cases younger than 10 years (13/21) and 36% for cases older than 10 (4/11). Sixty percent (9/15) of the WS males were classified as having ADHD, and 44% of the WS females (8/18). In contrast, there was not a statistically significant difference in the classification of oppositional-defiant disorder (ODD) between the Williams Syndrome subjects and controls (as only 3 subjects met this criterion).

Overnight Polysomnography

Sleep efficiency is defined as the total time spent asleep divided by the total time in bed (from lights out to lights on), expressed as a percentage. WS subjects had significantly decreased sleep efficiency compared to control children (paired $t=-2.67$, $df=34$, $p=0.012$); the mean difference between pairs was 4.5% (SD 9.9%) (see Table 4). The standardized effect size was -0.45. While there was not a significant difference in the overall arousal index between the two groups (Table 4), the arousal data were further evaluated by dividing the arousal index into respiratory, spontaneous, and technician-related arousals (i.e., arousals related to a polysomnographic technician's episodic adjustment of recording leads). With this further analysis, WS subjects had a statistically higher respiratory-related arousal index compared to controls ($p=0.014$), with the mean difference equal to 0.50 (SD 1.1); the 95% confidence interval around this point estimate was 0.11 to 0.90. No statistically significant difference was found between the two subject groups for spontaneous and technician-related indices.

Total sleep time was divided into rapid eye movement (REM) sleep and non-REM sleep; non-REM sleep was further divided into light non-REM sleep (stage 1 and stage 2) and deep non-REM sleep (slow wave sleep). Children with WS also had significantly increased slow wave sleep as a percentage of total sleep time, compared to control children (paired $t=-2.67$, $df=34$, $p=0.01$); the mean difference was 4.6% (10%). The standardized effect size was 0.45, which approaches the moderate range.[24] Interestingly, there was no significant correlation between percentage of slow wave sleep and sleep efficiency ($r = .17$, $p = 0.336$) among WS subjects, so the same children did not tend to have both sleep alterations. Subjects with WS had a higher mean obstructive apnea-hypopnea index (2.3) compared to controls (0.3), but this difference was not statistically significant. Moreover, no statistically significant differences were seen in sleep latency, REM sleep latency, REM sleep as a percentage of total sleep time, or the periodic limb movement index between patients with WS and matched controls (Table 4). 5.7% of both the WS and the control group had elevated PLM indices (>5/hour).

Correlations Among Specific Study Findings

Spearman correlation coefficients were calculated between each item of the parental sleep questionnaire and the polysomnography variables. This was done for all subjects, as well as separately for WS subjects and controls. Correlations were also performed for the

relationship between Gordon Diagnostic System delay and vigilance variables with polysomnographic variables.

For WS subjects only, the relationship between parental reports of repetitive leg movements and objective polysomnographic measures showed moderate and significant correlation of parental reported repetitive leg movements with total periodic limb movements in sleep ($r = 0.49$, $p = 0.038$), and periodic limb movements associated with arousal ($r = 0.48$, $p = 0.046$). There were significant correlations between objective measures of total periodic limb movements, the periodic limb movement index, and periodic limb movements associated with arousal, with parental reports of 'restless tossing and turning in sleep' ($r = 0.70$, $p < 0.001$; $r = 0.62$, $p < 0.001$; and $r = 0.47$, $p = 0.014$, respectively).

Parental reports of restlessness, nighttime arousal and prolonged arousals showed non-significant correlations with sleep efficiency ($r = -0.17$, $r = 0.30$, and $r = 0.02$, respectively) for Williams Syndrome subjects. Finally, parental ratings of snoring showed modest, albeit non-significant, correlations with objective measures of obstructive apnea-hypopnea index and total apnea-hypopnea index ($r = 0.18$ and $r = 0.23$, respectively).

The Gordon Diagnostic System variables showed only a significant moderate negative correlation between Total Efficiency Ratio scores for the delay task scores and Stage 1 sleep ($r = -0.48$, $p = 0.011$); the Total Efficiency Ratio indicates a subject's ability to develop a strategy for inhibiting behavior, and is therefore a useful indicator of impulsivity.

The prevalence of decreased sleep efficiency (less than or equal to 85%) in WS subjects was 48% (17 of 35 cases). Results of a series of regression analyses investigating the effect of various predictor variables on poor sleep efficiency yielded a significant relationship ($p = 0.040$) between parental ratings of arousal/awakening during the night and objective measures of poor sleep efficiency, when sleep efficiency was modeled as a continuous variable. No other parental report variables were significantly related to poor sleep efficiency.

We also explored whether subjects with WS and ADHD features ($n=18$) had more disturbed sleep than children WS subjects without ADHD features ($n=15$). When evaluating the parental sleep questionnaire response items that had been found different between WS and control subjects (difficulty falling asleep, repetitive leg movements, restlessness in sleep, nocturnal arousal/awakening, prolonged night-time arousal, and inability to keep still while awake), there were no significant differences between ADHD and non-ADHD WS subjects. We then compared sleep efficiency and percent slow wave from the overnight polysomnograms, and similarly found no significant differences among WS subjects based on the presence or absence of ADHD symptoms.

DISCUSSION

This is the largest polysomnography study exploring sleep in children with WS. The range of ages studied (2-18 years) spanned developmental periods associated with significant sleep architecture changes, and so an important feature of this study was the inclusion of an age-similar control group to allow meaningful comparisons. Our findings for the WS subjects include significantly increased parental reports of sleep issues and an increased prevalence of ADHD features, as well as decreased sleep efficiency and increased slow wave sleep compared to control subjects. Moreover, there was a significant relationship seen between parental ratings of arousals/awakenings during the night and sleep efficiency from overnight polysomnography as a continuous variable.

Sleep efficiency was significantly decreased in the WS subjects compared to controls. The polysomnography data do not clearly support periodic limb movements in sleep as being more prevalent in WS compared to controls. The lack of a significant difference in the periodic limb movement index and periodic limb movement arousal index between the two groups contrasts with an earlier report from our research team, which showed an elevated periodic limb movement index among seven children with WS.[8] A likely contributor to this discrepancy may be a referral bias, since only children described by parents as often or always having symptoms suggestive of a movement arousal disorder had polysomnography in the earlier study. Nevertheless, we did find significant correlations between parental reports of repetitive leg movements during sleep and periodic limb movements on polysomnography in children with WS, and we have confirmed that WS subjects may have periodic limb movements in sleep. On the other hand, WS subjects had greater respiratory-related arousals than controls, and these arousals may well have contributed to decreased sleep efficiency. Compared to the earlier study, the present study also shows that there is a high prevalence of sleep disorders even in WS subjects who had not been considered by their parents to have sleep problems and over a wide age range (2-17 years, compared to 1.8-7 years in the earlier study[8]). While anxiety could have played a role, parental reports of increased arousals/awakenings in children with WS correlated with sleep study findings and suggest that disturbed sleep in general and decreased sleep in particular are features of WS regardless of the sleeping environment.

The relationship between sleep and ADHD in WS may be complex. Leyfer and colleagues reported that 64.7% of WS subjects met criteria for ADHD.[25] While our study was not designed to establish clinical ADHD diagnoses in participating subjects, a majority (52%) of WS subjects had ADHD features based on symptom count scores on the ADHD Symptom Checklist-4, a validated screening instrument. Also consistent with prior report,[25] ADHD features in our WS subjects were higher in males (60%) compared to females (44%). A number of studies have explored the relationships between disturbed sleep in children and ADHD.[26-34] Ours is the first study, however, to evaluate associations between sleep disorders and ADHD features in Williams Syndrome. We could not demonstrate a clear association between sleep disturbance in WS and presence of ADHD symptoms based on parental completion of the ADHD-SC4 instrument. Future studies should explore if there is an association in WS children with clinically diagnosed ADHD and sleep disturbance, and if so whether such an association occurs as a consequence of sleep disturbances, or sleep disturbances (particularly decreased sleep efficiency) proceed from ADHD effects. Conceivably, both sleep disturbances and ADHD reflect underlying brain structural changes that have been recently detailed by sophisticated neuroimaging in patients with WS.[35, 36]

In our study, we matched children with WS with normally developing controls in order to determine the extent of sleep abnormalities in WS across the pediatric age spectrum. A limitation of this study, however, is that we cannot conclude that the abnormalities found are specific for WS; indeed, children with developmental disabilities associated with other disorders could have sleep disturbance profiles similar to those we have found for WS. Nevertheless, the choice of another suitable comparison group would be difficult, since the typical profile of scattered abilities and disabilities in WS would likely complicate any future study where children with WS were matched rigidly by I.Q. in other subjects. Further work will be needed to determine whether or not the population of children with WS might offer a distinct opportunity to assess genetic contributions to sleep disturbances in childhood.

In conclusion, this is the largest polysomnography study to date examining sleep in children with WS. WS subjects were found to have significantly increased parental reports of sleep issues and an increased prevalence of ADHD features, as well as decreased sleep efficiency,

increased time spent awake after sleep onset, and increased slow wave sleep compared to gender- and ethnicity-matched, age-similar control subjects. Moreover, we found a significant relationship between parental ratings of arousals/awakenings during the night and sleep efficiency from overnight polysomnography as a continuous variable.

Given our findings that children with Williams Syndrome have difficulty falling asleep, increased restlessness, and increased respiratory-related arousals, several therapeutic interventions could be considered. One approach could include behavioral sleep medicine techniques to address insomnia by instituting a consistent bedtime routine that would provide predictable, re-assuring structure and address any limit setting issues; such a routine would also help promote self-soothing skills to increase sleep efficiency overnight. When there is clinical concern for an intrinsic sleep disruptor, such as obstructive sleep apnea, then overnight polysomnography could provide important data; management of sleep-disordered breathing would include an assessment for possible adenotonsillectomy, or the institution of positive airway pressure therapy for non-surgical candidates. Finally, there could be a role for pharmacological therapy, but future study in children with Williams Syndrome would be needed to determine efficacy.

Acknowledgments

T.B.A.M. was supported by National Institutes of Health Grants K23 RR16566, MO1-RR-000240, and U54RR023567. We also thank the WS Association, as well as Greg Maislin of Biomedical Statistical Consulting for their assistance with this project.

The study was supported by National Institutes of Health Grants K23 RR16566, M01-RR-000240, and U54RR023567.

References

1. van Hagen JM, van der Geest JN, van der Giessen RS, Lagers-van Haselen GC, Eussen HJ, Gille JJ, et al. Contribution of CYLN2 and GTF2IRD1 to neurological and cognitive symptoms in Williams Syndrome. *Neurobiol Dis.* 2007; 26:112–24. [PubMed: 17270452]
2. Stromme P, Bjornstad PG, Ramstad K. Prevalence estimation of Williams syndrome. *J Child Neurol.* 2002; 17:269–71. [PubMed: 12088082]
3. Ewart AK, Morris CA, Atkinson D, Jin W, Sternes K, Spallone P, et al. Hemizygosity at the elastin locus in a developmental disorder, Williams syndrome. *Nat Genet.* 1993; 5:11–6. [PubMed: 7693128]
4. Mervis CB, Becerra AM. Language and communicative development in Williams syndrome. *Ment Retard Dev Disabil Res Rev.* 2007; 13:3–15. [PubMed: 17326109]
5. Bellugi U, Lichtenberger L, Jones W, Lai Z, St George MI. The neurocognitive profile of Williams Syndrome: a complex pattern of strengths and weaknesses. *J Cogn Neurosci.* 2000; 12(Suppl 1):7–29. [PubMed: 10953231]
6. Udwin O, Yule W, Martin N. Cognitive abilities and behavioural characteristics of children with idiopathic infantile hypercalcaemia. *J Child Psychol Psychiatry.* 1987; 28:297–309. [PubMed: 3584299]
7. Annaz D, Hill CM, Ashworth A, Holley S, Karmiloff-Smith A. Characterisation of sleep problems in children with Williams syndrome. *Res Dev Disabil.* 32:164–9. [PubMed: 20940094]
8. Arens R, Wright B, Elliott J, Zhao H, Wang PP, Brown LW, et al. Periodic limb movement in sleep in children with Williams syndrome. *J Pediatr.* 1998; 133:670–4. [PubMed: 9821427]
9. Rechtschaffen A, Kales A. A manual of standardized terminology, techniques and scoring systems for sleep stages on human subjects. National Institutes of Health. 1968
10. EEG arousals: scoring rules and examples: a preliminary report from the Sleep Disorders Atlas Task Force of the American Sleep Disorders Association. *Sleep.* 1992; 15:173–84. [PubMed: 11032543]

11. Marcus CL, Omlin KJ, Basinki DJ, Bailey SL, Rachal AB, Von Pechmann WS, et al. Normal polysomnographic values for children and adolescents. *Am Rev Respir Dis.* 1992; 146:1235–9. [PubMed: 1443877]
12. Standards and indications for cardiopulmonary sleep studies in children. American Thoracic Society. *Am J Respir Crit Care Med.* 1996; 153:866–78. [PubMed: 8564147]
13. Recording and scoring leg movements. The Atlas Task Force. *Sleep.* 1993; 16:748–59. [PubMed: 8165390]
14. Hening W, Allen R, Earley C, Kushida C, Picchietti D, Silber M. The treatment of restless legs syndrome and periodic limb movement disorder. *An American Academy of Sleep Medicine Review. Sleep.* 1999; 22:970–99. [PubMed: 10566916]
15. Gadow, KD.; S, J. ADHD Symptom Checklist-4 Manual. Stony Brook, NY: Checkmate Plus, Ltd; 1997.
16. Association AP. Diagnostic and Statistical Manual of Mental Disorders. Fourth Edition. Washington, D.C.: American Psychiatric Association; 1994.
17. Dickerson Mayes S, Calhoun SL, Crowell EW. Clinical validity and interpretation of the Gordon Diagnostic System in ADHD assessments. *Child Neuropsychol.* 2001; 7:32–41. [PubMed: 11815879]
18. Power TJ, Blum NJ, Jones SM, Kaplan PE. Brief report: response to methylphenidate in two children with Williams syndrome. *J Autism Dev Disord.* 1997; 27:79–87. [PubMed: 9018583]
19. Gordon M, Mettelman BB. The assessment of attention: I. Standardization and reliability of a behavior-based measure. *J Clin Psychol.* 1988; 44:682–90. [PubMed: 3192705]
20. Conover, WJ. Practical Non-parametric Statistics. New York: John Wiley & Sons, Inc; 1971.
21. Hosmer, DW.; Lemeshow, S. Applied Logistic Regression. New York: John Wiley & Sons, Inc; 1989.
22. Agresti, A. Categorical Data Analysis. New York: John Wiley & Sons, Inc; 1990. p. 347-52.
23. Cohen, J.; Cohen, C. Applied Regression/Correlative Analysis for the Behavioral Sciences. 2. Hillsdale, New Jersey: Lawrence Erlbaum Associates; 1983.
24. Cohen, J. Statistical Power Analysis for the Behavioral Sciences. 2. Hillsdale, NJ: Lawrence Erlbaum Associates; 1988. p. 567
25. Leyfer OT, Woodruff-Borden J, Klein-Tasman BP, Fricke JS, Mervis CB. Prevalence of psychiatric disorders in 4 to 16-year-olds with Williams syndrome. *Am J Med Genet B Neuropsychiatr Genet.* 2006; 141B:615–22. [PubMed: 16823805]
26. Chervin RD, Archbold KH, Dillon JE, Pituch KJ, Panahi P, Dahl RE, et al. Associations between symptoms of inattention, hyperactivity, restless legs, and periodic leg movements. *Sleep.* 2002; 25:213–8. [PubMed: 11902431]
27. Picchietti DL, Underwood DJ, Farris WA, Walters AS, Shah MM, Dahl RE, et al. Further studies on periodic limb movement disorder and restless legs syndrome in children with attention-deficit hyperactivity disorder. *Mov Disord.* 1999; 14:1000–7. [PubMed: 10584676]
28. Picchietti DL, Walters AS. Moderate to severe periodic limb movement disorder in childhood and adolescence. *Sleep.* 1999; 22:297–300. [PubMed: 10341379]
29. Walters AS, Mandelbaum DE, Lewin DS, Kugler S, England SJ, Miller M. Dopaminergic therapy in children with restless legs/periodic limb movements in sleep and ADHD. Dopaminergic Therapy Study Group. *Pediatr Neurol.* 2000; 22:182–6. [PubMed: 10734247]
30. Archbold KH, Pituch KJ, Panahi P, Chervin RD. Symptoms of sleep disturbances among children at two general pediatric clinics. *J Pediatr.* 2002; 140:97–102. [PubMed: 11815771]
31. Chervin RD, Archbold KH. Hyperactivity and polysomnographic findings in children evaluated for sleep-disordered breathing. *Sleep.* 2001; 24:313–20. [PubMed: 11322714]
32. Chervin RD, Archbold KH, Dillon JE, Panahi P, Pituch KJ, Dahl RE, et al. Inattention, hyperactivity, and symptoms of sleep-disordered breathing. *Pediatrics.* 2002; 109:449–56. [PubMed: 11875140]
33. Chervin RD, Ruzicka DL, Archbold KH, Dillon JE. Snoring predicts hyperactivity four years later. *Sleep.* 2005; 28:885–90. [PubMed: 16124670]

34. Owens J, Sangal RB, Sutton VK, Bakken R, Allen AJ, Kelsey D. Subjective and objective measures of sleep in children with attention-deficit/hyperactivity disorder. *Sleep Med.* 2008
35. Chiang MC, Reiss AL, Lee AD, Bellugi U, Galaburda AM, Korenberg JR, et al. 3D pattern of brain abnormalities in Williams syndrome visualized using tensor-based morphometry. *Neuroimage.* 2007; 36:1096–109. [PubMed: 17512756]
36. Marengo S, Siuta MA, Kippenhan JS, Grodofsky S, Chang WL, Kohn P, et al. Genetic contributions to white matter architecture revealed by diffusion tensor imaging in Williams syndrome. *Proc Natl Acad Sci U S A.* 2007; 104:15117–22. [PubMed: 17827280]

Abbreviations

WS	Williams Syndrome
PLMS	periodic limb movements in sleep
REM	rapid eye movement

Demographic and Baseline Characteristics of Williams Syndrome and Control Subjects

Table 1

	WS (N=35)	Control (N=35)	Diff ¹	LCL ²	UCL ³	p-value ⁴
Age (yrs.)						
Mean	9.34	9.52	-0.18	-0.31	-0.04	0.012
SD	4.89	4.87				
Body Mass Index (BMI) k/m ²						
Mean	18.4	20.2	-1.8	-4.2	0.5	ns
SD	4.4	6.3				
Body Mass Index Z-Score						
Mean	0.1	0.6	-0.5	-1.1	0.2	ns
SD	1.5	1.3				

Notes:

¹ Difference in means computed as WS-Control.

^{2,3} Lower/Upper 95% Confidence Limit for Mean Difference

⁴ P-value from paired t-test; ns= not significant.

Table 2Differences in the Sleep Questionnaire (Discrete Y/N Variables)¹ for Williams Syndrome and Control Subjects [Matched Pairs Only]

Outcome	Both (N) ²	Neither (N) ³	Total % Conc. ⁴	WS Only (N)	Control Only (N)	Total %Disc. ⁵	Odds Ratio (WS only vs. Control only)	p-value ⁶
Difficulty falling asleep	1	16	50.0%	15	2	50.0%	7.5	0.002
Difficulty breathing when asleep	0	24	88.9%	3	0	11.1%	3.8	ns
Snoring or noisy	2	20	68.8%	8	2	31.3%	4.0	ns
Repetitive leg movements	0	4	33.3%	8	0	66.7%	11.0	0.008
Restless, tossing, and turning in sleep	0	7	30.4%	16	0	69.6%	22.6	<.001
Arousal or awakening during night	2	13	50.0%	15	0	50.0%	21.1	<.001
Prolonged arousal during night	0	22	78.6%	6	0	21.4%	8.2	0.031
Sleepiness during day	0	26	81.3%	5	1	18.8%	5.0	ns
Difficulty falling asleep for nap	0	20	74.1%	6	1	25.9%	6.0	ns
Desire to move legs	0	21	80.8%	5	0	19.2%	6.7	ns
Tingling in legs/arms worse when still	0	20	95.2%	1	0	4.8%	1.0	ns
Inability to keep still before sleep	0	16	51.6%	15	0	48.4%	21.1	<.001
Tingling in legs/arms worse in evening	0	19	90.5%	2	0	9.5%	2.4	ns
Any ADHD Medication	0	29	82.9%	6	0	17.1%	8.17	0.031

Notes:¹ Discrete Variables: No=None/Sometimes, Yes=Often/Always² Both (N)= number of matched pairs that are concordant for the presence of an individual outcome³ Neither (N)= number of matched pairs that are concordant for the absence of an individual outcome⁴ Total % Conc.=total percentage of matched pairs that are concordant⁵ Total % Disc. =total percentage of matched pairs that are discordant⁶ p-value from McNemars test for matched data

Table 3
Differences in ADHD-SC4 Symptom Counts for Williams Syndrome and Control Subjects [Matched Pairs Only]^{1/}

Outcome	Both (N) ²	Neither (N) ³	Total % Conc. ⁴	WS Only (N)	Control Only (N)	Total % Disc. ⁵	Odds Ratio (WS only vs. Control only)	p-value ⁶
Category A: ADHD, Inattentive Type	0	16	48.5%	17	0	51.5%	22.6	<.001
Category A: ADHD, Hyper/Imp Type	1	22	69.7%	10	0	30.3%	12.5	0.004
Category A: Combined Type	0	23	69.7%	10	0	30.3%	12.5	0.004
Category B: Oppositional Defiant Disorder	0	30	90.9%	2	1	9.1%	2.0	ns

Notes:

^{1/} N=33 Matched Pairs

² Both (N)= number of matched pairs that are concordant for the presence of an individual outcome

³ Neither (N)= number of matched pairs that are concordant for the absence of an individual outcome

⁴ Total % Conc.=total percentage of matched pairs that are concordant

⁵ Total % Disc. =total percentage of matched pairs that are discordant

⁶ P-value from McNemars test for matched data; ns= not significant

Table 4

Polysomnography Measures for Williams Syndrome and Control Subjects

	WS (N=35)	Control (N=35)	Diff ¹	SD Diff ²	t-value	p-value ³
PLMS Index (n/hr.)	0.9	1.1	-0.2	3.3	-0.4	ns
Total Sleep Time (TST) (mins.)	421.6	438.9	-17.3	72.2	-1.4	ns
Sleep Latency (mins.)	32.2	25.9	6.3	35.3	1.1	ns
Sleep Efficiency (%)	82.2	86.7	-4.5	9.9	-2.7	0.012
REM Latency (mins.)	143.8	133.3	10.5	91.4	0.7	ns
Wake After Sleep Onset (mins.)	52.4	37.2	15.1	44.4	2.0	0.052
Stage 1 (%TST)	5.0	5.8	-0.8	4.5	-1.1	ns
Stage 2 (%TST)	47.1	50.4	-3.3	11.6	-1.7	ns
Slow Wave (%TST)	29.4	24.8	4.6	10.2	2.7	0.011
REM Sleep (%TST)	18.4	19.0	-0.6	7.1	-0.5	ns
Arousal Index (n/hr.)	11.6	11.4	0.2	5.5	0.3	ns
Respiratory-related arousal index	1.0	0.5	0.5	1.1	2.6	0.014
Spontaneous arousal index	9.8	9.0	0.8	4.8	1.0	ns
Technician-related arousal index	0.3	0.4	-0.2	1.1	-0.8	ns
Obstructive AHI	2.3	0.3	2.0	8.3	1.4	ns
Obstructive AHI > 1 (# subjects)	9 (25.7%)	4 (11.4%)				ns
Total AHI	2.8	0.9	1.9	8.2	1.4	ns

Notes:

¹ Difference in means computed as WS-Control.² Standard deviation of mean difference.³ P-value from paired t-test; ns= not significant