Journal of Sleep Disorders & Therapy
ISSN: 2167-0277

Dimitriou et al., J Sleep Disorders Ther 2013, 2:1
DOI: 10.4172/2167-0277.1000108

Case Report Open Access

Abnormal Endocrine and Behavioural Sleep Markers in a Child with Williams Syndrome and Siblings

Dagmara Dimitriou[1,2]*, Anna Sniecinska[3] and Ray K Iles[4]

[1]Department of Psychology and Human Development, Institute of Education, London, United Kingdom, UK
[2]School of Health and Social Science, Middlesex University, London, UK
[3]Faculty of Health, Social Care and Education, Anglia Ruskin University, Chelmsford, UK
[4]Eric Leonard Kruse Foundation for Health Research, Scotland

Abstract

Background: Sleep is critical for optimal child development. However, the role of different variables that influence sleep functioning is still debatable. Children with developmental disorders such as Williams syndrome (WS) suffer from sleep problems throughout their childhood. Little is known about sleep patterns of their siblings.

Methods: Triplets, one of whom has WS and four typically developing (TD) children matched on age (7.8 years old) and gender participated in the study. Sleep was measured using parental sleep questionnaire and actigraphy. Salivary melatonin and cortisol were measured at three time points during the day.

Results: Abnormal sleep patterns, levels of melatonin and cortisol were found in a child with WS and her siblings.

Conclusion: These findings indicate that siblings of children with developmental disorders may also exhibit similar sleep problems. Use of multi-level examination should be adapted by paediatricians to devise sleep management strategies for such children and their families.

Keywords: Williams syndrome; Siblings; Cortisol; Melatonin; Sleep disorders

Introduction

Sleep is a complex behaviour, influenced by a multifaceted interplay between genetic and environmental factors. In particular, induction and maintenance of healthy sleep requires a finely tuned interplay of endocrine, neural and genetic mechanisms with environmental inputs. Accumulating evidence demonstrates that individual sleep EEG patterns are heritable traits [1]. However, environmental factors such as room-sharing, watching TV before bedtime or diet may also play an important role in causal pathways of sleep problems.

High prevalence of sleep problems in developmental disorders such as Williams syndrome (WS) have been reported [2-6]. WS is a genetic disorder caused by the hemizygous microdeletion of some 28 genes on chromosome 7q11.23 [7]. The incidence of WS is approximately 1 in 20,000 live births. The main cognitive characteristics of WS include an IQ levels ranging from 40 to 90, with the majority scoring between 55 and 69; relatively good face recognition and language skills and poor visuo-spatial skills [8]. Children with WS have been reported to suffer from difficulty in settling down at bedtime/falling asleep; prolonged awakenings from sleep and restless sleep. Yet, there are no studies examining causality of their sleep problems and whether their sleep differs from typically developing (TD) siblings. Thus far, studies examining sleep disorders in WS used tools such as questionnaires, actigraphy and/or polysomography. This is the first study to examine sleep profile via analysis of endocrine indicators of sleep patterns, melatonin and cortisol, in the saliva of a child with WS and her siblings. Melatonin (*N*-acetyl-5-methoxytryptamine) is a neurohormone secreted by the pineal gland involved in the regulation of the sleep-wake cycle and plays an important role in neuroprotection in the brain [9]. The secretion of melatonin is inhibited by light, and its level remains low during the daytime [10]. Cortisol (hydrocortisone) is one of the major glucocorticoid hormones secreted by the adrenal cortex. Cortisol levels rise during sleep, rapidly increase after awakening and decrease over the course of the day with nadir early in the sleep period [11-13].

We report cortisol and melatonin profiles of dizygotic female triplets: two of whom are TD, one with WS and typically developing unrelated control children. This is the first study to examine sleep in sibling of a child with WS using multi-level approach, i.e., levels of endocrine markers of sleep-melatonin and/or cortisol, actigraphy, and scores from CSHQ.

Methods

Participants

One female with full WS deletions in the critical region (verified clinically and genetically), two female siblings (Sib1 and Sib2) and 4 TD children matched for chronological age and gender took part in the current study. All children were 7.8 year old. Children in the TD group were not on any current or past medical and did not have any psychiatric or medical diagnosis such as epilepsy and poorly controlled asthma or eczema. Factors such as demographic information, medical and developmental history, and health habits were included as co-variant variables.

At the time of study, the triplets did not suffer from any medical

***Corresponding author:** Dagmara Dimitriou, PhD, Department of Psychology and Human Development, Institute of Education, London, United Kingdom, Tel: +44 (0)20 7612 6229; Fax: +44 (0)20 7612 6304; E-mail: d.annaz@ioe.ac.uk

Received October 29, 2012; **Accepted** Ferbruary 23, 2013; **Published** February 28, 2013

Citation: Dimitriou D, Sniecinska A, Iles RK (2013) Abnormal Endocrine and Behavioural Sleep Markers in a Child with Williams Syndrome and Siblings. J Sleep Disorders Ther 2: 108. doi:10.4172/2167-0277.1000108

conditions and were not taking any medications. All children had normal vision. Child with WS and Sib1 are right-handed whereas Sib2 is left-handed.

The triplet family was contacted via the Williams Syndrome Foundation UK. TD children were recruited through local primary schools. Ethical approval was granted by the Institute of Education, University of London Research Ethics Committee and The Williams Syndrome Foundation, UK. Both, parental informed consent and the child's verbal assent were obtained prior to participation.

Measures

Actigraphy: Sleep patterns were measured using actigraphy (movement monitoring), a reliable and valid method for assessing sleep and wake, which shows more than 80% agreement with overnight polysomnographic studies [14].

Each child wore an Actiwatch Mini (CamNTech, Cambridge, UK) on the non-dominant wrist continuously for one week. Data were downloaded to computer and each one-minute epoch was scored as sleep or wake using Sleep Analysis 7 (CamNTech, Cambridge, UK). Sleep start and sleep end were marked as the start and end respectively of a period of 10 or more minutes of immobility. The actigraphy variables of interest are: bed time (time the child is in bed with lights off), time in bed, sleep latency (time from bed time to sleep start), assumed sleep time (time from sleep onset to offset), actual sleep time (assumed sleep minus any periods of wake), night wakings (number of), wake after sleep onset, sleep efficiency (percentage of time spent asleep from sleep onset to offset), moving time (percentage of time spent moving from sleep onset to offset) and fragmentation (an indication of restlessness where a higher figure denotes increased restlessness). In addition, to support analyses of actigraphy data, parents completed a sleep diary recording their child's bed time, getting up time, as well as any daytime naps and night-time awakenings for the duration of the study.

Children's Sleep Habits Questionnaire: Parents completed the Children's Sleep Habits Questionnaire - CSHQ [15]. This is a 45-item caregiver response questionnaire which screens for the occurrence of common sleep problem symptoms in school-aged children. Parents indicate whether each listed characteristic occurs often (5-7 nights per week), sometimes (2-4 nights per week) or rarely (0-1 nights per week) for behaviours such as going to bed (lights out) at the same time each night, sleepwalking, bruxism or snoring. Satisfactory test-retest reliability of CSHQ subscales has been reported for both normal and clinical populations [15].

Melatonin and Cortisol: Levels of melatonin and cortisol were analysed in saliva, collected at three time points: between 4 – 6 pm, evening before going to bed and morning after awakening, using a commercial immunoassays (Salivary Melatonin ELISA - IBL International, Germany; Salivary Cortisol ELISA, Salimetrics Europe, UK). Samples were transported in cardice, centrifuged for 10 min at 3000 rpm, aliquoted and stored at -20°C until analysis. Melatonin in saliva samples (100 µl) were assayed in duplicate by competitive enzyme linked immunosorbent assay (ELISA) with the use of reagents obtained from IBL International, Germany. After adding the substrate, chromophore was formed in inverse proportion to the amount of melatonin and the absorbance was measured by a plate reader (FLUOstar OPTIMA, BMG LABTECH) at 450 nm. The sensitivity of the assay was 0.3 $pgmL^{-1}$.

Levels of cortisol in saliva samples (25 µl) were assayed in duplicate by competitive enzyme immunoassay kit with the use of reagents from Salimetrics Europe, UK. The density of obtained colour was inversely proportional to the amount of cortisol in the analysed sample and the absorbance was measured by a plate reader (FLUOstar OPTIMA, BMG LABTECH) at 450 nm. The sensitivity of the assay was 0.003 μgdL^{-1}.

Although actual levels are recorded, due to the inherent high variability of levels of melatonin and cortisol between individuals and during the day, levels of both hormones were also normalised (set as 100%) based on morning levels of melatonin and cortisol. The usual pattern for melatonin is high at night and low during the day since the synthesis being suppressed by sunlight, in contrast, cortisol is high upon waking and lowering before sleep.

Results

Table 1 presents the results from triplets and matched TD controls on sleep measures and endocrine profiles. Data were analysed using SPSS for Windows, Version 19 (SPSS Inc., Chicago, IL). A number of *t*-tests were carried out followed by inter-group comparisons. Post-hoc comparisons were made using.

Discussion

In line with the previous studies [2,3], the current data based on CSHQ show that the child with WS suffers from sleep problems. However this study also reveals that siblings also suffer from sleep problems, namely, frequent night waking for all three children and daytime sleepiness was shown by the child with WS and Sib1 were

Measures	WS	Sib 1	Sib 2	TD (n=4)
CSHQ scores				
CSHQ total score	**47**	44	37	39‡
Bedtime resistance	7.0	6.0	6.0	7.0 (1.6)
Sleep onset delay	2.0	3.0	1.0	1.3 (.5)
Sleep duration	4.0	5.0	3.0	3.7 (1.1)
Sleep anxiety	4.0	4.0	4.0	5 (1.2)
Night waking	**6.0**	**5.0**	**5.0**	3.3 (.6)
Parasomnias	7.0	7.0	8.0	8.0 (1.4)
Sleep disordered breathing	3.0	3.0	3.0	3.2 (.5)
Daytime sleepiness	**16.0**	**13.0**	9.0	11.6 (2.5) †
Actigraphy scores				
Wake time (hr)	**1.85**	**1.25**	**1.73**	0.51*
Actual wake time (%)	**19.07**	**13.33**	**16.77**	5.3*
Actual sleep time (hr)	**7.83**	**8.13**	**8.57**	9.17*
Actual sleep time (%)	**80.93**	**86.67**	**83.23**	94.7*
Sleep latency	**69.33**	**86.67**	22.67	20.33†
Sleep efficiency	**72.3**	**75**	**79.13**	89.97*
Melatonin				
Afternoon Normalized	**0.75** **18.47**	**0.15** **2.64**	**0.26** **5.96**	3.27* 99.84*
Evening Normalized	**0.15** **3.69**	**0.15** **2.64**	**0.7** **16.05**	12.31* 375.45*
Morning	**4.06**	**5.67**	**4.36**	3.28
Cortisol				
Afternoon Normalised	0.1 **83.33**	0.06 **42.85**	**0.31** **96.87**	0.06 25*
Evening Normalised	0.05 **41.66**	0.02 14.28	0.04 12.5	0.03‡ 12.5
Morning	0.12	0.14	0.32	0.24

Significant problems are highlighted in **bold**.
* = Significant difference between TD and all siblings
† = Significant difference between TD and WS and Sib1
‡ = Significant difference between TD and WS

Table 1: Scores on sleep measures, melatonin and cortisol.

reported by parents. More sleep problems and similarities amongst siblings were seen in actigraphy data. Child with WS showed the highest actual wake time, and as a consequence, lowest actual sleep time during the night. Sleep efficiency was also the lowest in this child. The time taken to fall asleep by the child with WS was 69 minutes and her Sib1 showed even higher sleep latency of 86 minutes.

In healthy population, melatonin levels increase before bedtime what is a factor facilitating sleep [10]. This pattern was observed in TD controls, whereas the triplets' melatonin levels were remarkably lower in both the afternoon and evening respectively. Also, cortisol actual levels were lower in the afternoon and evening for controls, siblings and WS individual. However, the normalised cortisol level in the evening did not decrease as much as seen in controls and siblings. Indeed at 46% of morning maxima this is approximately 3 fold higher in the child with WS compared to the unaffected siblings and the TD control.

However, unlike the melatonin normalized levels, normalized cortisol revealed a much more significant difference to controls than the siblings. This may indicate that cortisol is more closely associated with the pathophysiology of sleep disturbance in WS whilst melatonin is more associated with environmental psychophysiology of sleep disturbance in households with WS individuals and unaffected siblings.

Thus far, very few studies have been carried out to analyse endocrine sleep markers in children with developmental disabilities and none of them included individuals with WS and their siblings. The current results confirm that the child with WS indeed has sleep disturbances. Moreover, it demonstrates that this may be a result of mixed aetiology of environmental and pathophysiology since the siblings also displayed clear evidence of sleep disturbance. Abnormal levels of melatonin may be linked to family environmental influence (i.e. lack of night routine and lights out management, one child waking up another etc.) whilst cortisol relates to stress and perhaps a pathophysiology anxiety which is a known feature of WS.

The current study shows that the use of clinical chemistry biomarkers may greatly advance the definition of "caseness" in psychology evaluations [16]. Sleep is a very complex state and can be influenced by multiple factors hence future studies ought to verify impact of home environment on the child's and family cognitive health. Moreover, if we are to establish successful sleep management for children with developmental disorders, careful assessment of family sleep profiles should also be taken [17,18]. What is apparent from sleep literature is that sleep problems have a huge negative impact on academic performance and family functioning as whole. Thus an appropriate intervention would be to train all siblings to adhere to sleep habits routine as early in development as possible [3,19,20].

Acknowledgements

We would like to thank all the parents and children for participating in this study, The UK Williams Syndrome Foundation, UK for their continuous support. This study was funded by the Autour des Williams, France.

References

1. Toth LA (2001) Identifying genetic influences on sleep: an approach to discovering the mechanisms of sleep regulation. Behav Genet 31: 39-46.
2. Annaz D, Hill CM, Ashworth A, Holley S, Karmiloff-Smith A (2011) Characterisation of sleep problems in children with Williams syndrome. Res Dev Disabil 32: 164-169.
3. Ashworth A, Hill CM, Karmiloff-Smith A, Dimitriou D (2013) Cross syndrome comparison of sleep problems in children with Down syndrome and Williams syndrome. Res Dev Disabil
4. Goldman SE, Malow BA, Newman KD, Roof E, Dykens EM (2009) Sleep patterns and daytime sleepiness in adolescents and young adults with Williams syndrome. J Intellect Disabil Res 53: 182-188.
5. Mason TB, Raanan Arens, Jaclyn Sharman, Brooke Bintliff-Janisak, Brian Schultz, et al. (2011) Sleep in children with Williams syndrome. Sleep Med 12:892-827.
6. Youssef NA (2012) ADHD, Sleep Disorders, and other General Medical Conditions: Recommendations for DSM V. J Sleep Disord Ther 1: e106.
7. Chen H (2006) Atlas of genetic diagnosis and counseling, Williams Syndrome. Humana Press:1040-46.
8. Annaz D, Karmiloff-Smith A, Johnson MH, Thomas MS (2009) A cross-syndrome study of Development of holistic face recognition in children with Autism, Down syndrome and Williams syndrome. J Exp Child Psychol 102: 456-486.
9. Clarke M, Crockett S, Sims B (2012) Melatonin Induces Neuroprotection via System Xc Regulation in Neural Stem Cells. J Stem Cell Res Ther 2:120.
10. Claustrat B, Brun J, Chazot G (2005) The basic physiology and pathophysiology of melatonin. Sleep Med Rev 9: 11-24.
11. Rai B, Kaur J (2012) Salivary Stress Markers, Depression, Mood State and Back Pain in Healthy Men in Two Bed Rest Conditions: Validation of Two Models for Human Space Flight. J Aeronaut Aerospace Eng 1:106.
12. Spath-Schwalbe E, Gofferje M, Kern W, Born J, Fehm HL (2003) Sleep disruption alters nocturnal ACTH and cortisol secretory patterns. Biol Psy 29: 575-584.
13. Talbott S (2007) The cortisol connection: Why stress makes you fat and ruins your health- And what you can do about it. (2ndedn), Hunter House.
14. Sadeh A. Hauri P, Kripke D, Lavie P (1995) The role of actigraphy in sleep medicine. Sleep, 18:288-302.
15. Owens JA, Spirito A, McGuinn M (2000) The Children's Sleep Habits Questionnaire (CSHQ): Psychometric properties of a survey instrument for school-aged children. Sleep 23: 1043-1051.
16. Shanker A (2011) Neuroendocrine crosstalk of immunity. J Blood Lymph 1: e105.
17. Baglioni C, Riemann D (2012) Cognitive-Behavioral Treatment for Insomnia Comorbid with Psychiatric Disorders. J Sleep Disorders Ther 1: e112.
18. Singh NK, Bhattacharjee D, Goyal N, Munda SK, Nizamie SH (2012) Perceive Family Environment among Parents, Spouses and Siblings of Alcohol Dependence Patients: A Comparative Study. J Addict Res Ther 3: 126.
19. Field T, Diego M, Delgado J, Medina L (2012) Yoga and Social Support Reduce Prenatal Depression, Anxiety and Cortisol. J Yoga Phys Ther 2: 124.
20. Susan E. Ramsey, Patricia A. Engler, Michael D. Stein, Richard A. Brown, Patricia Cioe, et al. (2011) Effect of CBT on Depressive Symptoms in Methadone Maintenance Patients Undergoing Treatment for Hepatitis C. J Addict Res Ther 2: 109.