Parent reported sleep problems in preschool children with Sickle Cell Anemia and controls in East London

[1]Michelle Downes, [1]Michelle de Haan, [1]Fenella J Kirkham, [2]Paul T Telfer,

[1]Developmental Neurosciences, UCL Institute of Child Health, London WC1N 1EH, UK, [2]Department of Haematology, Barts Health NHS Trust, Royal London hospital, Whitechapel road, London E1 1BB

Correspondence to:

Fenella Kirkham

Developmental Neurosciences,

UCL Institute of Child Health,

London WC1N 1EH,

UK

Phone: 00442079052644

Email: Fenella.Kirkham@ucl.ac.uk

WORD COUNT: Abstract- 104 words; Main text- 1330 words

TABLES: 2

RUNNING TITLE: Sleep in preschool children with Sickle Cell Anemia

SCA	Sickle cell anemia
SDB	Sleep disordered breathing
SES	Socio-economic status

Key words: sickle cell disease, sleep, sleep disordered breathing, snoring, obstructive sleep apnea, early intervention

Post-review; accepted for publication

`

Abstract

Snoring and poor sleep may affect cognition, particularly in young children with chronic conditions. Parents of London preschoolers with sickle cell anemia (SCA; n=22), matched controls (n=24) and unselected typically developing (n=142) preschoolers completed sleep questionnaires. Preschoolers with SCA had significantly more sleep problems when compared to matched controls and the larger population. Snoring occurred at least 1 to 2 nights a week for 79% of the SCA patient group. This is compared with 25% of matched controls and 33% of the larger population. Randomized controlled trials to improve sleep in young children with SCA, who are already at-risk for cognitive dysfunction, should be considered.

`

Introduction

Sleep problems are reported more frequently in preschool children than school-age children and are associated with poorer quality of life, behavioral problems, and higher rates of attention disorders.[1] More sleep problems have been reported in school-age children with sickle cell anemia (SCA) when compared to typically developing children.[2] An increased prevalence of sleep disorders such as sleep disordered breathing (SDB) and enuresis, as well as more disrupted sleep in general, has been reported in older children with SCA,[2] with abnormal polysomnography reported for up to 41%.[3] High glomerular filtration rate and other kidney complications related to sickle cell anemia can also lead to increased enuresis, illustrating the complex interaction of sleep problems in this patient population.

Nocturnal physiologic disturbances associated with SDB, such as hemoglobin oxygen desaturation,[4] can affect cognitive functioning, in addition to the impact of disrupted sleep and daytime tiredness on a child's ability to concentrate.[5] Research in the general pediatric population suggests that the impact of sleep problems on cognitive functioning can be detected at preschool age.[6] Sleep interventions have been found to be more effective in children younger than seven years,[7] indicating that early intervention may be particularly pertinent to young children with SCA who are already at a greater risk for cognitive dysfunction due to chronic desaturation associated with SCA.[8] Thus, data on the rates of sleep problems in preschool children with SCA are important to inform future research and practice. There is no published study that has focused on children with SCA in the preschool age

`

range using a matched control group.[9] To the authors' knowledge, this is the first study to investigate the rate of parent-reported sleep problems in preschool children with SCA with a comparison group matched for gender, age, ethnicity and socio-economic status (SES).

Methods

Participants

Ethical approval was obtained from the local NHS committee and site-specific approval was obtained from UCL Institute of Child Health and Barts Health NHS Trust. Parents of patients aged between 36 and 72 months, with HbSS genotype and no history of stroke or a co-morbid disorder, were approached for this study. Data were also collected from ethnicity-, age-, gender- and SES-matched control children recruited through the same clinics and local schools. Data collected from parents of a larger sample of typically developing preschool children through schools and preschools in Greater London were included to establish the prevalence of sleep issues in unselected preschool children in Greater London. Parents returned study packs with the questionnaires and consent form to schools where they were collected by the researcher.

Procedure

All parents filled out an adapted version of the Children Sleep Habits Questionnaire[10] previously used in a study that looked at rates of SDB in SCA.[3] The rater created weighted sleep composite scores based on the amount of poor sleep symptoms and their prevalence. Scores range from 0 (no symptoms observed) to the possible highest rating of 80 (all of the 20

`

potential symptoms occurring ‘6-7 nights’ a week). An independent t-test was used to compare the sleep composite score between groups. Chi-square analysis was used to compare the rates of parent-reported symptoms of sleep-disordered breathing.

Results

Cases and controls were all Black British. Parents of 22 patients (Mean age 4.8, SD= 0.94), completed the sleep questionnaire, representing 23% of the children with HbSS in this age range registered on the Barts Health NHS Trust database. Three families refused to participate. Parents of 26 ethnicity, age (Mean age 4.8, SD 0.88), gender and SES matched control children also completed the sleep questionnaires. Two matched controls did not fully complete the questionnaires, which were excluded from analysis. In the larger unselected group (n=153 approached), of 142 questionnaires returned, 99 (70%) parents identified as White British and 41 (29%) identified as Mixed Ethnicity or Other Minority while ethnicity data were missing for 2 (1%) children; questionnaires were not returned for 11 (8%).

The patients had a significantly higher rate of sleep problems as reflected by a higher sleep composite score (M=21.47, SD=11.67) when compared to the matched controls (M=11.21, SD=9.83; p=.002). The unselected London children had a slightly higher, but non-significant, mean sleep composite scores than the matched controls (M=14.83, SD=9.58, N=131). Twenty seven per cent of children with SCA, 2 (8%) of the matched controls and 10 (8%) of the unselected London children had sleep composite scores greater than 1.5 standard deviations above the mean for the unselected London children. The

`

relation between patient hemoglobin levels (mean=9.1, SD=1.9) and sleep score was explored. Interestingly, higher hemoglobin levels, which has been previously been reported for otherwise healthy patients with obstructive sleep apnea, was related to a higher sleep composite score (r= .52, p=.01). Table I shows the parent-reported rates for each of the 20 sleep problems, showing snoring, resisting bedtime, restless sleep and bed-wetting to be the most frequently reported issues for the patient group. The matched control group had a similar rate of sleep problems to the London norm, but there was a three-fold increase of sleep problems in preschool children with SCA.

Discussion

For patients with SCA, all except two (including the only patient who had adenoids and/or tonsils removed in order to alleviate obstructive sleep apnea) were reported to snore. For preschoolers with SCA, bed-wetting occurred at least 1-2 times a week in 59% and snoring in 79% (27% 6-7 nights per week), similar to previous findings in older children.[2] This is much higher than the 30% of 54-month-olds reported to experience bed-wetting at least once a week in the unselected Avon population-based cohort born in 1991-2 (n=13,973)[11] and the 13% of four year olds in the randomly selected Leicestershire cohort (n=1,100) reported to snore most nights.[12] There is a lack of data on sleep behavior and sleep hygiene for typically developing preschool children in the UK, but a recent study looked at typically developing 3 year-olds (n=84) and found a regular bedtime routine for 79% of their cohort,[13] similar to the rate of 77% reported for the current patient group.

`

Sleep problems may be an avenue for intervention in preschool children with SCA. The average sleep duration on a school night for the patient group was 10.5 hours. However, the sleep duration recommended by the UK National Health Service and the Royal College of Psychiatrists for three to five year olds is 11-12 hours. Table II shows that 33% of the group has at least one caffeinated drink during the day and 32% have televisions in their bedrooms. Mindell et al. found that preschool children (n=385) who consumed one or more caffeinated beverages slept over 40 minutes less than those who did not, and children with a TV in their own bedroom slept 30% less on average.[14] Behavioral interventions that focus on positive sleep hygiene, e.g. removing caffeine and TV from the environment and encouraging night-time reading,[14] may have a positive impact on sleep behaviors in children with SCA. Symptoms of SDB, particularly snoring, were reported frequently. Despite no medical evaluation for mechanically obstructed airways in the current study, there is accumulating evidence for improved SDB with medical interventions and potentially also a positive impact on cognitive outcomes. Encouragingly, a recent study found that older children with SCA who received 6 weeks of auto-adjusting continuous positive airways pressure for SDB improved on an attention control task.[15] There are no published investigations on the impact of sleep interventions in young children with SCA, despite positive findings for sleep interventions such as Montelukast and adenotonsillectomy in otherwise typically developing preschool children with obstructive sleep apnea.[16,17]

In conclusion, preschool children with SCA have a greater burden of sleep problems than matched controls. Hence, a future focus on sleep problems in

`

the preschool years, a developmental stage when problems typically emerge, and further establishing the impact on cognitive development, could lead to earlier targeted interventions. With the current evidence base, it is difficult to justify adenotonsillectomy for primary snoring in this vulnerable group, but our recently funded trial of Montelukast aims to investigate the natural history of SDB and the impact of a SDB intervention on cognition in preschool children with sickle cell anemia.

`

Conflict of Interest

No conflict of interest.

Acknowledgements

This study was funded by the award of funding for a PhD stipend to the first author by the Child Health Research Appeal Trust and supported by the National Institute for Health research Centre at Great Ormond Street Hospital for Children NHS Foundation Trust and University College London.

Author Contributions

MD, MDeH, FJK and PT designed the study; MD analysed the study and wrote the first draft of the manuscript under the supervision of the other authors; all authors edited the drafts and approved the final version.

References

1. Goodlin-Jones BL, Sitnick SL, Tang K, Liu J, Anders TF. The Children's Sleep Habits Questionnaire in toddlers and preschool children. *Journal of Developmental & Behavioral Pediatrics.* 2008;29(2):82-88.

2. Daniel LC, Grant M, Kothare SV, Dampier C, Barakat LP. Sleep patterns in pediatric sickle cell disease. *Pediatric blood & cancer.* 2010;55(3):501-507.

3. Rosen CL, Debaun MR, Strunk RC, et al. Obstructive Sleep Apnea and Sickle Cell Anemia. *Pediatrics.* 2014;134(2):273-281.

4. Hill CM, Hogan AM, Onugha N, et al. Increased cerebral blood flow velocity in children with mild sleep-disordered breathing: a possible association with abnormal neuropsychological function. *Pediatrics.* 2006;118(4):e1100-e1108.

5. Simola P, Niskakangas M, Liukkonen K, et al. Sleep problems and daytime tiredness in Finnish preschool-aged children-a community survey. *Child: care, health and development.* 2010;36(6):805-811.

6. Jackman AR, Biggs SN, Walter LM, et al. Sleep-disordered breathing in preschool children is associated with behavioral, but not cognitive, impairments. *Sleep Medicine.* 2012;13(6):621-631.

7. Bhattacharjee R, Kheirandish-Gozal L, Spruyt K, et al. Adenotonsillectomy outcomes in treatment of obstructive sleep apnea in children: a multicenter retrospective study. *American journal of respiratory and critical care medicine.* 2010;182(5):676-683.

8. Hogan AM, Pit-ten Cate IM, Vargha-Khadem F, Prengler M, Kirkham FJ. Physiological correlates of intellectual function in children with sickle cell disease: hypoxaemia, hyperaemia and brain infarction. *Developmental science.* 2006;9(4):379-387.

9. Hankins JS, Verevkina NI, Smeltzer MP, Wu S, Aygun B, Clarke DF. Assessment of Sleep-Related Disorders in Children With Sickle Cell Disease. *Hemoglobin.* 2014;38(4):244-251.

`

10. Owens JA, Spirito A, McGuinn M. The Children's Sleep Habits Questionnaire (CSHQ): psychometric properties of a survey instrument for school-aged children. *SLEEP-NEW YORK-.* 2000;23(8):1043-1052.
11. Butler RJ, Heron J. The prevalence of infrequent bedwetting and nocturnal enuresis in childhood: a large British cohort. *Scandinavian journal of urology and nephrology.* 2008;42(3):257-264.
12. Kuehni CE, Strippoli MF, Chauliac ES, Silverman M. Snoring in preschool children: prevalence, severity and risk factors. *European Respiratory Journal.* 2008;31(2):326-333.
13. Jones CH, Ball H. Exploring Socioeconomic Differences in Bedtime Behaviours and Sleep Duration in English Preschool Children. *Infant and child development.* 2014;23(5):518-531.
14. Mindell JA, Meltzer LJ, Carskadon MA, Chervin RD. Developmental aspects of sleep hygiene: findings from the 2004 National Sleep Foundation Sleep in America Poll. *Sleep medicine.* 2009;10(7):771-779.
15. Marshall MJ, Bucks RS, Hogan AM, et al. Auto-adjusting positive airway pressure in children with sickle cell anemia: results of a phase I randomized controlled trial. *haematologica.* 2009;94(7):1006-1010.
16. Goldbart AD, Greenberg-Dotan S, Tal A. Montelukast for children with obstructive sleep apnea: a double-blind, placebo-controlled study. *Pediatrics.* 2012;130(3):e575-e580.
17. Walter LM, Biggs SN, Cikor N, et al. The efficacy of the OSA-18 as a waiting list triage tool for OSA in children. *Sleep and Breathing.* 2015:1-8.

`

Table I Differences in rates of parent-reported nighttime symptoms between patients and matched-controls

Nighttime weekly symptom occurrence N (%)	**Never (Does not occur)**	**Not often (<1 night)**	**Sometimes (1 to 2 nights)**	**Often (3 to 5 nights)**	**Always (6 to 7 nights)**	**Don't Know/ Missing**	**P***
Snores							
Patients	2 (9.1)	3 (13.6)	9 (40.9)	2 (9.1)	6 (27.3)	-	<.001
Matched Controls	14 (58.3)	4 (16.7)	4 (16.7)	1 (4.2)	1 (4.2)	-	
London Cohort	52 (36.6)	26 (18.3)	36 (25.4)	8 (5.6)	3 (2.1)	17 (12)	
Difficulty breathing while asleep							
Patients	14 (63.6)	2 (9.1)	2 (9.1)	1 (4.5)	2 (9.1)	1 (4.5)	.002
Matched Controls	20 (83.3)	3 (12.5)	1 (4.2)	-	-	-	
London Cohort	112(78.9)	12 (8.5)	4 (2.8)	2 (1.4)	-	12 (8.5)	
Stops breathing during sleep							
Patients	19 (86.4)	1 (4.5)	2 (9.1)	-	-	-	.01
Matched Controls	23 (95.8)	-	1 (4.2)	-	-	-	
London Cohort	120(84.5)	2 (1.4)	1 (0.7)	-	-	18 (12.7)	
Noisy breathing							
Patients	10 (45.5)	1 (4.5)	6 (27.3)	2 (9.1)	3 (13.6)	-	.03
Matched Controls	17 (70.8)	2 (8.3)	1 (4.2)	-	2 (8.3)	2 (8.3)	
London Cohort	68 (47.9)	26 (18.3)	25 (17.6)	9 (6.3)	3 (2.1)	11 (7.7)	
Restless sleep *Patients*	6 (27.3)	4 (18.2)	6 (27.3)	4 (18.2)	2 (4.5)	-	<.001
Matched Controls	17 (70.8)	5 (20.8)	1 (4.2)	-	1 (4.2)	-	
London Cohort	45 (31.7)	46 (32.4)	26 (18.3)	9 (6.3)	1 (0.7)	15 (10.6)	
Sweating when sleeping							
Patients	9 (40.9)	1 (4.5)	8 (36.4)	2 (9.1)	1 (4.5)	1 (4.5)	.02

`

Matched Controls	18 (75.0)	2 (18.3)	4 (16.7)	-	-	-	
London Cohort	42 (29.6)	39 (27.5)	26 (18.3)	13 (9.2)	8 (5.6)	14 (9.9)	
Nightmares							
Patients	6 (27.3)	5 (22.7)	5 (22.7)	3 (13.6)	-	3 (13.6)	.03
Matched Controls	18 (75.0)	3 (12.5)	3 (12.5)	-	-	-	
London Cohort	47 (33.1)	59 (41.5)	18 (12.7)	5 (3.5)	-	13 (9.2)	
Sleep walking *Patients*							
	19 (86.4)	1 (4.5)	-	-	-	2 (9.1)	.84
Matched Controls	20 (83.3)	2 (8.3)	2 (8.3)	-	-	-	
London Cohort	118(83.1)	9 (6.3)	2 (1.4)	1 (0.7)	-	12 (8.5)	
Sleep talking							
Patients	9 (40.9)	7 (31.8)	3 (13.6)	1 (4.5)	1 (4.5)	-	.18
Matched Controls	18 (75.0)	3 (12.5)	1 (4.2)	1 (4.2)	-	-	
London Cohort	56 (39.4)	47 (33.1)	17 (12.0)	8 (5.6)	1 (0.7)	13 (19.2)	
Screaming in sleep							
Patients	15 (68.2)	2 (9.1)	4 (18.2)	-	-	-	.18
Matched Controls	19 (79.2)	2 (8.3)	2 (8.3)	-	-	1 (4.2)	
London Cohort	100(70.4)	21 (14.8)	9 (6.3)	-	-	12 (8.5)	
Kicks/jerks legs in sleep							
Patients	13 (59.1)	5 (22.7)	3 (13.6)	-	-	1 (4.5)	.14
Matched Controls	20 (83.3)	2 (8.3)	2 (8.3)	-	-	-	
London Cohort	66 (46.5)	24 (16.9)	20 (14.1)	9 (6.3)	4 (2.8)	19 (13.4)	
Uncomfortable feelings in legs before falling asleep							
Patients	12 (54.5)	1 (4.5)	4 (18.2)	2 (9.1)	1(4.5)	2(9.1)	.001
Matched Controls	19 (79.2)	3 (12.5)	1 (4.2)	1 (4.2)	-	-	
London Cohort	96 (67.6)	20 (14.1)	8 (5.6)	1 (0.7)	-	17(12.0)	
Resists going to bed at bedtime							
Patients	4 (18.2)	2 (22.7)	8 (36.4)	3 (13.6)	-	-	.08
Matched Controls	18 (75.0)	2 (8.3)	3 (12.5)	-	-	-	
London Cohort	51 (35.9)	41 (28.9)	25 (17.6)	11 (7.7)	3(2.1)	11(7.7)	
Trouble falling asleep							

`

Patients	8 (36.4)	6 (27.3)	4 (18.2)	2 (9.1)	1(4.5)	-	.41
Matched Controls	20 (80.3)	3 (12.5)	19 (4.2)	-	-	-	
London Cohort	56 (39.4)	48 (33.8)	17 (12.0)	6 (4.2)	2(1.4)	13(9.2)	
Feels like can't move arms/legs when falling asleep							
Patients	17 (77.3)	1 (4.5)	1 (4.5)	1 (4.5)	1 (4.5)	1 (4.5)	.02
Matched Controls	20 (83.3)	4 (16.7)-	-	-	-	-	
London Cohort	108(76.1)	9 (6.3)	6 (4.2)	1 (0.7)	-	18 (12.7)	
Wakes up at night							
Patients	6 (27.3)	4 (18.2)	5 (22.7)	4 (18.2)	1 (4.5)	2 (9.1)	.28
Matched Controls	12 (50.0)	7 (29.2)	4 (16.7)	1 (4.2)	-	-	
London Cohort	34 (23.9)	53 (37.3)	24 (16.9)	11 (7.7)	8 (5.6)	12 (8.5)	
Gets out of bed at night							
Patients	9 (40.9)	3 (13.6)	6 (27.3)	4 (18.2)	-	-	.09
Matched Controls	13 (54.2)	8 (33.3)	2 (8.3)	1 (4.2)	-	-	
London Cohort	60 (42.3)	35 (24.6)	16 (11.3)	11 (7.7)	6 (4.2)	14 (9.9)	
Trouble staying in bed at night							
Patients	9 (40.9)	3 (13.6)	3 (13.6)	2 (9.1)	3 (13.6)	-	.03
Matched Controls	18 (75.0)	4 (16.7)	1 (4.2)	1 (4.2)	-	-	
London Cohort	79 (55.6)	30 (21.1)	8 (5.6)	9 (6.3)	4 (2.8)	-	
Grinds his/her teeth							
Patients	15 (68.2)	1 (4.5)	1 (4.5)	3 (13.6)	1 (4.5)	-	.58
Matched Controls	18 (75.0)	2 (8.3)	-	3 (12.5)	-	-	
London Cohort	80 (56.3)	17 (12.0)	10 (7.0)	10 (7.0)	2 (1.4)	23 (16.2)	
Wets the bed							
Patients	6 (27.3)	2 (9.1)	9 (40.9)	1 (4.5)	3 (13.6)	-	<.001
Matched Controls	13 (54.2)	6 (25.0)	4 (16.7)	1 (4.2)	-	-	
London Cohort	77 (54.2)	22 (15.5)	16 (11.3)	9 (6.3)	3 (2.1)	15 (10.6)	

`

*P-values indicates group differences between patients and matched controls using Chi-square analysis

Table II. Sleep behavior habits of patients with SCA

Variable	**Mean (SD)**
School Bed Time (pm)	7.50 (2.5 hours)
School Actual Sleep Time (hours)	8.8 (1.02)
School Wake Time (am)	7.30 (.62 hours)
Hours asleep per night during week	10.38 (1.4)
Non-school Bed Time (pm)	9.40 (.89 hours)
Non-school Actual Sleep Time (hours)	9.8 (1.1)
Non-school Wake Time (am)	9.00 (1.3 hours)
Number of Naps during Day	1.2 (1.18)
Regular Bed Routine	77%
Own Bedroom	62%
Own Bed	77%
TV in Bedroom	32%
Typically has one or more caffeinated drinks during the day	33%

`

`

`