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Title: Increased sleep latency and reduced sleep duration in children with asthma

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Abstract

Study Objective: Sleep disturbance is reported to be more prevalent in children and adolescents with asthma than those without. However, this has not been described adequately using objective measures. The aim of this study was to objectively characterise sleep disturbance in asthmatic and non-asthmatic children and adolescents.

Methods: Retrospective analysis of polysomnography recordings from children aged 5-17yo, with (n=113) and without asthma (n=104), referred for a sleep study over the period 2005-2010 at the Paediatric Sleep Unit, John Hunter Children's Hospital in Newcastle, NSW Australia.

Results: Polysomnographic recordings were analysed to compare sleep quality and quantity between asthmatic and non-asthmatic children. Sleep latency was significantly longer in asthmatic children compared to controls. However, this result was significant for females only (46.2 (5.6) vs 33.2 (2.7) min, $p<0.05$). Male asthmatics had significantly shorter sleep duration (425.9 (5.4) vs 441.8 (5.4) min, $p<0.05$) than male controls.

Conclusions: Sleep disturbance exists in children with asthma, and manifests differently in males and females. Further investigation into the clinical implication of increased sleep latency and reduced sleep duration upon daytime functioning and lifestyle behaviours in children and adolescents with asthma is warranted.

Key words: adolescent; asthma; child; polysomnography; sleep

Abbreviations: AI arousal index; BMI body mass index; CVD cardiovascular disease; ECG electrocardiogram; EEG electroencephalogram; EMG electromyogram; FEV₁ forced expiratory volume in one second; FVC forced vital capacity; IQR interquartile range; PSG polysomnography; PEF pulmonary expiratory flow; PSU paediatric sleep unit; RDI respiratory disturbance index; REE resting energy expenditure; REM rapid eye movement; SEM standard error mean; TST total sleep time; TTA total time awake; OSA obstructive sleep apnea

Introduction

Asthma affects one in six children in Australia and is one of the most common chronic conditions affecting children and adolescents worldwide [1]. Asthmatic children experience more disturbed sleep than children without asthma according to parental report [2], with approximately 20% of children estimated to be woken by their asthma [3]. Children with asthma also rated significantly higher on a self-report scale for morning tiredness and difficulty waking [4]. The nature of this sleep disturbance has not been defined well, and objective data is required to better understand sleep disturbance in this group.

Not surprisingly, risk of nocturnal awakenings in children has been reported to be higher for those with more severe asthma, a lower forced expiratory volume in one second (FEV_1): forced vital capacity (FVC), and greater atopy [5]. Morning and evening peak expiratory flow (PEF) measurements have also been negatively associated with frequent night awakenings [4]. In addition, increased daytime sleepiness, self-reported depression, and significantly poorer parental reported mood and behavioural functioning, memory recall and learning difficulty, is evident in children suffering nocturnal asthma compared to healthy controls [6]. In adults, poor sleep quality is a significant predictor of poor asthma control in both severe and non-severe asthmatics [7]. However, interestingly, children with asthma reportedly experience more disturbed sleep compared to healthy controls even when their asthma is clinically stable [8].

Poor sleep quality and reduced duration has been linked to poorer cognitive performance and executive functioning in non-asthmatic children [9, 10]. Documented disturbances in key metabolic parameters in children self-reporting reduced sleep duration may also infer risk for chronic diseases [11]. Indeed, reduced sleep duration in children has been associated with a

significantly increased risk of overweight and obesity later in childhood [12], and is a risk factor for cardiovascular disease (CVD) [13-15].

Sleep disturbance has not been described well using objective measures in children with asthma. The majority of studies reporting sleep habits in children have used parental or self-report [5, 8, 16-18], while others have used actigraphy [4, 16] and one has used electroencephalographic studies [19]. Only two have used the gold-standard technique of PSG to study children with asthma, and these were confounded by the presence of obesity, obstructive sleep apnea (OSA) and uncontrolled asthma within the population studied [6, 20]. Therefore, the aim of this study is to compare sleep quality and quantity in children with and without asthma, using overnight PSG data, to assess whether sleep disruption is higher in children with asthma compared to non-asthmatic children.

Methods

This was a retrospective cross-sectional study comparing sleep quality and quantity, as measured by polysomnography (PSG), in non-obese children and adolescents aged 5-17yo, with and without asthma. Sleep quality may be defined by EEG arousals with (respiratory disturbance index (RDI)) or without (arousal index (AI)) a respiratory event, sleep efficiency (%) and rapid eye movement (REM) sleep (%). For this study, the primary outcome measure of sleep quality was sleep efficiency (%) while sleep quantity was determined by the primary outcome measure, total sleep time (TST).

Subjects

De-identified data from patients aged 5-17yo referred during the period January 2005-December 2010 to the Paediatric Sleep Unit (PSU) at the John Hunter Children's Hospital, Newcastle NSW, Australia were extracted from the PSU database. Patients were referred to the PSU for investigation of possible sleep disturbance including; snoring, suspected apnoeas, daytime somnolence, delayed initiation and/or maintenance of sleep, and daytime behavioural issues. Data were categorised into those with a diagnosis of asthma (n=113) and those without asthma (n=104). Asthma was defined as respiratory physician diagnosis as determined by written documentation in the medical notes. Demographic and anthropometric data were obtained from the PSG report and confirmed from the medical records. This data was collected as part of the quality assurance procedures in place at the Paediatric Sleep Unit and is considered an exempt protocol by the Hunter Area Research Ethics Committee. Exclusion criteria included obesity (BMI z -score ≥ 1.64); respiratory disease other than asthma; conditions which may cause pain or discomfort and potentially affect sleeping patterns e.g. current eczema; mood disorders and medications known to affect sleep patterns; diagnosed sleep disorders or obstructive sleep apnoea; patients receiving continuous positive

airway pressure; genetic conditions e.g. Trisomy 21; severe developmental delay or behavioural problems; or cranio-facial abnormalities (Fig. 1).

Polysomnography (PSG)

Overnight polysomnography was performed on patients using the modified 10-20 application system (E-Series, Compumedics Ltd, Victoria Australia). Monitoring included ECG; EEG; pulse rate; oximetry (SpO₂); airflow, via nasal thermistor and nasal prong pressure transducer where tolerated; transcutaneous CO₂ (tcCO₂); and diaphragmatic and respiratory effort via diaphragmatic EMG and Peizo respiratory bands located on the chest and abdomen. Scoring of polysomnographic recordings was carried out by a PSG Technician using Profusion PSG 2 software (Compumedics Ltd, Victoria Australia 2001-2007). Sleep-wake state was scored using R & K Rules criteria for children >6mths of age [21]. EEG arousals with (RDI, RDI in REM) and without (AI) a respiratory event were scored using modified American Thoracic Society criteria [22, 23]. Use of these scoring guidelines was under the direction of the paediatric respiratory sleep physicians. The PSU meets accreditation by the Thoracic Society of Australia and New Zealand (TSANZ), and the Australasian Sleep Association.

Data Storage and Analysis

De-identified data were analysed using Intercooled Stata Release 11.1 for Windows (StataCorp, College Station, Texas, USA 2009). Variables were assessed for normality before performing the Students *t*-test or Wilcoxon rank sum test. Results are presented as mean (standard error mean (SEM)) or median [interquartile range; IQR] and considered statistically significant if $p \leq 0.05$.

Results

The asthmatic (n=113) and control (n=104) groups were similar in age (7.4 [5.9, 8.8] y vs 6.6 [5.9, 9.1] y, $p=0.46$), gender distribution and anthropometric measures, $p>0.05$ (Table 1). Valid data on medication use was available on 25% of the asthmatic group. Of these children, 54% were prescribed SABA and 54% were prescribed an inhaled corticosteroid with an average daily dose of 90 beclomethasone equivalents.

Sleep latency was significantly longer in the asthmatic group compared to controls (35.5 [26.5, 57] min vs 29.5 [20.5, 44] min, $p=0.01$) (Table 2). However, TST, total time awake (TTA), and sleep efficiency did not differ between children with and without asthma.

Gender analysis revealed male asthmatics had significantly shorter TST (425.9 (5.4) min vs 441.8 (5.4) min, $p=0.04$) (Fig. 2) and lower sleep efficiency (79.9 (0.9)% vs 82.9 (0.9)%, $p=0.02$), compared to male controls (Table 3). Sleep latency was significantly longer in females with asthma compared to female controls (46.2 (5.6) min vs 33.2 (2.7) min, $p=0.03$) (Fig. 3). Female asthmatics also had significantly shorter TTA compared to female controls (49.9 (4.9) min vs 66.7 (5.4) min, $p=0.03$) (Table 4).

There were no differences in REM latency, REM sleep, the proportion or absolute time in the sleep stages, or in the number of arousals with or without a respiratory event (RDI, RDI in REM, AI) between the asthmatic and control groups, or within the groups between genders ($p>0.05$).

Discussion

The presented study objectively describes sleep disruption in children with and without asthma, referred for sleep assessment. Of interest, the results suggest that gender may be an important factor in the relationship between sleep disturbance and asthma. Asthmatic children had an extended time to sleep onset compared with controls. This trend was driven by females only. Surprisingly, females with asthma spent significantly less time awake after sleep onset than female controls. On the otherhand, asthmatic males had significantly reduced sleep duration and marginally lower sleep efficiency than males without asthma.

Previous studies using PSG data to describe sleep patterns in children with and without asthma [6, 20], were limited by their sample size, the use of self-reported asthma, and the presence of confounding factors, particularly obesity and OSA. Furthermore, gender comparisons were not reported and may have overlooked important differences. One study reported a significantly increased number of awakenings and poorer sleep efficiency in children with poorly controlled nocturnal asthma, compared to normative data [6]. However, it is unknown whether these differences remained following improvements in asthma control, as the control group was not measured at the post-intervention stage [6]. Despite a statistically significant difference in sleep efficiency between male asthmatics and controls in our study, both groups were at the lower limit of normal and the difference between the values was not clinically relevant. In contrast to our study, a previous retrospective analysis found a significantly increased AI in asthmatic children compared to controls [20]. However, this may be attributed to the high prevalence of obesity and diagnosed OSA in their dataset. Clinical abnormalities indicative of sleep disorders, OSA or uncontrolled asthma were not identified in our dataset.

Our study demonstrated a significantly lower TST in male asthmatics compared to controls. Although the magnitude of this difference in sleep quantity between the males in our study is comparable to previous reports of sleep duration in asthmatics versus controls [6, 20], the clinical significance is unknown. An inverse association exists between sleep duration and childhood obesity [11, 24, 25], which is particularly prominent in males [12]. Specific risk factors for weight gain, including frequent consumption of energy-dense foods and soft drink, reduced resting energy expenditure (REE), and lower levels of the appetite-suppressing hormone adiponectin [26, 27], have been inversely associated with sleep duration in boys only, while increased media usage and reduced physical activity is reportedly higher in both male and female short sleepers [26]. Interestingly, these risk factors are highly prevalent in children with self-reported sleep duration up to one hour below the recommended 9-10hrs. Marginal reductions in sleep duration have also been linked with poorer mathematical, neurodevelopmental, and behavioural test scores [28, 29]. In the presented study, sleep duration approximated 7hrs for all children, substantially below recommended levels. This indicates that these children may be vulnerable to significant lifestyle disease risk factors and poorer cognitive performance, and further investigation is required.

Contrasting previous studies, sleep onset was considerably delayed in asthmatic children compared to controls. However, this remained significant for females only, with the onset of sleep taking approximately 13 minutes longer in asthmatics. While the clinical relevance of increased sleep latency in children has not been assessed, a difference in sleep onset of 19 minutes was associated with significantly poorer cognitive performance in asthmatic versus non-asthmatic adults [30]. Increased sleep latency in non-asthmatic children has been linked with decreased physical activity, increased sedentary behaviour, and poorer mental health and eating patterns [31-33]. Sleep latency reportedly increases by 3 minutes and decreases by 5.7

minutes, for every respective hour of sedentary and vigorous activity [33]. It has also been suggested that delayed sleep initiation may lead to anxiety and consequent emotional eating, thereby increasing lifestyle disease risk [32]. Investigation into the clinical significance and potential health impact of delayed sleep onset in asthmatic children requires further investigation.

Our results demonstrated a shorter TTA in female asthmatics versus controls, of which the clinical significance is unknown. This may suggest that female asthmatics have difficulty initiating sleep but nil difficulty in maintaining sleep after onset. Alternatively, it is possible that the observed differences are the result of chance and multiple statistical comparisons, and as such, further investigation is warranted.

The presented study extends previous research through use of an objective gold-standard sleep assessment technique; unique access to a large sample with documented evidence of physician-diagnosed asthma; and the appropriate minimisation of potentially confounding factors. The PSG procedure (where the opportunity to sleep may be impeded by the laboratory hours and the unfamiliar environment) and the measurement of a small time period to estimate usual sleep patterns is a limitation common to the research and diagnostic setting. Although, the acquisition of data from a referral-based population with suspected sleep disturbances is not ideal, collection of PSG data from children without clinical indication is not practical.

The aim of the presented study was to examine the effects of asthma upon sleep and therefore patients with potentially confounding co-morbidities, such as OSA, were excluded. Indeed in adults, severe and non-severe asthma is associated with poorer sleep quality and extended sleep latency after accounting for asthma co-morbidities [7]. Being inflammatory diseases of the respiratory system, certain characteristics such as increased bronchial wall thickness and

airway hyper-reactivity, are reportedly common to both asthma and OSA and a recent review suggests an interaction effect upon sleep may exist [34, 35]. Given the co-presentation of these diseases, it is possible that asthmatic patients were excluded from our sample group due to the presence of OSA. Although an important area of research, due to the likely compounding effects of asthma and OSA upon sleep disturbance, the inclusion of subjects with OSA was deemed outside the aim of the presented study.

The retrospective design of this study is the primary methodological limitation to the interpretation of results. Comprehensive characterisation of lung function, asthma control and medication use was not possible. However, it can be confirmed that all subjects with asthma were stable as, under PSU guidelines subjects are rescheduled if currently exacerbating or unwell. Secondly, the method of statistical analysis involved multiple comparisons and it is possible that observed differences may be due to chance. Therefore, follow-up studies using a prospective design with attention to the thorough characterisation of asthma status and consideration of age and gender effects are warranted.

The presented study used an adequately characterised data-set, otherwise unavailable outside the clinical setting, to extend our knowledge of sleeping patterns in children with physician diagnosed asthma. Results suggest that asthma in childhood may impact the quantity, rather than the quality of sleep, and provides the first indication that gender-based differences in sleep disruption may exist between children with and without asthma. Males with asthma have shorter sleep duration and females with asthma have significant difficulty initiating sleep, compared to non-asthmatic children. The clinical implications of the presented findings require investigation using a prospective design that includes assessment of lifestyle factors

261 and daytime performance, the characterisation of asthma status and medication use, and the
262 thorough consideration of gender and age effects.

263

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267

268 Conflict of interest: The authors declare that they have no conflict of interest.

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Tables

Table 1: Characteristics of children with and without asthma referred to the sleep clinic for single overnight polysomnography (PSG).

Characteristic	Asthma	Control
n	113	104
Age (years); median [IQR]	7.3 [5.9, 8.8]	6.6 [5.9, 9.1]
Gender (M:F); n	72:41	54:50
Weight (kg); median [IQR]	26 [21.3, 33.3]	25 [20.9, 33.4]
Height (cm); median [IQR]	122.5 [116.1, 134.2]	122.1 [115.0, 132.2]
BMI z-score (SDS); mean (SEM)	0.55 (0.10)	0.56 (0.10)

SDS, standard deviation score.

393 **Table 2: Results from single overnight polysomnography (PSG): Asthmatics vs Controls**

Sleep Indices	Asthma	Control
TST (mins); mean (SEM)	430.9 (4.0)	436.9 (4.2)
Total awake time (mins); mean (SEM)	58.7 (3.4)	60.3 (3.1)
Sleep efficiency (%); mean (SEM)	80.9 (0.7)	82.0 (0.7)
Sleep latency (mins); median [IQR]	35.5 [26.5, 57]*	29.5 [20.5, 44]
Stage 1 (%); median [IQR]	0.5 [0, 1.5]	0.75 [0.1, 2.4]
Stage 2 (%); mean (SEM)	44.0 (0.8)	45.2 (0.9)
Stage 3 (%); mean (SEM)	17.1 (0.6)	16.7 (0.6)
Stage 4 (%); mean (SEM)	19.5 (0.6)	19.0 (0.7)
REM latency (mins); mean (SEM)	163.7 (5.6)	172.8 (6.1)
REM sleep (%); mean (SEM)	20.5 (1.9)	17.4 (0.5)
AI (n/hr); mean (SEM)	4.6 (0.3)	4.9 (0.4)
RDI (n/hr); median [IQR]	0.5 [0.1, 0.9]	0.3 [0, 1.5]
RDI in REM; median [IQR]	0.8 [0, 2.5]	0.9 [0, 3.5]

394 *Significantly different between asthma and control group ($p < 0.05$); TST, total sleep time;

395 REM, rapid eye movement; AI, arousal index; RDI, respiratory disturbance index.

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Table 3: Results from single overnight polysomnography (PSG): Male asthmatics vs controls

Sleep Indices	Male Asthma	Male Control
TST (mins); mean (SEM)	425.90 (5.35)*	441.81 (5.35)
Total awake time (mins); mean (SEM)	63.66 (4.44)	54.33 (2.98)
Sleep efficiency (%); mean (SEM)	79.95 (0.92)*	82.89 (0.84)
Sleep latency (mins); mean (SEM)	40.49 (2.76)	35.95 (2.97)
Stage 1 (%); median [IQR]	0.5 [0, 1.55]	0.7 [0.2, 2.6]
Stage 2 (%); mean (SEM)	43.53 (1.02)	44.82 (1.15)
Stage 3 (%); mean (SEM)	17.24 (0.79)	16.69 (0.88)
Stage 4 (%); mean (SEM)	19.16 (0.82)	18.65 (1.02)
REM latency (mins); mean (SEM)	166.89 (7.08)	165.80 (7.32)
REM sleep (%); mean (SEM)	21.52 (2.76)	17.76 (0.59)
AI (n/hr); mean (SEM)	4.82 (0.39)	5.01 (0.48)
RDI (n/hr); median [IQR]	0.4 [0.1, 0.9]	0.35 [0.1, 1.2]
RDI in REM; median [IQR]	0.7 [0, 2.25]	1.15 [0, 3.20]

*Significantly different between asthma and control group ($p \leq 0.05$); TST, total sleep time;

REM, rapid eye movement; AI, arousal index; RDI, respiratory disturbance index

Table 4: Results from single overnight polysomnography (PSG): Female asthmatics vs controls

	Female Asthma	Female Control
Sleep Indices	(n=41)	(n=50)
TST (mins); mean (SEM)	439.71 (5.67)	425.61 (8.49)
Total awake time (mins); mean (SEM)	49.87 (4.91)*	66.71 (5.43)
Sleep efficiency (%); mean (SEM)	82.54 (1.02)	80.95 (1.07)
Sleep latency (mins); mean (SEM)	46.16 (5.59)*	33.16 (2.69)
Stage 1 (%); median [IQR]	0.5 [0, 1.5]	0.9 [0, 2]
Stage 2 (%); mean (SEM)	44.74 (1.16)	45.50 (1.34)
Stage 3 (%); mean (SEM)	16.92 (1.08)	16.69 (0.94)
Stage 4 (%); mean (SEM)	20.19 (0.83)	19.3 (0.88)
REM latency (mins); mean (SEM)	158.13 (9.24)	180.38 (9.95)
REM sleep (%); mean (SEM)	18.57 (1.76)	17.01 (0.83)
AI (n/hr); mean (SEM)	4.28 (0.50)	4.70 (0.66)
RDI (n/hr); median [IQR]	0.6 [0.1, 0.8]	0.1 [0, 0.5]
RDI in REM; median [IQR]	1.2 [0, 3.2]	0.65 [0, 2.7]

*Significantly different between asthma and control group ($p \leq 0.05$); TST, total sleep time;

REM, rapid eye movement; AI, arousal index; RDI, respiratory disturbance index

Figure Legends

Figure 1. Flow chart of initial studies available between the years 2005-2010 and the main exclusion criteria applied to obtain the final sample size.

Figure 2. Total sleep duration (minutes) in male asthmatics versus male controls, measured using overnight PSG. *Significantly different between asthma and control group ($p<0.05$).

Figure 3. Sleep onset latency (minutes) and total time awake after sleep onset (minutes) in female asthmatics versus female controls, measured using overnight PSG. *Significantly different between asthma and control group ($p<0.05$).