Perinatal antecedents of sleep disturbances in schoolchildren

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Abstract

Study Objectives: Prematurity has been associated with an increased risk for sleep apnea. However, sleep disturbances in children born preterm have not been extensively investigated. Considering that determinants of sleep may originate early in life, the potential impact of prematurity on sleep disturbances later in life could be important. To establish the role of prematurity on sleep disturbances in a cohort of schoolchildren that were born preterm and compare them with healthy controls.

Methods: A cohort of 147 schoolchildren, 45 born at term (≥37 weeks) and 102 very preterm (<32 weeks), was recruited and evaluated at school age (5–9 years). The Pediatric Sleep Questionnaire (PSQ) and the Sleep Disturbance Scale for Children (SDSC) were used to assess sleep disturbances in different domains.

Results: PSQ score was significantly higher in former preterm children (0.26 ± 0.18 vs. 0.18 ± 0.14 in controls; p = 0.004), and SDSC total score was also significantly different among groups (21.7 ± 11.6 vs. 14.1 ± 12.6; p < 0.001). Regression models showed significant mean differences in PSQ score, total SDSC score, and two SDSC subscale scores (i.e. sleep-wake transition disorders, sleep-breathing disorders, and sleep hyperhidrosis) even after adjustment for confounders. Maternal age and type of delivery were not significantly associated with total PSQ scores.

Conclusions: Sleep disturbances may originate early in life since children born preterm exhibit an increased risk for developing long-term sleep problems. These findings may have important implications for management of preterm children and for implementation of early interventions focused on optimizing sleep habits.

Statement of Significance

Prematurity may influence long-term sleep characteristics in children. Early detection of risk factors and sleep habit interventions may help to modulate the detrimental effect of prematurity on sleep characteristics.

Key words: preterm; prematurity; newborn; insomnia; snoring; apnea
Introduction

Insufficient sleep duration, as well as sleep disturbances are associated with several adverse outcomes, including psychiatric disorders [1], poor neurocognitive performance [2], and metabolic and cardiovascular sequelae [3]. In children, sleep disturbances are frequent [2, 4–7], and is of special concern, as it may hamper the normal development of the central nervous system. Despite the rather expansive and consistent evidence on the consequences of poor sleep and sleep problems in children, much less is currently known about the origins of sleep disturbances in childhood.

Considering that factors leading to sleep disturbances may start very early in life, and that this condition may persist or even worsen with time, early identification of the children at risk for developing sleep disturbances would be highly desirable. Among the early nonmodifiable risk factors for sleep problems, prematurity has been associated with a higher prevalence of obstructive sleep apnea (OSA) in children and even in adults born preterm [8–10]. In one of these studies, Tapia et al. demonstrated almost 10% of prevalence of OSA [11]. This is a several fold higher frequency of the disease compared to general pediatric population [12]. Hence, former preterm-born children seem to have an overall higher risk for developing OSA later in life, and have also significantly more daytime symptoms, including sleepiness and snoring [8]. In contrast with the existing evidence associating OSA and perinatal factors such as prematurity, there is still sparse literature on the long-term role of prematurity and birth weight specifically on sleep characteristics later in life, especially in very preterm-born children.

In addition to OSA, there are several other sleep aspects that seem to be influenced by prematurity. Sleep duration, sleep quality, and awakenings during the night seem to be significantly affected by a history of prematurity [13]. Prematurity seems also affect sleep macro- and microarchitecture [14]. The effects of prematurity on sleep characteristics seem to be long-lasting, as some studies on adolescents born prematurely have uncovered significant sleep complaints and disturbances when compared to adolescents born at term [15]. Even in adults who were born preterm, sleep quality [16] and circadian sleep-wake rhythm seems to be affected when compared to adults born at term [17]. Some preterm-born children may have several comorbidities that may lead to an abnormal development of sleep, and in turn, be associated with neurocognitive and behavioral consequences [13]. Reasons that explain why some children born prematurely have persistent sleep problems, while others do not, are still unknown. Plausible mechanisms that may help to understand this association are multiple, and include altered function of the hypothalamic-pituitary-adrenocortical axis [18], early exposure to an extraterine overlooked and noisy environment [19–21], medications, feeding routines, and even change in parental routines and behavioral overprotection [22], all of which may impact the development of the circadian cycle and sleep characteristics. In one of the few studies we found on this topic, smaller body size at birth was associated with poor sleep and with a higher risk for clinically significant sleep disturbances among children born at term [23].

In light of the growing number of preterm deliveries worldwide, the impact of prematurity on sleep merits further exploration. Therefore, and considering the possible long-term impact that prematurity may impose on sleep, we conducted the present study to establish whether prematurity leads to sleep disturbances in children reaching school age.

Methods

Subjects

A cross-sectional study of 147 prepubertal schoolchildren, 45 born at term (≥37 weeks) and 102 very preterm (<32 weeks), was performed. The preterm children were recruited from preterm outpatient clinics in different urban areas from south-east Santiago de Chile, and term children were mostly relatives of the preterm children. The included areas correspond to working-class neighborhoods, have almost 1 million inhabitants, and an average monthly income around 500–1,000 US$ (www.reportescomunales.bcn.cl). Pubertal stage, as assessed by medical examination, was classified according to Tanner; girls with Tanner 1 breasts and boys with Tanner 1 gonads (testes < 4 cc) were considered prepubertal. According to their birth weights (INTERGROWTH21 references), children were classified as: (1) “appropriate for gestational age” (between –2.0 and +2.0 SD scores), (2) “small for gestational age” (lower than –2.0 SDs), and (3) “higher for gestational age” (higher than +2.0 SDs) [24]. Children were included in the study if they met the following inclusion criteria: (1) prepubertal stage of development, as assessed by medical examination and classified according to Tanner (girls with Tanner 1 breasts and boys with Tanner 1 gonads), (2) absence of any current chronic disease like renal, gastrointestinal, neurological, and hepatic conditions, or genetic syndromes, (3) absence of any current chronic treatment like diuretic, antihypertensive, respiratory, corticosteroids, nor psychotropic drugs.

Anthropometrics

All recruited subjects underwent a complete physical examination and were evaluated by pediatric endocrinologists at the Pontificia Universidad Católica de Chile from January 2016 to August 2018. Height was measured using a stadiometer (Health o meter model 402 KL, Illinois) with 0.1-cm precision, and weight was measured using a precision scale (Omron model HBF-510, Japan). Height and body mass index (BMI) are expressed according to WHO references [25]. The protocol was approved by the Ethics Committee of the Faculty of Medicine of the Pontificia Universidad Católica de Chile in accordance with the Helsinki Declaration (approval number 180327001). The parents or legal representatives signed an informed consent form before the children entered the study.

Pediatric Sleep Questionnaire

Parents were asked to complete the Spanish version of the Pediatric Sleep Questionnaire (PSQ) [26]. This questionnaire was validated in its local Spanish version in our center and was used for screening for OSA. Methods used for its application and score calculations are both described in a previous study of our group [27]. In brief, the sleep-related breathing disorders scale of the PSQ was used for the purposes of the current study. Parents were asked to answer 22 questions concerning following symptoms: snoring characteristics (specifically snoring duration, intensity,
frequency), presence of episodes of apnea, mouth breathing, presence of enuresis, excessive daytime sleepiness, headache, weight and height percentile, symptoms of hyperactivity-impulsivity and/or inattention. Answers for each of the items were “yes” = 1, “no” = 0, or “don’t know” = missing. The score was calculated, as recommended, by summing total count of all “yes” answers/total count of all “no” and “yes” answers. A cutoff value of 0.33 was used which would be most effective in identifying pediatric OSA according to previous studies [28, 29].

Sleep Disturbance Scale for Children

The second questionnaire used in the present study was the Sleep Disturbance Scale for Children (SDSC). This scale was developed originally by Bruni et al. and is a widely used 26-item questionnaire [18], with answers that are based on a Likert scale ranging from 1 to 5 points. As previously described, it consists of six subscales: (1) disorders of initiating and maintaining sleep (DIMS), (2) sleep-breathing disorders (SBD), (3) disorders of arousal (DA), (4) sleep-wake transition disorders (SWTD), (5) disorders of excessive somnolence (DOES), and (6) sleep hyperhidrosis (SHY). A cutoff of the SDSC score > 39 was defined as “pathological” based on the original recommendations by Bruni et al. [18]. Sleep duration in hours and minutes was asked additionally to parents in the same questionnaire.

Statistics

Descriptive statistics (mean, SD for normally; and median, min–max for not normally distributed variables) were used to describe general subject characteristics. Comparisons between very preterms and controls were made using t-test or the nonparametric Mann–Whitney U-test, depending on its distribution. Linear regression analyses were then used to explore differences in sleep variables based on prematurity status. Following initial examination in unadjusted models, models were adjusted for child variables, including sex, age, and BMI, as well as mother’s age and delivery type. Natural log transformations were applied to outcomes with strong positive skew. Because some variables were positively skewed, including SDSC total score, SDSC subscores, and PSQ total score, we explored regression models using natural log transformations of these variables in addition to the untransformed variables to ensure our results were robust. The significance pattern for results was the same, so untransformed results were reported here for simplicity of interpretation. Control variables were chosen a priori based on clinical expectation and previous publications [11], as they could be related to the outcomes of interest and possibly account for variability in these outcomes or serve as confounders of the relationships between them and prematurity status (e.g. presence of inclusion, sex, BMI, mother’s age, delivery type). All analyses were done with the statistical software SPSS 20.0 (Statistical Package for the Social Science 20.0 for MAC, Chicago, IL). A p-value of < 0.05 was considered to be statistically significant.

Results

Of the 147 subjects who were initially recruited, 3 were excluded: one had Noonan Syndrome, one had several neurological pathologies, and one was withdrawn from the study by his parents (Figure 1). In total, 144 overall healthy term and very preterm pre-pubertal children were studied, including 73 girls (4.9–8.9 years old) and 71 boys (5.0–8.6 years old). Among those children born at term (n = 45; 24 boys) 44 were appropriate, and 1 low for gestational age; and among the very preterm children (n = 99, 47 boys), 73 were appropriate, 22 small, and 4 low for gestational age. Acute and chronic comorbidities of the included children during the perinatal period are shown in the Supplementary Table. At the time of enrolment, there were no children with any relevant neurologic, respiratory, cardiac, or chronic disease. All children had a normal development and attended school. Children born at term or very preterm showed no differences in gender, age, height (SDS), BMI (percentile), abdominal perimeter at the time of enrollment. As expected, gestational age and birth weight were different (see Table 1). There were 34 (34.3%), and 4 (8.9%) of children with sleep-disordered breathing (SDB) in the preterm, and control groups, respectively (p = 0.002).

PSQ score was significantly higher in former preterm children than in controls (0.26 ± 0.18, vs. 0.18 ± 0.14; p = 0.004). The SDSC total score was also significantly different among groups: 21.7 ± 11.6, versus 14.1 ± 12.6, respectively (p < 0.001). Sixteen (16.3%) former very preterm versus 2 (4.4%) controls had an abnormal SDSC (p = 0.04). There were no significant differences in total sleep duration among the groups. Table 1 provides more details on sleep questionnaire findings.

Regression models showed significant mean differences in PSQ scores even after adjustment for child variables (see Table 2), but may be considered marginally significant when adjusting for mother’s age and delivery type as well. Maternal age and type of delivery were not significantly associated with total PSQ scores. Significant differences based on prematurity status were also identified in SBD, SWTD, SHY, and total SDSC scores, even after adjustment for child and maternal variables (see Table 3).

Discussion

The present study has identified significant differences in the presence of sleep disturbances in pre-pubertal children born...
Several sleep characteristics seem to be affected by prematurity, like sleep structure and efficiency [30]. According to parent-based questionnaire studies, children born preterm seem to have a shorter sleep duration, as well as more irregular sleep schedules than those born at term [31]. In addition, studies like that by Stangenes et al. showed that the history of prematurity seems to lead to longer sleep-onset latency, increased night waking, and prolonged sleep duration [32]. Effects of prematurity on sleep quality seem to last long, even affecting adolescents and young adults. In an actigraphy-based study on 16- to 19-year-old adolescents, Hibbs et al. showed that those subjects with a history of prematurity demonstrated significantly earlier sleep initiation, wake times, and sleep midpoints than those born at term [15].

The present findings confirm previous reports concerning the higher frequency of SDB in children born very prematurely. Indeed, SDB scores were significantly higher in children born preterm compared to controls. As mentioned earlier, Tapia et al. showed in a group of 197 children that OSA was very frequently present, and that it was associated with a history of chorioamnionitis and multiple gestation in ex-preterms children [11]. In that study, almost 10% of the former preterms met polysomnographic criteria for OSA, and almost 2.5 times more (i.e. 26%) clinical criteria for SDB based on polysomnography or history of tonsillectomy/adenoidectomy [11]. Furthermore, in a recent study, we have shown that a history of preterm birth operates as a major risk factor for SDB in young symptomatic children younger than 2 years referred for an overnight sleep study [10]. In line with those results, we found a higher frequency of SDB in preterm children enrolled in this study. Children previously born prematurely showed almost 8.5 times higher frequency of SDB symptoms compared to controls. The present cohort was somewhat younger than the ex-preterms enrolled in Tapia et al.’s study (6.5 vs. 9.5 years, respectively). Possible mechanisms for the higher prevalence of SDB in preterms are not yet fully delineated, but could include pharyngeal hypotonia, potential differences in upper airway length growth kinetics [33], increased adenotonsillar growth [11], and altered function of the hypothalamic-pituitary-adrenocortical axis [18], the latter also potentially affecting. In light that chorioamnionitis emerged as a risk factor for future OSA, one theory posited that perinatal exposure to inflammation may lead later to an increased growth of tonsillar and adenoidal tissues [11]. In a study by Guillemainault et al. it was shown how orofacial growth and pharyngeal tone may be significantly affected by prematurity, and therefore be a risk factor for OSA [34]. In that study, children with a history of prematurity exhibit mouth breathing, and a narrow palatal conformation at the age of 4 years [34]. As SDB has been associated with several neurocognitive consequences in children [35–38], including hyperactivity [39, 40], inattentiveness [41], poor school performance [35], and daytime somnolence [42] identifying formerly preterm-born children at risk of SDB may be particularly important.

The present findings add to the extant literature by showing that in addition to a higher prevalence of SDB, preterm-born schoolchildren show significantly higher prevalence of sleep disturbances compared to their peers. In addition, in the present study we included specifically very preterm-born children, i.e. <32 weeks gestational age at birth. In children born at term, previous studies have shown a possible role of perinatal factors,
particularly birth weight, on sleep disturbances and poor sleep efficiency [23]. Small birth weight was postulated as a marker of disturbances in the fetal environment; hence, its relationship with an abnormal sleep could be quite plausible as it may affect several hormonal and neurologic domains. In an actigraphic study on 99 formerly preterm borns, Schwichtenberg et al. showed that at 2 years of age, preterms that had a more regular 24-hour circadian cycle showed better neurocognitive results, and fewer medical visits at 6 years of age [43]. We hypothesize that sleep hygiene and routine may help to attenuate the effects of prematurity on sleep and in turn, with neurocognitive consequences.

We found significant differences in SDSC’s total scores, and specifically in the sleep-wake transition disorders, and sleep hyperhidrosis subscale. These findings agree with the aforementioned studies concerning children born at term. In one of these studies, a cohort of 8-year-old children born at term showed significantly increased risk (1.4-fold) for the presence of disorders of initiating and maintaining sleep according to SDSC questionnaire [23]. In the present study, even after adjusting for several child and maternal variables, total SDSC scores and two subscale scores remained significantly associated with prematurity. Interestingly, the DIMS score showed a significant difference in the group analysis. However, after the regression, prematurity was not a significant factor associated with this particular score. This may have several reasons; we speculate that probably the adjustment by age may have led to this result. However, maternal age and type of delivery were also factors that modified the association of prematurity and PSQ score.

Interestingly, there were no significant differences found in total sleep duration among the two groups. One previous study showed that children born preterm were more likely to exhibit reduced total sleep time [31]. However, no comparisons with children born at term were included in that study. Cultural perceptions of sleep duration, and the approach to quantify sleep duration may be potential explanations for these differences. Despite the presence of SDB, children born preterm may develop several other sleep disturbances later in life. Previous studies have shown an increased risk for developing periodic leg movements in children with a history of prematurity [44].

The present study has some limitations to acknowledge. First, there was a relatively small number of subjects included. However, the population of very low birth weight and extremely premature infants is somehow difficult to follow like in the present study, and therefore to include in study these subjects at school age. On the other hand, we did not measure sleep duration using actigraphy, and we did not conduct overnight polysomnography to evaluate SDB. Notwithstanding, the use of two widely used, validated, and clinically available questionnaires (i.e. PSQ and SDSC) demonstrated significant differences in children born preterm compared to controls. Therefore, we postulate that use of these simple tools may help clinicians to assess sleep problems in children born preterm and promote exploration of such positive screening to achieve more definitive diagnoses using objective approaches. Finally, we are keenly aware that multiple factors may influence sleep in children. In this study, we aimed to control for both social and health factors by including children from the same socioeconomic environments and who were deemed as being healthy after a thorough medical examination. However, the impact on sleep disturbances by prematurity could also be determined by exposures to different extraterine environments such as light, noise, and nursing in a neonatal intensive care unit, and the effects of such exposures remain unknown. Parental concern on sleep and potential overprotection of these children may be also factors that could impact normal sleep development and perpetuate altered sleep patterns well into late childhood.

Conclusions
This study suggests that sleep disturbances may be associated with a history of prematurity, as children born preterm exhibit an increased risk for developing long-term sleep problems. These results may have important implications for the clinical management of sleep in very preterm children and for implementation of early educational initiatives aimed at providing optimization of sleep habits very early in life, particularly among premature infants.

Supplementary Material
Supplementary material is available at SLEEP online.

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