Sleep Medicine 63 (2019) 137–141

Contents lists available at ScienceDirect

Sleep Medicine

journal homepage: www.elsevier.com/locate/sleep

Original Article

Sleep disorders in low-risk preschool very preterm children

Domenico M. Romeo [a, *], Giuseppina Leo [a], Leonardo Lapenta [a], Daniela Leone [a], Ida Turrini [a], Claudia Brogna [a], Francesca Gallini [b], Francesco Cota [b], Giovanni Vento [b], Eugenio Mercuri [a]

[a] Pediatric Neurology Unit, Fondazione Policlinico Universitario A. Gemelli, IRCCS, Rome, Italy
[b] Neonatal Intensive Care Unit, Fondazione Policlinico Universitario A. Gemelli, IRCCS, Rome, Italy

ARTICLE INFO

Article history:
Received 27 October 2018
Received in revised form
17 April 2019
Accepted 19 April 2019
Available online 27 May 2019

Keywords:
Preterm children
Sleep disorders
Preschool age
Control group

ABSTRACT

Objectives: (i) to assess the presence of sleep disorders in a population of very preterm children (ie, with a gestational age [GA] $\leq$ 31 weeks) of preschool age with no history of neurological disabilities using a questionnaire standardized for this age group and (ii) to identify possible differences in a control group of term-born children.
Methods: A total of 146 low-risk preterm children (mean gestational age 28 weeks; range: 25–30), were assessed at a preschool age (mean age 3.8 years; range 3–6 years) using the sleep disturbance scale for children (SDSC) to assess sleep problems. As controls, 146 typically developing children matched for age and gender were also evaluated using the SDSC.
Results: An abnormal total sleep score (>70) was found in 7% of preterm children, while 21% had an abnormal score on at least one SDSC factor. No significant differences were reported according to the age of assessment or gestational age. The preterm group reported higher significant median scores on SDSC total, sleep-disordered breathing, sleep hyperhidrosis and difficulty in initiating and maintaining sleep factors.
Conclusions: Low-risk very preterm children showed only a slightly higher incidence of sleep disorders than term-born peers at preschool age, with higher scores in specific sleep factors. These data could be useful to clinicians for screening those preterm children at risk for sleep disorders who need a more detailed assessment for a conclusive diagnosis and treatment.

1. Introduction

Sleep disorders are widespread in typically developing children with a prevalence ranging from 5% to 40% [1–5]. While there are several studies assessing sleep in children with developmental disabilities [1,6–13], fewer have been reported in children born prematurely, especially at a younger age [14–23]. The findings regarding the incidence and patterns of sleep problems in this population are controversial and the results are discordant, mainly due to different inclusion criteria regarding gestational age, age of assessment, or presence of brain lesions [14–23]. The majority of the studies of preterm children assessed at school-age both at low and high risk, showed that the prevalence of sleep problems increased with increasing neurodevelopmental disabilities and decreasing gestational age (GA) [17–20,22]. The primary sleep disorders included nocturnal and early morning awakening, earlier bed and wake times, and disturbed sleep usually due to sleep-related breathing disorders [19–23]. However, during childhood, preterm children reported more sleep problems than controls even in the absence of neurodevelopmental disabilities [16,18,21]. These included restlessness and breathing problems during the night, more problems in falling asleep, waking up frequently during the night, and waking up early in the morning. The expected differences between preterm and full-term children are suggested by factors associated with impaired neurodevelopment and functional connectivity of the brain due to prematurity per se, and to a higher incidence in preterms of sleep-disordered breathing [20–22], clinical treatments or behavioral factors [19] or to altered micro- and macro-sleep architecture indicative of reduced sleep quantity and quality [14,15,21–23]. A recent study also showed differences

* Corresponding author. Pediatric Neurology Unit, Fondazione Policlinico Universitario A. Gemelli, IRCCS, Largo Gemelli, 8, 00168, Rome, Italy. Fax: +39 0630154363.
E-mail address: domenicomarco.romeo@policlinicogemelli.it (D.M. Romeo).

https://doi.org/10.1016/j.sleep.2019.04.016
1389-9457/

between very preterm (ie, with a GA ≤ 31 weeks) and full-term children regarding sleep anxiety (more frequent in preterm children), sleep duration problems (less frequent in preterm children) and earlier sleep onset times on polysomnography (PSG) in preterm children compared to full-term children [24].

In contrast, other authors suggested a better sleep quality in preterm children as they had fewer and shorter night awakenings than the term-born children, with significantly fewer arousals on actigraphy and were reported to be more rested and alert in the morning and less sleepy, especially in adolescents [15].

The association between preterm birth and sleep disorders is therefore still not well understood. It has mainly been investigated in school age and adolescent children; only a few studies assessed sleep disorders in low-risk preterm preschool aged children to reduce possible bias linked to brain damage or neurodevelopmental disabilities [16,21]. Another limitation in some published studies is that the data was collected using a sleep questionnaire not standardized for children. Consequently, the goals of the present study are (i) to assess the presence of sleep disorders in a population of very preterm children at preschool age, with no history of brain damage or neurodevelopmental disabilities, using a questionnaire standardized for this age group and (ii) to identify possible differences from a control group of term-born children.

2. Methods

2.1. Study population

The children included in the present study are part of a prospective project on preterm children regularly followed at the Pediatric Neurology Unit and the Neonatal Intensive Care Unit of the Fondazione Policlinico Universitario A. Gemelli of Rome, between January 2014 and December 2016. We only included very preterm children with a GA ≤31 weeks, a gestation with no history of major prenatal, perinatal or postnatal medical complications, and who were examined between the age of three and six years. The exclusion criteria were the presence of being small-for-gestational-age (weight below the 10th percentile), significant cerebral lesions observed at US scans or congenital malformations, severe postnatal infectious diseases, metabolic complications, cerebral palsy, and epilepsy.

2.2. Sleep assessment

Sleep disturbances were assessed with the Sleep Disturbance Scale for Children (SDSC) validated for preschool children [5]. The SDSC investigates the occurrence of sleep disorders during the previous six months and contains 26 items with Likert scale values of 1–5 (higher numerical values reflect a higher clinical severity of symptoms). The sum of scores provide a total sleep score with a possible range from 26 to 130; a T-score of more than 70 (>95th percentile) was regarded as abnormal, and a score of 70 or less as normal.

This questionnaire analyzes six sleep disturbance factors representing the most common areas of sleep disorders in preschool children: parasomnias (PAR) related to arousal disorders (sleep-walking, sleep terrors), nightmares, and sleep-wake transition disorders; difficulty in initiating and maintaining sleep factor (DIMS) related to sleep duration and latency, problems in falling asleep and night awakenings; sleep-disordered breathing (SDB); disorders of excessive somnolence (DOES) related to daytime somnolence and sleep attacks; sleep hyperhidrosis (SHY) referred to as falling asleep as well as night sweating and nocturnal hyperkinesia; and nonrestorative sleep (NRS) concerning items like "the child is unusually difficult to wake up in the morning" or "the child awakes in the morning feeling tired." This questionnaire was distributed to the primary caregiver of the children during the routine neurological assessment in our units.

The SDSC was further distributed to the primary caregivers of a group of children recruited via nurseries and considered as the control group, composed of children mostly from families with a working and middle-class background, randomly selected from four public schools of Rome, two in the city center, one on the Southern and one on the Northern outskirts of the city. Questionnaires were filled out by the mothers during school hours under the supervision of the researchers that distributed the questionnaires (authors: CB, DL); no missing values were reported. All children in the control group attended regular classes in a mainstream nursery school; those with obvious or reported signs of mental, developmental or physical disabilities, according to school medical records or receiving on-going prescription medication (antiepileptic drugs, antihistaminic drugs, benzodiazepine, melatonin) were excluded.

The study protocol was approved by the Ethics Committee of our Institution, and informed consent was obtained from parents.

2.3. Statistical analysis

Data were presented as mean values and range for continuous variables normally distributed and as count and percentages for categorical variables. The comparison between preterm children and the control group for SDSC total and the six factors scores was performed using the non-parametric Mann–Whitney U test; comparisons for the gender and gestational age were performed using the Fisher's exact test.

A correlation analysis was done between the age of sleep assessment, birth-weight, days of hospitalization and SDSC scores, using the Spearman Rank correlation. The association between caffeine or xanthine use and sleep disorders was assessed comparing each of the six factors scores and the exposure to the drugs, using the Mann–Whitney U-test. A 2-tailed value of $p < 0.05$ was considered significant.

3. Results

During the study period 146 preterm children (*77 M*, *69 F*), with a mean gestational age of 28 weeks (range: 25–30) and a mean birth-weight of 1215 g (range: 510–1750) fulfilled the inclusion criteria. Table 1 reports the demographic characteristic of this population. All parents gave consent, and each mother filled out the questionnaire in all cases. The mean age was 3.8 years (range 3–6 years).

The questionnaire was also completed by parents of 146 typically developing children (*77 M*, *69 F*) with a median age of 3.8 years (range 3–6 years). This control group had the same age and gender distribution of the preterm group ($P > 0.05$).

A reliability analysis was performed on item scores using Cronbach's alpha; it was very high both for the preterm group

Table 1
Baseline characteristic and neonatal course of preterm population.

Gestational Age, weeks, median (range)	28 (25–30)
Birth weight, grams, median (range)	1215 (510–1750)
Gender, male, n (%)	77 (53)
Days of hospitalization, median (range)	61 (15–206)
Bronchopulmonary disease, n (%)	30 (21)
Use of caffeine, n (%)	136 (93)
Use of Xanthine, n (%)	25 (24)

(0.74) and for the control group (0.83) indicating a good level of internal consistency among the 26 items of the SDSC questionnaire.

3.1. SDSC results in the preterm population

An abnormal total sleep score (>70) was found in 10/146 children born prematurely (7%); an abnormal score on at least one SDSC factor was found in 31 children (21%): parasomnias 3%, difficulty in initiating and maintaining sleep 3%, sleep-disordered breathing 7%, disorders of excessive somnolence 5%, sleep hyperhidrosis 8%, and nonrestorative sleep 3% respectively. No significant correlation ($P > 0.05$) was reported between the age of assessment and the SDSC scores (total and sleep factors).

On intergroup comparison, among the four GA, no significant differences ($P > 0.05$) were reported for SDSC total or factor scores (Table 2).

No relation was been found between SDSC scores and any neonatal outcomes (ie, Bronchopulmonary disease, use of caffeine or xanthines, days of hospitalization, birth-weight).

3.2. SDSC results in term born population

An abnormal total sleep score (>70) was found in 4/146 term-born children (3%); a total of seven children (4%) had an abnormal score on at least one SDSC factor: parasomnias 1%, difficulty in initiating and maintaining sleep 3%, sleep-disordered breathing 0%, disorders of excessive somnolence 0%, sleep hyperhidrosis 0%, nonrestorative sleep 0% respectively.

3.3. Comparison of sleep disorders between preterm and control group

Preterm children had higher significant median scores than controls on SDSC total (51.3 vs 49.2, $p < 0.01$), and difficulty in initiating and maintaining sleep (51.1 vs 49.3, $p < 0.05$), sleep-disordered breathing (49.6 vs 47.6, $p < 0.05$), sleep hyperhidrosis (52.2 vs 49.6, $p < 0.05$), whereas no statistical differences were reported on parasomnias (51.3 vs. 51.0), disorders of excessive somnolence (50.6 vs 50.5), and nonrestorative sleep (49.8 vs 50.4) (Tables 2 and 3). SDSC scores in preterm and control group are reported in Tables 2 and 3

4. Discussion

The main goal of the present study was to assess sleep disorders in low-risk preschool preterm children using a questionnaire specifically designed for this age group. The SDSC represents one of the most frequently used questionnaires to assess sleep in both typically developing children and in several other cohorts with different neurodevelopmental disabilities [5–7,9–13,16]. However, only a few studies used the SDSC in preschool children [5,9,13,16] and only one in preschool preterm children [16].

Our results reported that an abnormal total sleep score was found in 7% of the preterm population. As reported in the literature the incidence of global sleep disorders in preterm children is only slightly higher than those of term-born infants (5% vs. 7%), with specific higher scores only for sleep hyperhidrosis and sleep-disordered breathing. When compared to our controls, preterm children showed significantly higher median scores not only on SDSC total, sleep-disordered breathing and sleep hyperhidrosis but also on the difficulty in initiating and maintaining sleep, with an overall 21% of children showing at least one SDSC factor.

The presence of sleep-disordered breathing has been previously reported in preterm children at school-age; our results seem to confirm this data at younger ages. This has been related to different factors such as mild maternal pre-eclampsia, bronchopulmonary dysplasia, xanthine use and intubation in the delivery room, palatal deformation secondary to intubation, hypotonia, and abnormalities in ventilatory control [15,22,23,25] or to changes in peripheral nervous system sensitivity and responses due to prematurity per se [23,25].

We also found a high incidence of sleep hyperhidrosis which had not been previously reported in the preterm population. Localized and generalized forms of hyperhidrosis exist at this age, due to underlying medical conditions or medications or idiopathic [26]. Moreover, some studies reported hyperhidrosis in children with cerebral palsy [6], and neurofibromatosis [7] indicating a poor sleep quality related to medical conditions involving hypothalamus and cerebral cortex, as well as drugs and medications that could cause secondary hyperhidrosis [27]. In our cohort, significant cerebral lesions or congenital malformations were excluded; there are no other obvious causes for hyperhidrosis. Based on a recent report [8] showing impaired autonomic control in preterm infants with possible risks of cardiovascular dysfunction later in life, one may hypothesize an autonomic dysregulation of the neural control of the sweat glands leads to increased sweating.

The presence of difficulty in initiating and maintaining sleep in preterm children has been previously reported in the literature, and it is probably related to early neonatal stressors [27,28]. Prematurity may have a life-long impact on sleep due to adverse *in utero* exposures or early neonatal stresses, both of which may influence the development of sleep-wake and circadian control centers [15]. An abnormal environment, frequently including non-ideal nutrition, stress, and hypoxia, as well as exposure to abnormal light conditions (eg, the constant light environment of neonatal intensive care units) could further influence maturation of the suprachiasmatic nucleus [19]; in addition, melatonin rhythmicity may develop more slowly in premature than term infants [29].

Our results are not entirely in agreement with those of Caravale et al. [16], who also explored the sleep patterns in preschool preterm children using the SDSC and who reported more medically

Table 2
SDSC Total and Factor scores in preterm children according to gestational age.

Gestational Age	Total	PAR	DIMS	SBD	DOES	SHY	NRS
<27 (n = 24)	48,2 ± 8,1	51,2 ± 8,7	48,8 ± 7,8	46,8 ± 5,4	49,5 ± 9,8	51,6 ± 10,7	47,1 ± 6,4
27 (n = 26)	49,2 ± 6,5	49,6 ± 6,0	50,0 ± 7,1	46,0 ± 7,1	48,3 ± 7,2	51,2 ± 11,3	49,2 ± 8,7
28 (n = 29)	51,2 ± 10,1	51,0 ± 9,1	51,3 ± 10,0	51,3 ± 14,4	47,6 ± 6,7	50,7 ± 11,7	48,2 ± 5,7
29 (n = 30)	51,6 ± 9,5	49,6 ± 8,2	51,0 ± 8,9	48,5 ± 7,8	50,9 ± 8,0	50,7 ± 7,8	49,0 ± 7,1
30 (n = 37)	57,6 ± 11,6	54,6 ± 9,3	54,4 ± 8,6	55,8 ± 14,1	55,8 ± 16,7	55,5 ± 15,2	54,0 ± 12,3
Preterm group	51,3 ± 10,1*	51,3 ± 8,5	51,1 ± 8,7*	49,6 ± 11,4*	50,6 ± 11,2	52,2 ± 11,8*	49,8 ± 9,0
Control group	49,2 ± 9,1	51,0 ± 8,7	49,3 ± 7,5	47,6 ± 7,2	50,5 ± 10,1	49,6 ± 8,8	50,4 ± 9,4

PAR: Parasomnias; DIMS: difficulty in initiating and maintaining sleep; SDB: sleep disordered breathing; DOES: disorders of excessive somnolence; SHY: sleep hyperhidrosis; NRS: non-restorative sleep.
*P < 0.05 Control group Vs preterm group.

Table 3
SDSC scores in preterm and control groups.

	SDSC total	PAR	DIMS	SDB	DOES	SHY	NRS
	>70	>70	>70	>70	>70	>70	>70
Preterm group (n = 146)	10 (7%)	4 (3%)	4 (3%)	10 (7%)	7 (5%)	12 (8%)	4 (3%)
Control group (n = 146)	4 (3%)	1 (1%)	4 (3%)	0	0	0	0

PAR: parasomnias; DIMS: difficulty in initiating and maintaining sleep factor; SDB: sleep disordered breathing; DOES: disorders of excessive somnolence; SHY: sleep hyperhidrosis; NRS: nonrestorative sleep.

related sleep problems in the preterm group as nocturnal movement, restlessness during the night and breathing problems. Nevertheless, they reported no differences between a preterm and term-born population on sleep patterns as bedtime, rise time and nocturnal/daytime sleep durations [16]. However, a real comparison between our study and that of Caravale et al., is not possible, as these authors included preterm children at younger ages (two years) and used a revised version of the SDSC adapted for toddlers with different sleep disturbance factors.

We did not find a significant association between sleep disorders and gestational age at birth; this is in agreement with previous studies in the literature, reporting an increase of sleep problems with decreasing gestational age in preterm infants in the presence of neurodevelopmental disabilities [17,18]. The homogeneous selection of our population consisting only of low-risk preterm infants excluded preterm children who could present with severe sleep problems related to the presence of brain lesions and associated neurodevelopmental disabilities especially at lower gestational ages. Furthermore, in our population, no clear relationship has been found between SDCS scores and other neonatal outcomes, such as the use of caffeine/xanthines or the presence of bronchopulmonary disease or the days of hospitalization.

Study limitations must be acknowledged. As parental reports of children's sleep alone are used, a more structured in-depth interview or objective assessment may have provided better information on sleep disorders and allowed a more accurate diagnosis. Parental reports of children's sleep could be influenced by factors such as the parent's expectations of their children's sleep or even their own sleep problems [30]. On the other hand, parental information is an effective method for the detection of sleep disturbances [31]. In addition, the SDSC has been validated in children from three to 16 years, and it was used in the last 20 years in several studies. Furthermore, it appears to be useful in evaluating sleep disturbances in different population of infants. Recently it showed a good relationship with more objective measures like actigraphy [10,32].

Another limitation of our study was the lack of information regarding the parents' socio-economic status/educational level which could be a factor influencing the sleep environment or sleep hygiene, and regarding factors or complications like maternal smoking, pre-eclampsia, or gestational diabetes, which may potentially affect the development of sleep/wake cycles *in utero*.

In conclusion, our results confirm that low-risk preterm children show only a slightly higher incidence of sleep disorders than term-born peers at preschool age, with specific higher scores in SBD, DIMS, and SHY. Further studies may help to establish a possible association with perinatal or neonatal risk factors (eg, children's BMI and breastfeeding) that have been found to have a potential effect on the mechanisms underlying sleep disorders [17].

As sleep disorders in childhood may cause behavioral problems, poor growth and reduced quality of life [6], clinicians involved in a follow-up program for prematurity should be aware of this risk and facilitate early screening using questionnaires for parents to identify the children needing a more detailed assessment for a conclusive diagnosis and treatment.

Conflict of interest

The authors declare that they have no conflict of interest.

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: https://doi.org/10.1016/j.sleep.2019.04.016.

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