Article

Not peer-reviewed version

Restless Sleep Disorder and Periodic Limb Movements During Sleep in Children with a History of Prematurity

Lourdes M. DelRosso *, Hovig Artinian, Maria P. Mogavero, Oliviero Bruni, Raffaele Ferri

Posted Date: 28 August 2023

doi: 10.20944/preprints202308.1849.v1

Keywords: restless sleep disorder; periodic leg movements during sleep; prematurity; iron deficiency

Article

Restless Sleep Disorder and Periodic Limb Movements during Sleep in Children with a History of Prematurity

Lourdes M. DelRosso [1,2,*], Hovig Artinian [1], Maria P. Mogavero [3,4], Oliviero Bruni [5] and Raffaele Ferri [6]

[1] University of California San Francisco, Fresno, CA, USA; lourdesdelrosso@me.com
[2] Seattle Childrens Hospital, Seattle, WA, USA
[3] Vita-Salute San Raffaele University, Milan, Italy; paola_mogavero@libero.it
[4] Sleep Disorders Center, Division of Neuroscience, San Raffaele Scientific Institute, Milan, Italy
[5] Department of Developmental and Social Psychology, Sapienza University, Rome, Italy; oliviero.bruni@uniroma1.it
[6] Sleep Research Centre, Department of Neurology IC, Oasi Research Institute - IRCCS, Troina, Italy; rferri@oasi.en.it
* Correspondence: lourdesdelrosso@me.com

Abstract: Children with history of prematurity are at higher risk of complications, comorbidities and iron deficiency. In this study we assess the prevalence of restless sleep disorder, as well as that of periodic leg movements during sleep (PLMS) in these children. Retrospective chart review of sleep studies in children aged 1-18 years, with history of prematurity. Only diagnostic studies in children without diagnosis of a genetic syndrome or airway surgery or tracheostomy were included. Three groups were compared, children with PLMS index>5, children with restless sleep disorder (RSD), and children with neither elevated PLMS index nor RSD. During the study, 2,577 sleep studies were conducted. Ninety-two studies fit our criteria and were included in analysis. Median birth age was 31 weeks, interquartile range (IQR) 27-34 weeks. Thirty-two (34.8%) children were referred for restless sleep and 55 (59.8%) for snoring; after polysomnography 18% were found to have PLMS index >5/hour, 14% fit the criteria for RSD. There were no statistically significant differences in polysomnographic parameters between the children with RSD, PLMS and the remaining group, except for lower obstructive apnea/hypopnea index (Kruskal-Wallis ANOVA 8.621, p=0.0135) in the RSD group (median 0.7, IQR 0.3-0.9) than in the PLMS (median 1.7, IQR 0.7-3.5), or than in the nonRSD/nonPLMS group (median 2.0, IQR 0.8-4.5). There was elevated frequency of RSD and elevated PLMS in children with history of prematurity that might be linked to the increased risk of iron deficiency in premature infants. These new results add new knowledge on the prevalence of RSD in these children.

Keywords: restless sleep disorder; periodic leg movements during sleep; prematurity; iron deficiency

1. Introduction

The World Health Organization defines preterm birth when it occurs earlier than at 37 weeks gestational age or less than 259 days [1]. Approximately 5 to 18% of births are premature, from which extremely preterm is defined as birth at less than 28 weeks, very preterm is birth between 28 to 32 weeks, moderate preterm is birth at 32 to 33 weeks, and birth at 34-36 weeks gestational age is considered late pre-term.

Preterm birth has been associated with a higher risk of complications during birth and perinatal comorbidities, including pulmonary consequences due to alveoli underdevelopment, cerebral palsy, and seizures, among others. Despite improvements in management of perinatal complications, long-term consequences of prematurity are still unknown [2]. Studies have shown that adults with history of prematurity have a higher vulnerability to kidney disease, asthma, neurodevelopmental disorders, and endocrine disorders [3]. While neonatal mortality and morbidity has improved in infants born

 doi:10.20944/preprints202308.1849.v1

prematurely, there has been little improvement in the incidence of neurodevelopmental disability [4]. Male infants and those born extremely premature are at highest risk for adverse neurodevelopmental outcomes [5]. Children born prematurely also demonstrate decreased grey matter, white matter, basal ganglia, and cerebellar volumes; to the extent that data is available, infants born premature exhibit differences in electroencephalographic spectral values, in total sleep time and in arousal thresholds as compared to infants born full term [6].

Only a few studies have looked at sleep consequences in children or adults with a previous history of prematurity. In a cohort study of adults that were preterm-born and controls, the risks of chronic snoring was 2.2 times higher in the very-low-birth-weight premature group compared to the control group [7]. A large national cohort in Sweden, demonstrated also an increased risk of sleep disordered breathing in adults with a history of prematurity, with those born extremely preterm having a higher adjusted hazard ratio 2.63 (CI, 2.41-2.87) [8]. Our group has previously demonstrated an increased periodic limb movements during sleep (PLMS) index in infants with prematurity [9].
In this new investigation, we examined diagnostic studies from older children with history of prematurity who underwent polysomnography. We hypothesized that older children with history of prematurity might have increased motor activity during sleep, as reflected by PLMS index and large muscle group movement (LMM) index [10], characterizing the newly identified restless sleep disorder (RSD) [11,12].

2. Materials and Methods

2.1. Subjects

This study consisted of a retrospective chart review of sleep studies in children aged 1-18 years. Selection criteria included diagnostic studies performed from July 2020 to July 2021 at Seattle Children's Hospital, Seattle, WA, in children with history of prematurity documented in the chart. Exclusion criteria: children with genetic syndromes, studies other than diagnostic (titration, split, ventilator), children with tracheostomy, infants younger than 12 months. The study was approved by the local ethics committee.

2.2. Polysomnography

Polysomnography (PSG) was performed according to the American Academy of Sleep Medicine (AASM) criteria [13] and data were recorded using the Sandman Elite Natus system. Parameters recorded included: electroencephalogram (EEG: two frontal, two central, and two occipital channels, referred to the contralateral mastoid); electro-oculogram, electromyogram (EMG) of the submentalis muscle, EMG of the right and left tibialis anterior muscles, respiratory signals, effort signals for thorax and abdomen, oximetry, capnography, a single-lead electrocardiogram, video and audio recording. Calibrations were performed per routine standard by technicians. Sleep stages and PLMS were scored by a certified sleep technologist and board-certified sleep physician according to the AASM criteria [13]. Large muscle movement incex (LMM) was calculated per current criteria [10].

2.3. Statistical Analysis

Descriptive statistics were carried out using the commercially available software STATISTICA v.6, StatSoft Inc., Tulsa. Because of the non-normal distribution of data, nonparametric descriptives were used. The chi-square test was used to compare frequencies. In order to test an eventual effect of gestational age at birth on PLMS index or LMM index, we also carried out two multiple regression analyses by taking into consideration them, in turn, as dependent variables. A set of independent predictors that was considered to be able to influence these parameters as well, such as gestational age at birth, age at PSG, sleep efficiency, arousal index, oAHI, and LMM index if the dependent variable was PLMS index, and vice versa. Following the recommendations by Cohen [14], correlation coefficients of 0.1 were considered to be small, 0.3 medium, and 0.5 or above large. Statistical significance was set at $p<0.05$.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 28 August 2023 doi:10.20944/preprints202308.1849.v1

3. Results

During the study, 2,577 sleep studies were conducted, 162 were in children with documented history of prematurity (6%). The following were excluded: 25 were split or titration studies (14%), 29 children had syndromes (Down, Prader Willi, Wiedmann Beckmann, Achondroplasia), 4 tracheostomy studies, 6 in infants aged <12 months and 6 were post airway intervention.

Ninety-two diagnostic studies were included in the analysis. The median gestational age at birth was 31 weeks, interquartile range (IQR) 27-34 weeks.

Thirty-two (34.8%) children were referred for restless sleep and 55 (59.8%) for snoring, the remaining five were referred for insomnia. Sixteen (17.4%, two girls and 14 boys) had PLMS index >5/hour (median 8.7, interquartile range 6.6-13.5), 13 (14.1%, six girls and seven boys) had LMM index >5/hour (median 6.2, interquartile range 5.5-7.5); the remaining 63 children included 22 girls and 41 boys (sex distribution among groups: chi-square 4.18, NS). Altogether, children with LMM index >5/hour and those with PLMS index >5/hour had restless sleep as an indication for their sleep study in 72.4% of cases (21 out of 29) while snoring was the prevalent indication in the nonRSD/nonPLMS group (48 out of 63, chi-square 76.2, $p < 0.000001$). Details on the demographics and gestational age at birth of patients, subdivided by sex, are reported in Table 1.

Table 1. Age and gestational age at birth of the subjects enrolled in this study.

		age, years		gestational age, months	
	number	median	IQR	median	IQR
total	92	4.0	2.0-6.0	31.0	27.0-34.0
females	30	4.5	2.0-8.0	31.5	27.0-34.0
males	62	3.0	2.0-6.0	30.5	26.0-34.0

IQR = interquartile range.

Table 2 shows the descriptive statistics of PSG parameters obtained in our group of premature-born children.

Table 2. Descriptive statistics of polysomnographic parameters in premature-born children.

	Median	Minimum	Maximum	Lower Quartile	Upper Quartile
Total sleep time, min	453.5	182.0	579.0	423.0	493.5
Sleep latency, min	25.5	0.0	159.0	11.0	45.0
Sleep efficiency, %	87.0	41.0	98.0	82.0	92.0
Sleep stage N1, %	7.0	0.9	29.0	3.0	11.0
Sleep stage N2, %	40.5	14.0	70.0	33.0	48.0
Sleep stage N3, %	31.0	14.0	57.0	25.0	39.5
Sleep stage R, %	19.0	0.0	29.0	14.5	23.0
Arousal index, n/hour	11.0	3.9	35.0	8.0	13.5
Obstructive AHI, n/hour	1.6	0.0	21.0	0.7	3.7
Central AHI, n/hour	0.9	0.0	6.5	0.3	1.9
PLMS index, n/hour	1.4	0.0	30.7	0.0	3.3
LMM index, n/hour	3.6	0.0	14.5	1.7	6.0
Total sleep time, min	453.5	182.0	579.0	423.0	493.5

PLMS = periodic leg movements during sleep; AHI = apnea/hypopnea index; LMM = large muscle group movements.

The results of the multiple regression analysis between PLMS index or LMM index (used as dependent variables) and selected PSG parameters (used as independent factors) in premature-born children are reported in Table 3.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 28 August 2023 doi:10.20944/preprints202308.1849.v1

Table 3. Results of the multiple regression analysis between PLMS index or LMM index (dependent variables) and selected PSG parameters (independent factors) in premature-born children.

	PLMS index				LMM index		
	partial correlation	R^2	p		partial correlation	R^2	p
Age	0.026	0.182	0.902	Age	0.254	0.127	0.221
GA at birth	0.192	0.040	0.357	GA at birth	-0.067	0.072	0.749
Sleep efficiency	-0.217	0.345	0.297	Sleep efficiency	0.019	0.376	0.928
Arousal index	0.054	0.391	0.798	Arousal index	0.321	0.323	0.118
oAHI	-0.404	0.280	0.045	oAHI	-0.397	0.284	0.049
LMM index	-0.143	0.250	0.495	PLMS index	-0.143	0.217	0.495

GA = gestational age; oAHI = obstructive apnea/hypopnea index; LMM = large muscle group movements; PLMS = periodic leg movements during sleep.

PLMS index was positively correlated with gestational age at birth (with a small-to-medium correlation coefficient), although this did not reach statistical significance; however, it was negatively correlated with sleep efficiency (with a similar medium-size correlation coefficient, although not significant) and negatively correlated with oAHI (with a medium-to-large and significant correlation coefficient). Conversely, LMM index did not appear to be correlated with gestational age at birth but was negatively and significantly correlated with oAHI (again with a medium-to-large correlation coefficient) and positively (but not significantly) correlated with arousal index and age (with medium-size correlation coefficients). There was also a negative correlation between LMM and PLMS indexes (with a small-to-medium correlation coefficient), although also this correlation did not reach statistical significance.

4. Discussion

In this study we found a high frequency of RSD (14.1%) and PLMS index >5/hour (17.4%) in children with history of prematurity. We have previously reported that, among children referred to the Seattle Children's Hospital Sleep Center, the prevalence of RSD is 7.7% and that of PLMS is 9.3%. This increased risk of PLMS and RSD in children with history of prematurity could be secondary to the high risk of iron deficiency during infancy. Prematurity, maternal anemia, and low birth weight are known risk factors for anemia in infancy [15]. We have previously identified increased iron deficiency in infants with history of prematurity [9]. Studies in children with past history of iron deficiency during infancy, have shown persistence of an increased leg muscle activation and leg movements during sleep, when measured at school age [16]. While most studies on motor activity in infants with prematurity have focused mainly on identifying predictors of cerebral palsy or neurologic deficits [17], polysomnographic studies focusing on sleep related movement disorders are scarce.

Our study also shows an interesting correlation between PLMS with sleep efficiency and LMM and arousal index, similarly to what has recently been reported in healthy adults [18]. A previous study has shown that infants born from mothers with anemia during pregnancy when compared to infants born to mothers without anemia, had shorter nocturnal sleep duration, with infants from mothers that took iron supplementation during pregnancy sleeping longer than infants from mothers who did not take iron supplementation during pregnancy [19].

Iron deficiency is a well-established cause of restless legs syndrome, periodic limb movement disorder and a suspected contributor to RSD, due to its importance in brain dopamine production and neurotransmitter systems development [20]. Interestingly, however, adults with a history of very preterm birth but without macroscopic perinatal brain injury, demonstrated no significant differences in presynaptic dopamine synthesis capacity from controls [21]. This raises the question of whether prematurity is affected not as much by the amount of iron or dopamine produced but by structural or functional connections that may be contributing to the increased PLMS and increased LMM seen in children with history of prematurity. In this regard, it is very interesting to note that

studies on premature children have highlighted alterations of the basal ganglia (6), such as studies on RLS and PLMS in adults[22] (which reinforces the fact that mechanisms of altered connectivity and neuroplasticity may actually contribute to the pathogenesis of the disorder.

In our study PLMS correlated positively with gestational age. This may indicate that pathways involved in PLMS may not develop appropriately in prematures. Most cerebral pathways and networks are built in the second half of gestation, thalamocortical pathways develop between 20-32 weeks, callosal and long cortico-cortical pathways between 24–35 weeks, while maturation of oligodendroglia and myelination develops during the third trimester [23]. A full term infant brain rearranges cortical inhibition, excitation fibers and forms many new synapses. Prematurity compromises these neural maturation processes limiting sensory-driven brain connectivity and synaptic pruning, potentially leading to future impairment [24].

Polysomnographic studies in former premature children have mainly been focused on obstructive sleep apnea. Jaleel et al. [25] reported an increased AHI in children with history of prematurity but full polysomnographic parameters including PLMS index and arousal index were not included in the study. Manuel et al. [26] studied children with prematurity referred to otolaryngology and found increased respiratory comorbidities, but polysomnography was not performed. Questionnaire based studies including the Brief Infant Sleep Questionnaire revealed that two year old children with history of prematurity were more restless during sleep and sleep difficulties and shorter sleep duration correlated with increased motor activity, furthermore daytime symptoms included lower attention and increased negative emotions [27]. A review of the literature in children with history of prematurity,Not sure this is the main reason, also demonstrated that reduced sleep efficiency and poor sleep quality tended to persist through life [28].

Another observation in our study is the younger age of our patient population, despite reviewing all charts of children undergoing polysomnography. This may indicate a younger referred population, or the fact that movements during sleep decrease with maturation.[29,30]

Limitations to our study include single center experience and retrospective study protocol.

In conclusion these new results confirm previous reports of increased PLMS and add new knowledge on the prevalence of LLM and RSD in children with history of prematurity. These findings suggest that prematurity places children at risk of persistent sleep related movement disorders at older age.

Author Contributions: Conceptualization, L.M.D.; methodology, L.M.D. and R.F.; investigation, L.M.D. and H.A.; data curation, R.F.; writing—original draft preparation, L.M.D. and R.F.; writing—review and editing, L.M.D., H.A., M.P.M., O.B. and R.F. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Review Board of the Seattle Children's Hospital, Seattle, WA (STUDY00002559- Effective date of Approval 7/10/2020)

Informed Consent Statement: Patient consent was waived due to retrospective nature of study

Data Availability Statement: The data that support the findings of this study are available from the corresponding author, L.M.D., upon reasonable request.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Delnord, M.; Zeitlin, J. Epidemiology of late preterm and early term births - An international perspective. *Semin Fetal Neonatal Med* **2019**, *24*, 3-10, doi:10.1016/j.siny.2018.09.001.
2. Platt, M.J. Outcomes in preterm infants. *Public Health* **2014**, *128*, 399-403, doi:10.1016/j.puhe.2014.03.010.
3. Luu, T.M.; Rehman Mian, M.O.; Nuyt, A.M. Long-Term Impact of Preterm Birth: Neurodevelopmental and Physical Health Outcomes. *Clin Perinatol* **2017**, *44*, 305-314, doi:10.1016/j.clp.2017.01.003.
4. Ment, L.R.; Vohr, B.R. Preterm birth and the developing brain. *Lancet Neurol* **2008**, *7*, 378-379, doi:10.1016/S1474-4422(08)70073-5.
5. Larroque, B.; Ancel, P.Y.; Marret, S.; Marchand, L.; Andre, M.; Arnaud, C.; Pierrat, V.; Roze, J.C.; Messer, J.; Thiriez, G., et al. Neurodevelopmental disabilities and special care of 5-year-old children born before 33

weeks of gestation (the EPIPAGE study): a longitudinal cohort study. *Lancet* **2008**, *371*, 813-820, doi:10.1016/S0140-6736(08)60380-3.
6. Gogou, M.; Haidopoulou, K.; Pavlou, E. Sleep and prematurity: sleep outcomes in preterm children and influencing factors. *World J Pediatr* **2019**, *15*, 209-218, doi:10.1007/s12519-019-00240-8.
7. Paavonen, E.J.; Strang-Karlsson, S.; Raikkonen, K.; Heinonen, K.; Pesonen, A.K.; Hovi, P.; Andersson, S.; Jarvenpaa, A.L.; Eriksson, J.G.; Kajantie, E. Very low birth weight increases risk for sleep-disordered breathing in young adulthood: the Helsinki Study of Very Low Birth Weight Adults. *Pediatrics* **2007**, *120*, 778-784, doi:10.1542/peds.2007-0540.
8. Crump, C.; Friberg, D.; Li, X.; Sundquist, J.; Sundquist, K. Preterm birth and risk of sleep-disordered breathing from childhood into mid-adulthood. *Int J Epidemiol* **2019**, *48*, 2039-2049, doi:10.1093/ije/dyz075.
9. DelRosso, L.M.; Mindell, J.; Bruni, O.; Mogavero, M.P.; Ferri, R. Periodic leg movements during sleep and iron status in infants with prematurity, Down syndrome and Prader-Willi syndrome. *J Sleep Res* **2022**, 10.1111/jsr.13813, e13813, doi:10.1111/jsr.13813.
10. Ferri, R.; DelRosso, L.M.; Provini, F.; Stefani, A.; Walters, A.S.; Picchietti, D.L. Scoring of large muscle group movements during sleep: an International Restless Legs Syndrome Study Group position statement. *Sleep* **2021**, *44*, doi:10.1093/sleep/zsab092.
11. DelRosso, L.M.; Ferri, R.; Allen, R.P.; Bruni, O.; Garcia-Borreguero, D.; Kotagal, S.; Owens, J.A.; Peirano, P.; Simakajornboon, N.; Picchietti, D.L., et al. Consensus diagnostic criteria for a newly defined pediatric sleep disorder: restless sleep disorder (RSD). *Sleep medicine* **2020**, *75*, 335-340, doi:10.1016/j.sleep.2020.08.011.
12. DelRosso, L.M.; Picchietti, D.L.; Spruyt, K.; Bruni, O.; Garcia-Borreguero, D.; Kotagal, S.; Owens, J.A.; Simakajornboon, N.; Ferri, R.; International Restless Legs Syndrome Study, G. Restless sleep in children: A systematic review. *Sleep medicine reviews* **2021**, *56*, 101406, doi:10.1016/j.smrv.2020.101406.
13. Berry, R.B.; Brooks, R.; Gamaldo, C.; Harding, S.M.; Lloyd, R.M.; Quan, S.F.; Troester, M.T.; Vaughn, B.V. AASM Scoring Manual Version 2.6. **2019**.
14. Cohen, J. *Statistical power analysis for the behavioral sciences (2nd ed.)*; Erlbaum: Hillsdale, NJ, 1988.
15. Kitaoka, H.; Shitara, Y.; Kashima, K.; Ochiai, S.; Chikai, H.; Watanabe, K.; Ida, H.; Kumagai, T.; Takahashi, N. Risk factors for anemia of prematurity among 30-35-week preterm infants. *Fukushima J Med Sci* **2023**, 10.5387/fms.2022-21, doi:10.5387/fms.2022-21.
16. Peirano, P.; Algarin, C.; Chamorro, R.; Manconi, M.; Lozoff, B.; Ferri, R. Iron deficiency anemia in infancy exerts long-term effects on the tibialis anterior motor activity during sleep in childhood. *Sleep medicine* **2012**, *13*, 1006-1012, doi:10.1016/j.sleep.2012.05.011.
17. Pires, C.D.S.; Marba, S.T.M.; Caldas, J.P.S.; Stopiglia, M.C.S. Predictive Value of the General Movements Assessment in Preterm Infants: A Meta-Analysis. *Rev Paul Pediatr* **2020**, *38*, e2018286, doi:10.1590/1984-0462/2020/38/2018286.
18. Ibrahim, A.; Ferri, R.; Cesari, M.; Frauscher, B.; Heidbreder, A.; Bergmann, M.; Hogl, B.; Stefani, A. Large Muscle Group Movements during Sleep in Healthy People: Normative Values and Correlation to Sleep Features. *Sleep* **2023**, 10.1093/sleep/zsad129, doi:10.1093/sleep/zsad129.
19. Zhang, L.; Ma, S.; Dai, F.; Li, Q.; Wu, L.; Yu, L.; Xie, T.; Zhu, D.M.; Zhu, P. Anemia in pregnancy and sleep of 6-month-old infants: A prospective cohort study. *Front Nutr* **2023**, *10*, 1049219, doi:10.3389/fnut.2023.1049219.
20. Allen, R. Dopamine and iron in the pathophysiology of restless legs syndrome (RLS). *Sleep Med* **2004**, *5*, 385-391, doi:10.1016/j.sleep.2004.01.012.
21. Froudist-Walsh, S.; Bloomfield, M.A.; Veronese, M.; Kroll, J.; Karolis, V.R.; Jauhar, S.; Bonoldi, I.; McGuire, P.K.; Kapur, S.; Murray, R.M., et al. The effect of perinatal brain injury on dopaminergic function and hippocampal volume in adult life. *Elife* **2017**, *6*, doi:10.7554/eLife.29088.
22. Mogavero, M.P.; Mezzapesa, D.M.; Savarese, M.; DelRosso, L.M.; Lanza, G.; Ferri, R. Morphological analysis of the brain subcortical gray structures in restless legs syndrome. *Sleep medicine* **2021**, *88*, 74-80, doi:10.1016/j.sleep.2021.10.025.
23. Cameron, E.C.; Maehle, V. Comparison of active motor items in infants born preterm and infants born full term. *Pediatr Phys Ther* **2006**, *18*, 197-203, doi:10.1097/01.pep.0000229969.02895.d6.
24. Dubois, J.; Benders, M.; Cachia, A.; Lazeyras, F.; Ha-Vinh Leuchter, R.; Sizonenko, S.V.; Borradori-Tolsa, C.; Mangin, J.F.; Huppi, P.S. Mapping the early cortical folding process in the preterm newborn brain. *Cereb Cortex* **2008**, *18*, 1444-1454, doi:10.1093/cercor/bhm180.
25. Jaleel, Z.; Schaeffer, T.; Trinh, C.; Cohen, M.B.; Levi, J.R. Prematurity: A Prognostic Factor for Increased Severity of Pediatric Obstructive Sleep Apnea. *Laryngoscope* **2021**, *131*, 1909-1914, doi:10.1002/lary.29473.
26. Manuel, A.; Witmans, M.; El-Hakim, H. Children with a history of prematurity presenting with snoring and sleep-disordered breathing: a cross-sectional study. *Laryngoscope* **2013**, *123*, 2030-2034, doi:10.1002/lary.23999.
27. Caravale, B.; Sette, S.; Cannoni, E.; Marano, A.; Riolo, E.; Devescovi, A.; De Curtis, M.; Bruni, O. Sleep Characteristics and Temperament in Preterm Children at Two Years of Age. *J Clin Sleep Med* **2017**, *13*, 1081-1088, doi:10.5664/jcsm.6728.

28. Bennet, L.; Walker, D.W.; Horne, R.S.C. Waking up too early - the consequences of preterm birth on sleep development. *The Journal of physiology* **2018**, *596*, 5687-5708, doi:10.1113/JP274950.
29. Grigg-Damberger, M.; Gozal, D.; Marcus, C.L.; Quan, S.F.; Rosen, C.L.; Chervin, R.D.; Wise, M.; Picchietti, D.L.; Sheldon, S.H.; Iber, C. The visual scoring of sleep and arousal in infants and children. *Journal of clinical sleep medicine : JCSM : official publication of the American Academy of Sleep Medicine* **2007**, *3*, 201-240.
30. Scholle, S.; Beyer, U.; Bernhard, M.; Eichholz, S.; Erler, T.; Graness, P.; Goldmann-Schnalke, B.; Heisch, K.; Kirchhoff, F.; Klementz, K., et al. Normative values of polysomnographic parameters in childhood and adolescence: quantitative sleep parameters. *Sleep Med* **2011**, *12*, 542-549, doi:10.1016/j.sleep.2010.11.011.