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Research paper

Distinctive sleep problems in children with perinatal moderate or mild hypoxic-ischemia

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HIGHLIGHTS

- Sleep problems are highly associated with perinatal HI children.
- Children with moderate HI have a high risk of sleep breathing issues.
- Children with mild HI have a high risk of circadian rhythmic issues.
- Pineal cysts occur mostly in children with mild, but not moderate, HI.

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ABSTRACT

Extensive studies focus on the cognitive and motor impairments after perinatal hypoxic-ischemia (HI). Sleep problems, although reported to be associated with cerebral palsy (CP), are often overlooked in non-severe HI patients. Here, by investigating the sleep qualities of children with different degrees of HI, we discovered that sleep initiation and maintenance, sleep-related breathing problems, or circadian rhythmic issues were highly associated with children of moderate or mild HI, respectively. Follow-up MRI studies in 2-year old patients showed that periventricular white matter lesions including periventricular leukomalacia (PVL) were prevalent in moderate, but not mild, HI children. In contrast, the occurrence of pineal cysts had a high risk in children with mild HI. Our study provides novel insights into the mechanisms of distinctive sleep problems associated with children of different degrees of HI, and therefore sheds light on the studies of targeted therapeutic treatments for sleep disorders in children who suffer from HI.

1. Introduction

The outcomes of perinatal hypoxic-ischemia (HI), depending on its severity, vary between death and relatively normal neurological functions [1–3]. Although moderate to severe HI is highly associated with significant motor impairments, for example, cerebral palsy (CP), and cognitive deficits [1–3], patients with mild perinatal HI are often reported to be comparable to normal full-term children [4,5]. Recent studies, however, revealed that asymptotic patients are at high risk of developing a low IQ [6], indicating patients with mild HI might be substantially overlooked, probably due to their relatively unimpaired motor functions.

Magnetic resonance imaging (MRI) studies revealed a large spectrum of brain lesions ranging from the basal ganglion, thalamus to the frontal lobe in patients with variable degrees of HI [7,8]. Therefore, multiple neurological impairments, besides cognitive and motor defects, might develop in patients with perinatal HI. For example, moderate to severe HI could cause a delay of the sleep–wake cycle (SWC) onset [9–11]. Consequently, patients who suffer from CP tend to develop sleep disorders, due to muscle

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spasm, epilepsy, visual and respiratory problems [12,13]. However, the systematic studies of the relationships between sleep problems and HI of variable degrees, to our knowledge, were rarely reported.

Chronic sleep problems can significantly compromise children's life quality and affect their neurobehavioral development, yet they are often paid less attention by neurologists and rehabilitation doctors [14]. In this study, by performing a cohort analysis of 216 patients, we sought out to investigate whether an increased risk of sleep problems is associated with perinatal HI patients during development, especially those with mild HI, who are often overlooked. By performing MRI scanning, we also studied how the anatomical changes in the brain might correlate with various sleep problems in perinatal HI patients. Our study therefore sheds light onto targeted therapeutic treatments for HI patients with different sleep issues.

2. Material and methods

2.1. Participants

Two hundred and forty-eight participants, who were transferred to Children's Hospital of Soochow University within 1 week after birth between May 2010 and August 2013, were initially selected. Exclusion criteria included severe HI, history of an acquired brain injury or other major neurological or psychiatric conditions after birth (for children with CP, this refers to events subsequent to the onset and diagnosis) or inability of the parent or guardian to provide demographic and medical information, and/or questionnaire. Children were also excluded if they had a change in medications within the past months that could affect sleep such as anticonvulsant medications, sedatives, and neurostimulant medications. Meanwhile, children were excluded for any injuries or congenital, developmental abnormalities that could cause severe up-airway obstruction. The criteria for children with different degrees of HI were based on the Sarnat Grading Scale [15]. The included participants were divided into three groups: children with moderate prenatal HI ($n = 44$), children with mild HI ($n = 84$) and normal full-term children ($n = 88$). The research protocol was approved by the hospital medical ethics committee. All parents gave their informed consent.

2.2. Questionnaire

Self-designed infant sleep quality questionnaire was adapted from the Brief Infant Sleep Questionnaire (BISQ) [16] and the Sleep Disturbance Scale for Children (SDSC) [13,17]. The inclusion of sleep related breathing problems in our questionnaire (variables 5 & 6) was based on both literature review [7,13] and our clinic follow-ups. The questionnaire variables included: (1) unfixed nocturnal sleep-onset time (the clock time at which the child falls asleep at night); (2) longer settling time (latency to falling asleep for the night, >20 min); (3) insufficient sleep (<11 h); (4) change in daily sleep schedule (changes in nap onset time, duration, and night sleep duration); (5) snore loudly; (6) Sleep breathing problems (shortness of breath, and intermittent pauses of breath during sleep); (7) Frequent wakes at night (>2 times/night). For each variable, a 0–2 scale was applied: 0, never happened in the past 6 months; 1, occurs ≤3 times/week in the past 6 months; 2, occurs >3 times/week in the past 6 months. A sleep score is the sum of all the seven variables. The parents were instructed to refer to their child's sleep conditions. When referring to sleep related breathing problems, parents were carefully introduced to the details of symptoms including snoring loudly, shortness of breath, and intermittent pauses of breath. If any sleep related breathing problems were reported, children received a physical examination to exclude any injuries and/or developmental abnormalities that could cause up-airway obstruction. All data were by test-retest reliability [18]. Briefly, parents were interviewed twice using the same questionnaire with a 3-week interval. The kappa coefficients were calculated for each variable (Table 2).

Table 1
Characteristics of the participants.

Sample characteristics	Moderate HI ($n = 44$)	Mild HI ($n = 84$)	Normal ($n = 88$)
Age (years)	3.32 ± 1.65[1]	3.37 ± 1.15	3.24 ± 1.28
Gender	80% male	74% male	71% male
Gestational age (weeks)	37.41 ± 6.24*	38.45 ± 4.02*	40.22 ± 4.38
Birth weight (grams)	2.97 ± 1.77	3.04 ± 1.32	3.21 ± 1.51
CP	3	0	0

Note: All data are present as mean ± s.d.
* $p < 0.05$.

2.3. MRI scanning

Sixty-eight children with HI (moderate HI: 31; mild HI: 37) received brain MRI. MRI examinations were performed on a 3.0T scanner (GE, America) using a head coil. All children were sedated before MR examination. The children were positioned supine inside the scanner. After a localizer T1-weighted (T1-W) spin-echo (SE) images [repetition time (TR) 2220 ms; echo time (TE) 26 ms; time of acquisition 1 min 25 s] in sagittal and axial planes were obtained. The axial sequence in T2-weighted fast-echo (TR/TE 4245/102 ms; time of acquisition 1 min 25 s) were obtained. Slice thickness was 6.0 mm for all sequences and the interslice gap was 1.0 mm. The field of view (240 mm) and matrix (512×512) was for all images. All MR images were uploaded to Picture Archiving and Communication Systems (PACS; Neusoft, Shenyang, China).

The follow-up MRI examinations were performed around 2–3 years of age. Brain MRIs were reviewed for abnormalities by an experienced radiologist, unaware of the clinical condition of the children. Based on previous studies and our own observation, the intracranial lesions were categorized into five groups [19–21], (1) normal, (2) periventricular white matter lesions and leucomalacia (PVL), (3) basal ganglion and thalamus, (4) cortical and watershade white area lesions, and (5) pineal cyst.

2.4. Statistical analysis

The comparison of each scale was implemented by the Wilcoxon signed-rank test. A two-sided value of $p < 0.05$ was considered statistically significant. All data analysis was performed by SPSS17.0.

3. Results

3.1. General characteristics

Characteristics of the participants showed no significant differences in age, gender,or birth weight (Table 1). The gestational age, however, was earlier in both moderate and mild HI patients, probably due to various stress factors affecting the delivery.

3.2. Distinctive sleep problems associated with HI patients with variable degrees

The total sleep scores, which is the sum of the seven variables listed in the questionnaire, in the moderate and mild HI patients were both significantly higher than those in the normal control (Table 2), indicating that the prenatal HI is highly associated with sleep problems. When analyzing the details of how different sleep problems were affected by different HI, we identified that patients with moderate HI tend to have longer settling time, more frequent