An observational study of sleep in childhood post-neonatal encephalopathy

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Abstract

Aim: Neonatal encephalopathy (NE) is associated with altered cognitive, motor, sensory abilities and behavioural outcomes. This case-control study aimed to assess whether Quality of Life (QoL) and sleep disorders are affected in older children following NE compared to age-matched controls.

Methods: Children at school-age post-NE were recruited and compared to age-matched controls. Sleep and QoL were assessed with the Pediatric Quality of Life Inventory and the Child Sleep Habit Questionnaire.

Results: One hundred children were recruited with an age range of 4–6 years, including children post-NE (n = 45) and age-matched controls (n = 55). Significantly higher pathological sleep scores were evident in 58% of children post-NE compared to controls (43.8 vs 40.2; \( p = 0.001 \)). Children post-NE had increased bedtime resistance (\( p = 0.028 \)) and sleep anxiety (\( p = 0.01 \)) compared to controls. Children in the post-NE group had lower total QoL scores versus controls (mean score 82.5 vs 95.8; \( p < 0.01 \)). Children with mild NE also had lower total QoL scores than controls (90.0 vs 95.8, \( p = 0.003 \)). There was a strong correlation between low QoL with high total sleep scores (Rho 0.339, \( p = 0.014 \)).

Conclusion: There were high rates of sleep issues in school-aged children with mild and moderate-severe NE. Consideration and management of sleep problems may improve QoL in childhood post-NE.

Keywords
hypoic-ischaemic encephalopathy, Neonatal Encephalopathy, quality of life, sleep

INTRODUCTION

Neonatal encephalopathy (NE) is characterised by an altered level of consciousness, seizures, poor tone and an inability to initiate or maintain respiration.1 The term hypoxic-ischaemic encephalopathy (HIE) is often used interchangeably with NE although it should, more correctly, be thought of as a subgroup of NE.2 The incidence of NE is reported to occur in up to 3 per 1000 live births.3 The current gold-standard treatment for moderate to severe neonatal encephalopathy is therapeutic hypothermia, which significantly reduces, but does not eliminate, mortality and adverse neurodevelopmental sequelae.4 Importantly, 25% of those classified as having mild neonatal encephalopathy have been found to have abnormal outcomes at ≥18 months of age5 and current evidence is insufficient to recommend therapeutic hypothermia in this cohort.6

Abbreviations: CP, Cerebral Palsy; NE, Neonatal Encephalopathy; CSHQ, Children’s Sleep Habit Questionnaire; PedsQL, Pediatric Quality of Life Inventory; QoL, Quality of Life.
The prevalence of sleep disorders in school children varies from 10% to more than 40% in different epidemiological studies. This may be even higher in children with underlying conditions such as cerebral palsy (CP) with a sixfold to eightfold increase in sleep disorders. NE may lead to altered cognitive, motor, sensory abilities and behavioural outcomes. These complications may affect the quality of life (QoL) of the child and their families.

We hypothesised that children with NE have increased sleep disturbance and altered quality of life compared to age-matched controls. We aimed to assess whether QoL and sleep disorders are affected in older children following NE compared to age-matched controls using the Pediatric Quality of Life Inventory (PedsQL) and Child Sleep Habit Questionnaire (CSHQ).

2 METHODS

2.1 Ethical Approval

Ethical approval was received from the Research Ethics Committee of the National Maternity Hospital, Dublin and Children’s Health Ireland (CHI) at Tallaght, Dublin. Written, informed consent was obtained from all participants in the study.

2.2 Patient Groups

This is a case-control observational study which followed a cohort of infants with NE who were recruited in the neonatal period and reviewed at school-age. Details of recruitment of these children in the neonatal period and school-age period have been previously published. The recruitment period for this follow-up study was 2018 to 2019.

The NE group consisted of school-age children, aged between 4–6 years, post-NE. Children following NE were classified according to the modified Sarnat & Sarnat criteria as follows: mild NE (peri-natal asphyxia (PA)/grade I) and moderate-severe NE (grade II-III). Those assigned to the PA group had evidence of perinatal asphyxia but did not meet the criteria for NE.

The control group consisted of healthy school-age children between 4 and 6 years who were admitted for a day-case procedure with typical development, no intellectual impairment, and no prior neuropsychiatric illness or mental health problems. In addition, the participants in the control group had no chronic medical or neurological condition.

2.3 Questionnaires

All children recruited had sleep and QoL questionnaires completed. The CSHQ is a parent-report sleep screening survey specifically designed for school-aged children although it has since been used in toddlers and preschool children. The Child Sleep Habits Questionnaire (CSHQ) is a screening tool for school-aged children based on their clinical symptoms of common sleep disorders. A cut-off total CSHQ score of 41 identifies children with a clinical sleep problem with a sensitivity of 0.80 and specificity of 0.72. Eight subscales in the CSHQ (including bedtime resistance, sleep onset delay, sleep duration, sleep anxiety, night waking, parasomnias, sleep-disordered breathing and daytime sleepiness) were measured, which together generated a total sleep disturbance score. The CSHQ was filled by parents during the outpatient visit and scored by the clinician according to the answers to the 33 questions provided by the parents. In our study, we used the total sleep score of ≥41, which has been shown to indicate a paediatric sleep disorder.

The PedsQL measurement model is a tool to measure health-related quality of life in healthy children and adolescents and those with acute and chronic health conditions. The age-specific PedsQL inventory questionnaires for children in the control group and for children with mild to moderate NE were used to measure of QoL. The PedsQL CP module was used for children with NE who developed CP. The Parent-Proxy measures were used in all cases.

2.4 Statistical Analysis

Statistical analysis was performed using the PASW statistical package version 24 (www.ibm.com/SPSS_Statistics). Continuous normally distributed data were displayed as means and standard deviations (SD) and comparisons were made using the independent Student t test. Significance was assumed for values p <0.05. Spearman’s correlation was calculated to assess the association between sleep and QoL scores.

3 RESULTS

3.1 Demographic information

In the post-NE group (n=45, 27 male), children were in the aged 4–6 years. They were classified as per grade of encephalopathy in the neonatal period as mild (PA/NE I; n=15) and moderate-severe encephalopathy (NE II/III; n=30) as per Sarnat Staging. Seven
children had motor impairment using the Gross Motor Function Classification Scale (GMFCS) as follows: GMFCS V (n=2) and GMFCS II/III (n=5). Epilepsy was diagnosed in 3 children with NE (2 of whom also had CP), and 2 children had visual impairment (both of whom had CP). None of the children had any sleep interventions/treatments in place for sleep disorders at the time of the study.

The sleep pattern and QoL of 45 school-age children who had mild and moderate-severe neonatal encephalopathy (NE) were assessed and compared with 55 controls, using the CSHQ and Peds QL. Children in the control group (n = 55, 35 male) were aged 4–6 years.

3.2 | Sleep scores

A higher pathological sleep score was seen in 30 out of 45 children (58%) post-NE compared to children in the control group (42.5 ± 36 vs 40.4 ± 0.5). In the control group, 10 children had an abnormal sleep score. Children post-NE had an increased prevalence of sleep problems including bedtime resistance (p = 0.028) and sleep anxiety (p = 0.01) compared to age-matched controls.

Although children with moderate-severe NE trended towards high total sleep scores compared to children with mild NE, this was not statistically significant (mean total CSHQ score 44.53 ± 7.8 vs 42.65 ± 8.4; p = 0.4). Children with NE II/III received hypothermia in the neonatal period (n = 24). Out of these, 10 had high total sleep scores. The most common sleep problem noted in children with moderate-severe NE was sleep onset delay (SOD). Children with moderate-severe NE had significantly higher SOD scores compared to children with mild NE (mean scores 1.52 ± 0.6 vs 1.21 ± 0.4; p = 0.04). Subscale scores for bedtime resistance, sleep duration, sleep anxiety, night waking, parasomnias, sleep-disordered breathing and daytime sleepiness were also high in children with moderate-severe NE in comparison with subscale scores of children with mild NE but failed to reach statistical significance (Table 1).

3.3 | Quality of Life

Children in the NE group had significantly lower total QoL scores compared to children in the control group (mean score 82.5 vs 95.8; p < 0.01). Children with NE had significantly lower scores in all domains of QoL, especially in physical functioning, emotional, social functioning and school activities.

Comparing children with mild NE with the control group (Table 2), QoL total scores were significantly lower in children with mild NE compared to the control group (mean total QoL score 90.03 ± 7.4 vs 95.8 ± 3.8; p = 0.003). Children with mild NE had lower scores in physical functioning (mean 97.2 ± 4.4 vs 89.6 ± 8.3; p = 0.01) and school activities (97.8 ± 4.1 vs 90 ± 12; p = 0.016) but there was no statistically significant difference in the emotional or social subscales (Table 2).

On comparison between mild and moderate-severe NE (Table 3), children with mild NE had higher total QoL scores compared to children with moderate-severe NE (mean 90 ± 7.5 vs 78.3 ± 2.5; p = 0.007). Children with moderate-severe NE had significantly lower scores in domains of physical ability and in school activities compared to children with mild NE (80.26 ± 8.4 vs 89.6 ± 8.39; p = 0.021 and 85.11 ± 15.7 vs 90.08 ± 12.8; p = 0.02).

There was strong correlation between low QoL scores with high GMFCS level and children with GMFCS level I/II had high total QoL scores compared to children with GMFCS level III/IV (mean score 89 vs 44; p = 0.001). Lower scores were also associated with comorbidities including epilepsy, intellectual disability and visual impairment.

3.4 | Correlation of QoL with Sleep Scores

There was a strong correlation of low QoL with high total sleep scores. As the data were not normally distributed Spearman

| CSHQ Score | Mild NE (n=15) Mean (SD) | Moderate-Severe NE (n=30) Mean (SD) | p-value |
|------------|------------------------|------------------------------------|---------|
| Sleep score (Total) | 42.65 (8.4) | 44.53 (7.8) | 0.40 |
| Bedtime resistance | 8.11 (2.6) | 9.26 (93.2) | 0.17 |
| Sleep Onset Delay | 1.21 (0.4) | 1.52 (0.6) | 0.04 |
| Sleep Duration | 3.47 (1.3) | 3.42 (1.1) | 0.80 |
| Sleep Anxiety | 5.89 (2.3) | 6.32 (2.2) | 0.50 |
| Night wakening | 4.42 (1.8) | 4.94 (1.6) | 0.34 |
| Parasomnias | 8.95 (1.7) | 9.39 (2.4) | 0.50 |
| Sleep-disordered breathing | 3.79 (1.1) | 3.52 (1.1) | 0.40 |
| Daytime sleepiness | 9.84 (2.8) | 9.45 (2.5) | 0.60 |

Note: Data are means (standard deviation) calculated for sleep total and subscores. Abbreviations: CSHQ, Children’s Sleep Habits Questionnaire; NE: Neonatal Encephalopathy; PA, Perinatal Asphyxia.

*p value significant at <0.05.
TABLE 2 QoL scores of children with Mild NE vs Control Group.

| QoL SCORE | CONTROL (n=46) | Mild NE (n=20) | p-value |
|-----------|----------------|----------------|---------|
| TOTAL QoL | 95.8 (3.8)     | 90 (7.4)       | 0.003   |
| PHYSICAL  | 97.2 (4.4)     | 89.6 (8.3)     | 0.01    |
| EMOTIONAL | 88.3 (3.6)     | 85.8 (6.7)     | 0.05    |
| SOCIAL    | 99.1 (4.1)     | 95.5 (8.2)     | 0.07    |
| SCHOOL    | 97.8 (4.1)     | 90 (12)        | 0.016   |

Note: Data are means (standard deviation) calculated for QOL total and subscores.

Abbreviations: NE, Neonatal Encephalopathy; QoL, Quality of Life.
*p value significant at <0.05.

TABLE 3 QoL scores of children with Mild NE vs Moderate-Severe Group.

| QoL Score       | Mild NE Mean (SD) | Moderate-Severe NE Mean (SD) | p-value |
|-----------------|-------------------|-------------------------------|---------|
| Total           | 90.0 (7.5)        | 78.3 (2.5)                   | 0.007   |
| Physical Ability| 89.6 (8.39)       | 80.26 (8.24)                 | 0.02    |
| Emotional       | 85.8 (6.7)        | 87.7 (6.9)                   | 0.07    |
| Social          | 95.5 (8.2)        | 93.3 (8.8)                   | 0.09    |
| School          | 90.08 (12.8)      | 85.11 (15.7)                 | 0.02    |

Note: Data are means (standard deviation) calculated for QOL total and subscores.

Abbreviations: NE, Neonatal Encephalopathy; QoL, Quality of Life.
*p value significant at <0.05.

correlation was used for analysis and correlation was noted (Rho 0.339, p = 0.014).

4 | DISCUSSION

This is the first description of sleep disorders in school-age children post-NE, especially in those with PA/mild encephalopathy (Grade I). We have demonstrated a high rate of sleep disorders in children with mild and moderate-severe NE in comparison with controls. More than half of all children with NE have sleep disorders. Sleep anxiety and bedtime resistance were the most common sleep disorders overall, but sleep onset delay was the most common in children who had moderate-severe NE. Children who had moderate-severe NE and motor impairment all had sleep scores suggestive of a sleep disorder. This is in keeping with research which shows that children with CP have a high rate of sleep disorders.20

Quality of life is a multidimensional construct of a person's overall subjective well-being. It takes into account their physical and mental health, financial situation, interpersonal relationships and contribution to society.21 We found a significant association between sleep disorders in children with NE and reduced QoL. This has been also shown in other studies including in children with neurological disorders. Sleep has a huge impact on the quality of life of children and their families and thus, needs to be monitored and managed appropriately.11,22,23 Chaput et al performed a systematic review of sleep duration in healthy children and found that the available evidence shows that shorter sleep duration is associated with adverse mental and physical health outcomes.22 Sandella et al examined this relationship in children with CP and found that insomnia was associated with poorer psychosocial QoL, and excessive daytime somnolence was associated with lower physical QoL.24 Management of sleep disorders involves maintaining good sleep hygiene, behaviour therapy and medications such as melatonin.25

Angriman et al reviewed sleep disorders in children with other neurodevelopmental disabilities, as well as with CP, finding that these children often have sleep disorders which require treatment to improve their QoL.26 We did not assess parental QoL in this study, but it is an important consideration as it is significantly affected by their child's sleep.17,27

A strength of this study includes that it is a follow-up study of a previously recruited cohort of children with NE. Limitations include that this is an observational study and that we did not gather socioeconomic data which would have the potential to influence our results. The sample size may, initially, be considered small and, therefore, a limitation of the study. However, when taken in the context of much of the existing research in NE, this study is relatively large. Also, to our knowledge, this is the first such study reporting on sleep disorders and quality of life in children with NE and future research may help to confirm our findings. QoL is a subjective measure and the PedsQL, as with all questionnaires, only gives information about one particular point in time. This may vary over time and be influenced by other external factors. Longitudinal studies would be useful to help resolve this issue. Finally, parent-proxy reports were used in this study. Although these are validated in the literature, it would be useful to gather child-reported QoL measures to compare with parent reports.

Sleep disorders in childhood can be treated and should be identified in clinical practice. Treatment involves behavioural strategies,28 good sleep hygiene29 such as a consistent bedtime routine and medications such as melatonin. The use of melatonin has been widespread in the treatment of sleep disorder in children with neurodisabilities including CP, intellectual disability (ID) genetic syndromes, neuromuscular disorders and autism.30 In a meta-analysis of 9 studies (n=541) melatonin showed a significant improvement in total sleep time and analysis of 11 studies (n=581) showed benefits in reducing sleep onset latency.30 The same meta-analysis found no evidence of a reduction in the frequency of night-time awakenings.30

5 | CONCLUSIONS

Sleep problems in children post-neonatal encephalopathy (NE) have not been assessed previously. We found high rates of sleep problems in school children with both mild and moderate-severe NE, thus, assessment of sleep problems in children especially in those at high risk could be incorporated into routine practice. Treatment of sleep
problems in children should be prioritised with the possibility of improving not only the quality of life and well-being and of the child but also of the parents or caregiver.

CONFLICTS OF INTEREST
The authors declare no conflict of interest. The sponsor of the study has no role in the study design, collection, analysis or interpretation of data, writing the paper or in the decision to submit the manuscript for publication.

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