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Original article

Polysomnography in preterm infants with perinatal pathology: first 5-year experience in Ukraine

Dariia Kostiukova[1,2], Anastasiya Babintseva[3], Thomas Erler[4], Yelyzaveta Shunko[5], Maksym Roziaiev[6]

[1]Shupyk National Medical Academy of Postgraduate Education, Kyiv, Ukraine
[2]Cabinet "Complex Neuromonitoring with the Children's Sleep Laboratory", Department of Intensive Care of Preterm Infants, National Children's Specialized Hospital "OKhMATDYT", Kyiv, Ukraine
[3]Department of Pediatrics, Neonatology and Perinatal Medicine, Higher State Educational Establishment of Ukraine "Bukovinian State Medical University", Chernivtsi, Ukraine
[4]Department of Pediatrics, Neonatology and Perinatal Medicine "Klinikum Westbrandenburg Potsdam", Teaching Hospital of the Brandenburg Medical School Theodor Fontane, Potsdam, Germany
[5]Department of Neonatology, Shupyk National Medical Academy of Postgraduate Education, Kyiv, Ukraine
[6]National Children's Specialized Hospital "OKhMATDYT", Kyiv, Ukraine

Abstract

Background: Polysomnography (PSG) is an important component in comprehensive neuromonitoring that allows timely evaluation of the sleep maturation quality and diagnosis of Sleep-Related Breathing Disorders (SRBD) in preterm infants (PIs).

Aim: To determine PSG indices in PIs of different gestational age with perinatal pathology.

Methods: This was the first original single-center observational study conducted in Ukraine. The groups of observation consisted of a total of 61 PIs with perinatal pathology: 16 infants of 24-28 weeks (Group I), 33 infants of 29-32 weeks (Group II), and 12 infants of 33-36 weeks (Group III). Non-parametric methods were used for statistical analyses.

Results: A maximum level of Respiratory Disturbance Index during Quiet Sleep (p_{I-II} = 0.016, p_{I-III} = 0.014), and Respiratory Disturbance Index Total and Respiratory Disturbance Index during Active Sleep was found in Group I with an average postmenstrual age (PMA) of 36 weeks, as well as a maximum frequency of SRBD with predominance of hypopnea and obstructive apnea. A statistically valuable decrease in Respiratory Disturbance Index during Quiet Sleep was determined in Group II with an average PMA of 35 weeks, with a stable decrease in all other indices. Minimum values were found in of all the PSG indices in Group III with an average PMA of 38 weeks. Mean values of Arousal Index in all the groups of observation were higher than 20. The minimum level

of oxygen saturation during SRBD was diagnosed in infants from Group I ($p_{I-III} = 0.0072$).

Conclusions: Disorders of physiological sleep formation and pathological respiratory events during sleep were found in the majority of PIs with perinatal pathology, which stipulates the necessity to conduct careful monitoring of vital functions and differential treatment of various apnea types.

Keywords

Preterm infants, polysomnography, sleep-related breathing disorders, apnea.

Corresponding author

Anastasiya Babintseva, MD, PhD, Associate Professor, Department of Pediatrics, Neonatology and Perinatal Medicine, Higher State Educational Establishment of Ukraine "Bukovinian State Medical University", 2 Teatralna sq., Chernivtsi, Ukraine; mob.: +380506662230; e-mails: babintseva@bsmu.edu.ua, babintsevanastia@gmail.com.

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Introduction

The identification of sleep problems in children is important because of the growing evidence of the effects of sleep disorders on physical, cognitive, emotional and social development [1]. Sleep disturbances associated with difficult breathing during sleep are classified as Sleep-Related Breathing Disorders (SRBD) [2]. SRBD in preterm infants (PIs) are singled out in section P28.3-28.4 [3] according to the 10th Revision of the International Statistical Classification of Diseases and Related Health Problems and the International Classification of Sleep Disorders – Third Edition.

For all patients under 18 years of age, it is necessary to use the classification of respiratory disorders according to the recommendations of the American Academy of Sleep Medicine (2007) and Rules for Scoring Respiratory Events in Sleep (2012) [4].

PIs have some functioning features of the respiratory regulation system, which are associated with the gradual behavioral development of the premature baby in the synactive model (transition from fetal to postnatal state) and the influence of adverse factors (hypoxia, excessive oxygenation, medication, etc.). At present, there are no separate sleep staging rules for PIs, but it is possible to use the visual scoring of sleep in infants from 0 to 2 months of age by Grigg-Damberger [5].

Joosten et al. (2017) presented a literature review on the features of SRBD in PIs [6]. In particular, the authors noted respiratory phenomena such as periodic breathing, various types of apnea (central, obstructive, mixed), hypopnea (HYP) and hypoventilation. Apnea in prematurity is defined as the cessation of breathing by a PI that lasts for more than 20 seconds and/or is accompanied by hypoxia or bradycardia [7]. The majority of apneic episodes in PIs are mixed events, in which the obstructed airflow results in a central apneic pause, or vice versa [8]. The incidence of apnea of prematurity is inversely related to gestational age (GA). Distinct from apnea of prematurity, periodic breathing is a normal immature breathing pattern for neonates and occurs in both term and preterm infants. Excessive periodic breathing (> 10% of the sleeping time) or an abrupt increase over prior baseline may reflect illness or physiological stressors, or may occur without any apparent clinical event, but its occurrence warrants consideration for potential pathology [6].

In addition, PIs are at a higher risk for obstructive sleep apnea. Many central apneas (CAs) involve loss of airway tone that may result in intermittent airway obstruction and, as a consequence, prolong apnea. Infants with bronchopulmonary dysplasia (BPD) have more obstructive apneas (OAs) observed in quiet sleep than infants without BPD. Symptoms of obstructive sleep apnea may be subtle or absent in infants. These are snoring, noisy respirations, labored breathing, mouth breathing, and profuse sweating. Occasionally, infants with obstructive sleep apnea may present with failure to thrive, and developmental delay [6].

PIs have an increased risk of Apparent Life-Threatening Events (ALTEs) at the age of < 1 year with a peak frequency of 10 to 12 weeks of life; some of these events remain unexplained and are referred to as Brief Resolved Unexplained Events (BRUEs). Both ALTEs and BRUEs need a risk assessment, management and implementation of recommendations based on future research in this direction [9]. About 4-10% of infants who die from Sudden Infant Death Syndrome (SIDS) had a history of two or more BRUE episodes. However, unlike SIDS, the incidence of ALTEs did not decrease in response to the Safe to Sleep® campaign [10, 11].

At the present stage, there are debatable questions about the prolongation or cessation of respiratory support, oxygen therapy, pharmacological agents or surgery, monitoring of SRBD, determination of ALTE and BRUE risk while taking care of a newborn and follow-up of PIs, prevention of SIDS, and sudden unexpected death in epilepsy in risk groups [12]. In order to identify these issues, polysomnography (PSG) is the gold standard for assessing the severity of functional and organic changes during the implementation of an individualized care program for premature infants with perinatal pathology [13-17].

The objective of our research is to study PSG indices and the frequency of respiratory disorders during sleep in PIs of different GA.

Materials and methods

Subjects

The groups of observation consisted of 61 PIs with perinatal pathology and GA ranging from 24 to 36 weeks. The children were divided into three groups according to the GA: Group I consisted of 16 children born at the GA of 24-28 weeks, Group II – 33 children born at the GA 29-32 weeks, and Group III – 12 children who were born at the GA of 33-36 weeks.

Inclusion criteria: the GA is more than 24 weeks and less than 37 weeks; body weight at birth is more than 500 g and less than 2,500 g; signs of perinatal pathology.

The study was a component of a comprehensive neuromonitoring program (a patented model of the diagnostic methods for paroxysmal conditions in PIs which includes clinical observation, neuroimaging, electroencephalographic [EEG], near infrared spectroscopy, PSG). This model is implemented at the consulting room "Complex Neuromonitoring with the Children's Sleep Laboratory" at the Department of Intensive Care of Preterm Infants at the National Children's Specialized Hospital "OKhMATDYT", Kyiv, Ukraine.

The study was approved by the Research Ethics Committee of Shupyk National Medical Academy of Postgraduate Education (Kyiv, Ukraine). Informed written consent was obtained from parents prior to enrollment of their babies into the study. All studies were conducted in compliance with the basic provisions of the Good Clinical Practice (1996), Council of Europe Convention on Human Rights and Biomedicine (1997), Helsinki Declaration of the World Medical Association on Ethical Principles for Medical Research (1964-2008).

Video-polygraphic recordings

PIs were admitted to the sleep laboratory for a daytime PSG. The recordings were performed in a quiet and darkened room, with temperature ranging between 22°C and 26°C. In most cases, children were sleeping supine, only in exceptional cases was the sleep partially in prone position and on the side (congenital maxillofacial anomalies). Recordings started around 11:00, duration 281.5-367.0 min. If necessary, the baby was breastfed, or fed by means of a bottle, a gastric probe, or a combination of both.

The following variables were recorded simultaneously: EEG using the international 10/20 system to place electrodes in standardized scalp locations (F3A2, F4A1, C3A2, C4A1, O1A2, O2A1), electrooculogram (LEOGA2, REOGA1), submental electromyogram (KEMG), and electrocardiogram (EKG1). Thoracic and abdominal movements were recorded with inductance plethysmography (Pleth), and air flow pressure with nasal cannula. Oxygen saturation was recorded continuously with a transcutaneous sensor (pulse oximetry). Data were collected on the diagnostic polysomnographic system Philips "Respironics Alice LDE 6" (USA). The recordings were subdivided into 30-second epochs.

Data analysis

Sleep staging and sleep respiratory analysis were scored (visually, manually and automatically) blindly, using standard criteria and definitions by an investigator [18-23].

The Anders Manual provided the criteria for coding physiological and behavioral state characteristics in PSG of infants only, leaving specific sleep scoring criteria to the individual investigator [24].

Standardized PSG norms for PIs have not yet been determined, but according to the recommendations of the Pediatric Task Force [25], sleep of infants younger than 2 months after birth should be assessed as Quiet Sleep (QS), Active Sleep (AS), and Indeterminate Sleep (IS).

Our decision was to score apneas in PIs when they lasted more than 10 seconds with saturation of ≤ 89% [26-28].

According to the respiratory rules for children [29], a respiratory event was evaluated as HYP when the peak signal excursions dropped by ≥ 30% of the initial baseline, registered by means of nasal pressure and with a duration of ≥ 10 seconds. The CAs were classified when flat tracings were obtained simultaneously from the strain gauges and the nasal

cannula. OAs were defined as continuous deflections from the strain gauges, with a flat tracing recorded from the nasal cannula. Mixed apnea (MIXA) was defined as CA directly followed by an obstructive episode. MIXAs were scored together with the obstructive episodes. The recordings were analyzed visually and manually by one of the investigators, then automatically according to Polysomnographic-Report «Infant Sleep» (Philips "Respironics Alice LDE").

Cortical arousal and subcortical activation

Arousals were subdivided into subcortical activations or cortical arousals, according to the consensus on arousal scoring in healthy infants younger than 6 months of age [30]. A subcortical activation was scored if no apparent change in the EEG was seen, while at least 2 of the following changes occurred: a gross body movement detected by movement sensors or seen as an artefact movement in the somatic channels, changes in heart rate (at least 10% of baseline values), or changes in breathing pattern (frequency and/or amplitude). A cortical arousal was scored using the above criteria, with the addition of the occurrence of an abrupt change in EEG background frequency of at least 1 Hz, for a minimum of 3 seconds. EEG arousals in young infants may provoke an abrupt diffuse decrease in EEG amplitude called a "decremental response," and this was scored as an arousal.

Statistical methods

All statistical analyses were performed using the statistical software Statistica™ (version 10, StatSoft Inc., USA). The results were expressed as median (Me) and interquartile range (IQR): lower quartile (Lq) and upper quartile (Uq). Nonparametric Kruskal-Wallis analyses (KW-test) of variance test were performed to compare the multiple groups and χ^2 test with posteriori comparison. The Fisher's exact test was used for categorical variables as appropriate. The correlation between parameters was evaluated using Spearman's rank correlation analysis. A p-value of < 0.05 was considered statistically significant.

Results

Patient characteristics

Patient characteristics are presented in **Tab. 1**.

The children were divided into three groups according to GA: Group I (GA 24-28 weeks) – 16 children including 9 boys (56.3%), Group II (GA 29-32 weeks) – 33 children including 18 boys (54.5%), and Group III (GA 33-36 weeks) – 12 children including 4 boys (33.3%). The groups were significantly different in body weight at birth and postmenstrual age (PMA). It should be noted that the groups of observation were gender-representative, but with a slight predominance of girls in Group III.

The average age of the mothers of the neonates from Group I was 30.8 ± 1.5 years, Group II – 32.0 ± 1.0 years, Group III – 32.7 ± 2.6 years, $p > 0.05$; the average age of the parents was 34.9 ± 1.9 years, 34.8 ± 1.1 years and 34.9 ± 2.5 years, respectively, $p > 0.05$. The average values of pregnancy parity in Group I was 2.4 ± 0.4, in Group II – 1.7 ± 0.2, in Group III – 1.5 ± 0.2, $p > 0.05$; the average values of childbirth parity were 1.7 ± 0.2, 1.4 ± 0.1, 1.4 ± 0.7, $p > 0.05$, respectively. Only 3 women (18.8%) from Group I, 1 woman (3%) from Group II, and 2 women (20%) from Group III were less than 23 years old at the time of childbirth, $p > 0.05$. A previous pregnancy had occurred less than 2 years before in 17.6%, 18.8% and 10% of the mothers in the respective study groups, $p > 0.05$.

Determining the peculiarities of pregnancy revealed a higher frequency of abortions and stillbirths

Table 1. Characteristics of the patients (n = 61).

Parameter	Group I (n = 16)	Group II (n = 33)	Group III (n = 12)	p-value [a]	Posteriori comparison [b]
GA, weeks	24-28	29-32	33-36	-	-
Birth body weight, grams	1,045.0 [867.0; 1,150.0]	1,470.0 [1,350.0; 1,590.0]	2,055.0 [1,812.5; 2,465.0]	< 0.0001	$p_{I-II} = 0.0002$ $p_{I-III} < 0.0001$ $p_{II-III} = 0.0029$
PMA, weeks	36.0 [34.5; 39.0]	35.0 [34.0; 37.0]	38.0 [37.0; 42.5]	0.0004	$p_{I-III} = 0.0251$ $p_{II-III} = 0.0003$

Data are presented as Me [Lq; Uq].
[a] Statistics are significant at the 0.05 level; the p-values are for the comparison among all three groups calculated with Kruskal-Wallis test for continuous variables. [b] Posteriori comparisons were performed by two-by-two χ^2 test.
GA: gestational age; PMA: postmenstrual age.

in previous pregnancies among women of Group I (47.1%) compared to women of Group II (18.8%) and III (20%), $p > 0.05$. When interviewing mothers, none indicated smoking before and during pregnancy, nor after giving birth. One woman (6.3%) from Group I and 1 woman (3%) from Group II noted the presence of occupational hazards during pregnancy. Only 3 children (18.8%) from Group I, 3 children (9.1%) from Group II and 1 child (8.3%) from Group III were born by caesarean section, $p > 0.05$.

During the study, we surveyed mothers to determine possible risk factors for adverse events in premature infants. Thus, 2 mothers (6.1%) from Group II noted the predisposition of older children to bronchitis. One mother (6.3%) from Group I and 1 mother (3%) from Group II testified to cases of sudden and unexpected death among previous children. None of the mothers in either study group reported having a family history of epilepsy or febrile seizures.

The occurrence of perinatal pathology in children from the groups of observation is presented in **Tab. 2**. The groups of observation were not representative by the structure of perinatal pathology, since they were formed according to GA.

EEG recording during comprehensive neuromonitoring of PIs made it possible to detect seizures in 42 children out of 61: 14 children in Group I (87.5%) and in 24 children in Group II (72.7%), which is statistically significantly higher than the frequency of seizures in children of Group III (4, 33.3%), $p_{I\text{-}III} = 0.0036$, $p_{II\text{-}III} = 0.0172$. Children with seizures received anticonvulsant therapy with subsequent clinical and EEG monitoring.

From the infants' medical history, we know that 15 children (93.8%) in Group I required both mechanical ventilation and continuous positive airway pressure (CPAP) in previous stages of treatment, with 1 child (6.3%) requiring CPAP only. In Group II 19 children (57.6%) required both mechanical ventilation and

Table 2. The neonatal and neurological pathologies at the patients (n = 61).

Perinatal pathology	Group I (n = 16)	Group II (n = 33)	Group III (n = 12)	p-value [a]
Neonatal pathology				
Hypoxic-ischemic encephalopathy	3 (18.8)	12 (36.4)	6 (50.0)	NS
BPD	11 (68.8)	5 (15.2)	1 (8.3)	$p_{I\text{-}II} = 0.0002$ $p_{I\text{-}III} = 0.0017$
Respiratory distress syndrome	-	4 (12.1)	-	NS
Neonatal pneumonia	7 (43.8)	11 (33.3)	-	NS
Neonatal sepsis	4 (25.0)	4 (12.1)	-	NS
Necrotizing enterocolitis	4 (25.0)	8 (24.2)	2 (16.7)	NS
Congenital eye malformations	1 (6.3)	-	-	NS
Congenital heart malformations	-	1 (3.0)	1 (8.3)	NS
Congenital laryngeal stridor	-	-	1 (8.3)	NS
Retinopathy of prematurity	9 (56.3)	13 (39.4)	1 (8.3)	$p_{I\text{-}II} = 0.0488$ $p_{I\text{-}III} = 0.0101$
Anemia of prematurity	12 (75.0)	22 (66.7)	-	NS
Hyperbilirubinemia	1 (6.3)	9 (27.3)	3 (25.0)	NS
Hypothyroidism premature	2 (12.5)	4 (12.1)	1 (8.3)	NS
Gastroesophageal reflux	2 (12.5)	3 (9.1)	1 (8.3)	NS
Neurologic pathology				
Intraventricular hemorrhage (non-traumatic) I-II	1 (6.3)	2 (6.1)	-	NS
Intraventricular hemorrhage (non-traumatic) III	2 (12.5)	3 (9.1)	-	NS
Meningitis	1 (6.3)	-	-	NS
Posthemorrhagic hydrocephalus	8 (50.0)	6 (18.2)	-	$p_{I\text{-}II} = 0.0222$
Periventricular leukomalacia	4 (25.0)	10 (30.3)	-	NS
Ventriculitis	2 (12.5)	-	-	NS

Data are presented as n (%).
[a] Statistics are significant at the 0.05 level; the p-values are for the comparison calculated with Fisher's exact test.
BPD: bronchopulmonary dysplasia; NS: not significant.

CPAP, 12 children (36.4%) required only CPAP, and 2 children (6.1%) did not require any type of respiratory support. In Group III 3 children (25%) required both mechanical ventilation and CPAP, 3 children (25%) needed CPAP, and 6 children (50%) did not receive any respiratory support. All preterm infants were treated with methylxanthines (caffeine citrate) until the PMA reached 36 weeks.

Conducting PSG for children of different gestational groups provided an opportunity to make an effective correction of respiratory management, namely, to determine the need for continued CPAP therapy, oxygen titration and/or treatment with methylxanthines.

Results of polysomnography

The average duration of the PSG study in Group I was 322.0 [281.5; 358.9] minutes, in Group II – 340.0 [304.0; 367.0] minutes, in Group III – 310.8 [285.9; 328.0] minutes (KW-test: H [2, N = 61] = 3.92, p = 0.1408).

The results of PSG in children of the groups of observation are presented in **Tab. 3**.

The results show that there is no statistically significant difference in the Arousal Index (AI), which reflects the frequency of sleep interruption, between all the 3 groups of observation. A tendency toward lower values of this indicator in children with GA of 33-36 weeks (Group III) was noted, compared with Groups I and II of the study. Overall in all PI groups, a very low power correlation between AI and PMA was found ($r = -0.27$, $p < 0.05$).

According to the data obtained the maximum values of Respiratory Disturbance Index Total (RDI.TOT) were observed in children born in the GA of 24-28 weeks (Group I). Children with GA 29-33 weeks (Group II) had a tendency toward lower values of this index compared with Group I of the study. PIs born between 33-36 weeks of gestation (Group III) showed marked tendencies toward low values of RDI.TOT compared with Groups I and II of the study.

Respiratory Disturbance Index during Active Sleep (RDI.AS) was also the highest in Group I. Tendencies toward lower values of this indicator were found in children in Groups II and III, compared with Group I. Yet this difference was not statistically significant.

It should be noted that the Respiratory Disturbance Index during Quiet Sleep (RDI.QS) in children born in GA of 24-28 weeks, statistically significantly exceeded the value of this index in children with GA of 29-32 weeks and children with GA 33-36 weeks, with no statistical significance between Groups II and III of observation.

Overall in all PI groups we found a very low power negative correlation between RDI.AS and GA ($r = -0.29$, $p < 0.05$); and low power negative correlation between RDI.QS and GA ($r = -0.41$, $p < 0.05$). Low power correlation between RDI.QS and PMA was also determined ($r = -0.33$, $p < 0.05$).

The SRBD score showed the maximum values in the group of children who were born in the gestation period of 24-28 weeks (Group I). There were marked tendencies towards the lower value of this indicator

Table 3. The parameters of polysomnography (PSG) of the patients (n = 61).

Parameter	Group I (n = 16)	Group II (n = 33)	Group III (n = 12)	p-value [a]	Posteriori comparison [b]
AI	24.2 [17.4; 26.7]	25.7 [21.7; 33.7]	20.7 [15.2; 27.5]	0.0521	NS
RDI.TOT, n/h	11.7 [5.1; 16.2]	8.4 [2.7; 11.9]	2.9 [1.8; 21.4]	0.2216	NS
RDI.AS, n/h	13.9 [6.9; 24.8]	5.7 [3.7;12.9]	3.0 [1.9; 20.0]	0.0496	NS
RDI.QS, n/h	6.5 [3.1; 24.2]	1.3 [0.0; 4.7]	1.4 [0.6; 1.6]	0.0044	$p_{I\text{-}II} = 0.016$ $p_{I\text{-}III} = 0.014$
SRBD, n	67.5 [31.5; 106.0]	33.0 [17.0; 79.0]	15.0 [8.0; 74.0]	0.0806	NS
OA, n	10.0 [4.0; 14.0]	6.5 [2.0; 17.0]	5.0 [1.0; 25.0]	0.8165	NS
HYP, n	44.5 [14.5; 87.0]	14.0 [4.0; 45.0]	7.0 [2.0; 28.0]	0.0690	NS
MIXA, n	1.5 [0.0; 4.0]	1.0 [0.0; 4.0]	1.0 [0.0; 1.5]	0.6718	NS
CA, n	1.0 [0.0; 2.0]	1.0 [0.0; 3.0]	0.0 [0.0; 3.0]	0.5858	NS

Data are presented as Me [Lq; Uq].
[a] Statistics are significant at the 0.05 level; the p-values are for the comparison among all three groups calculated with Kruskal-Wallis test for continuous variables. [b] Posteriori comparisons were performed by two-by-two χ^2 test.
AI: Arousal Index; RDI.TOT: Respiratory Disturbance Index Total; RDI.AS: Respiratory Disturbance Index during Active Sleep; RDI.QS: Respiratory Disturbance Index during Quiet Sleep; SRBD: Sleep-Related Breathing Disorders; OA: obstructive apnea; HYP: hypopnea; MIXA: mixed apnea; CA: central apnea; NS: not significant.

in the group of children with GA of 29-32 weeks (Group II) and with GA of 33-36 weeks (Group III), compared with the first group of the study. Significant tendencies towards the lower SRBD values were also observed in Group III children compared with Group II. In the overall PI group, a very low power correlation between SRBD and GA was found ($r = -0.29$, $p < 0.05$).

According to the results, the maximum frequency of OA episodes was observed in children born in GA of 24-28 weeks (Group I). The tendency for a lower incidence of sleep apnea of this type was observed in children in Groups II and III compared with Group I, with no statistical significance between the two groups of observation.

The maximum incidence of HYP in sleep was also found in children in Group I. PIs with GA 29-32 weeks (Group II) showed pronounced tendencies to a lower incidence of HYP compared with Group I of the study. The lowest incidence of HYP was detected in children born in 33-36 weeks' gestation (Group III).

The results of the study indicated that there was no statistically significant difference in the frequency of CA and MIXA episodes between all three groups of observation.

An important indicator that characterizes a child's sleep state is the level of oxygen saturation (SpO_2). Thus, in children in Group I the minimum level of this indicator during SRBD (min SpO_2) was 62.0% [51.5; 70.0], in children in Group II – 72.0% [55.0; 77.0], in children in Group III – 81.5% [66.5; 86.0] (KW-test: H [2, N = 59] = 9.23, $p = 0.0099$, $p_{I-III} = 0.0072$). Accordingly, children with GA of 24-28 weeks have the lowest level of this indicator. Compared with Group I, children in Group II and Group III had a statistically significantly higher level of this indicator with no difference between the two groups of the study, but it was lower than the physiological values (89%).

In the overall cohort of PIs, a weak positive correlation between the min SpO_2 and GA ($r = 0.38$, $p < 0.05$), and PMA ($r = 0.35$, $p < 0.05$) was established. The direction and strength of the correlation between the min SpO_2 in children of different groups of observation and separate PSG indices are demonstrated in **Tab. 4**.

It should be noted that at the time of the PSG study no child received respiratory support, and 6 children (37.5%) from Group I and 6 children (18.2%) from Group II were receiving methylxanthines (caffeine citrate) in a maintenance dose of 5 mg/kg/day.

Table 4. Correlation between min SpO_2 and polysomnography (PSG) in infants of different study groups (r, $p < 0.05$).

Parameter	Group I (n = 16)	Group II (n = 33)	Group III (n = 12)
min SpO_2 : RDI.TOT	-0.79	-0.65	-0.64
min SpO_2 : RDI.AS	-0.85	-0.60	-0.68
min SpO_2 : RDI.QS	-	-0.52	-
min SpO_2 : SRBD	-0.84	-0.65	-0.65
min SpO_2 : OA	-0.63	-0.53	-0.71
min SpO_2 : HYP	-0.67	-0.56	-0.58
min SpO_2 : CA	-	-0.39	-

min SpO_2: minimum pulse oximetry measured oxygen saturation during PSG; RDI.TOT: Respiratory Disturbance Index Total; RDI.AS: Respiratory Disturbance Index during Active Sleep; RDI.QS: Respiratory Disturbance Index during Quiet Sleep; SRBD: Sleep-Related Breathing Disorders; OA: obstructive apnea; HYP: hypopnea; CA: central apnea.

Using the results of the PSG, the children underwent correction of respiratory therapy. Thus, in Group I of the study 5 children (31.3%) were prescribed oxygen titration, 4 children (25%) – CPAP with supplemental oxygen, 6 children (37.5%) – CPAP with supplemental oxygen titration and prolongation of methylxanthines, and 1 child (6.3%) – supplemental oxygen titration with prolongation of methylxanthines. Surgical correction was performed in 2 children (12.5%) of this group with GERD (gastroesophageal reflux disease).

In Group II, 11 children (33.3%) required oxygen titration, 6 (18.2%) children – CPAP with supplemental oxygen titration, 9 children (27.3%) – CPAP with supplemental oxygen titration and prolongation of methylxanthines, 6 (18.2%) children – supplemental oxygen titration with prolongation of methylxanthines. Only 1 child did not need respiratory support.

In Group III, 2 children (16.7%) required oxygen titration, 4 children (33.3%) – CPAP with supplemental oxygen titration, 1 child (8.3%) – methylxanthine therapy; 5 children (41.7%) in this study group did not require respiratory therapy.

The results of this study led to the introduction of a new method of non-invasive respiratory therapy for PIs such as high flow oxygen therapy in our hospital.

Fig. 1 presents a graphical record of PSG of a boy K. who was born at 30 weeks of gestation. The recording was performed at 35 weeks of PMA. The main pathology is intraventricular hemorrhage (non-traumatic) of grade III. The PSG demonstrates a progressive increase in the number and duration of OA, MIXA with desaturation, and impaired sleep phases with a sharp reduction in deep sleep.

The child had required repeated respiratory support and neurosurgical treatment due to progression of hydrocephalus.

Fig. 2 presents a PSG record of a girl S. born at 28 weeks of gestation. The examination was performed at 36 weeks of PMA. The main pathology

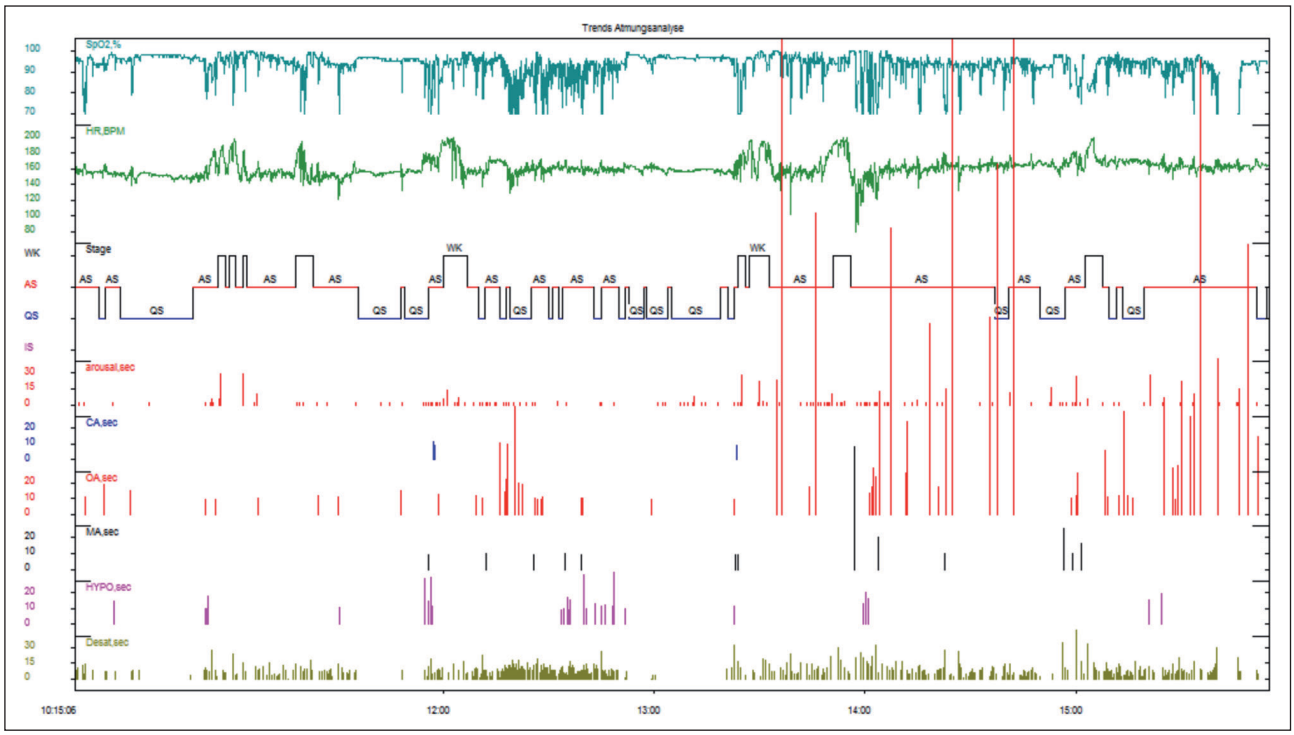

Figure 1. Patient 1, K., male, gestational age (GA) 30 weeks, postmenstrual age (PMA) 35 weeks.
SpO_2, %: level of saturation; HR, BPM: heart rate; Stage: stage of sleep; WK: wake; AS: Active Sleep; QS: Quiet Sleep; IS: Indeterminate Sleep; CA, sec.: central apnea; OA, sec.: obstructive apnea; MA, sec.: mixed apnea; HYPO, sec.: hypopnea; Desat, sec.: desaturation.

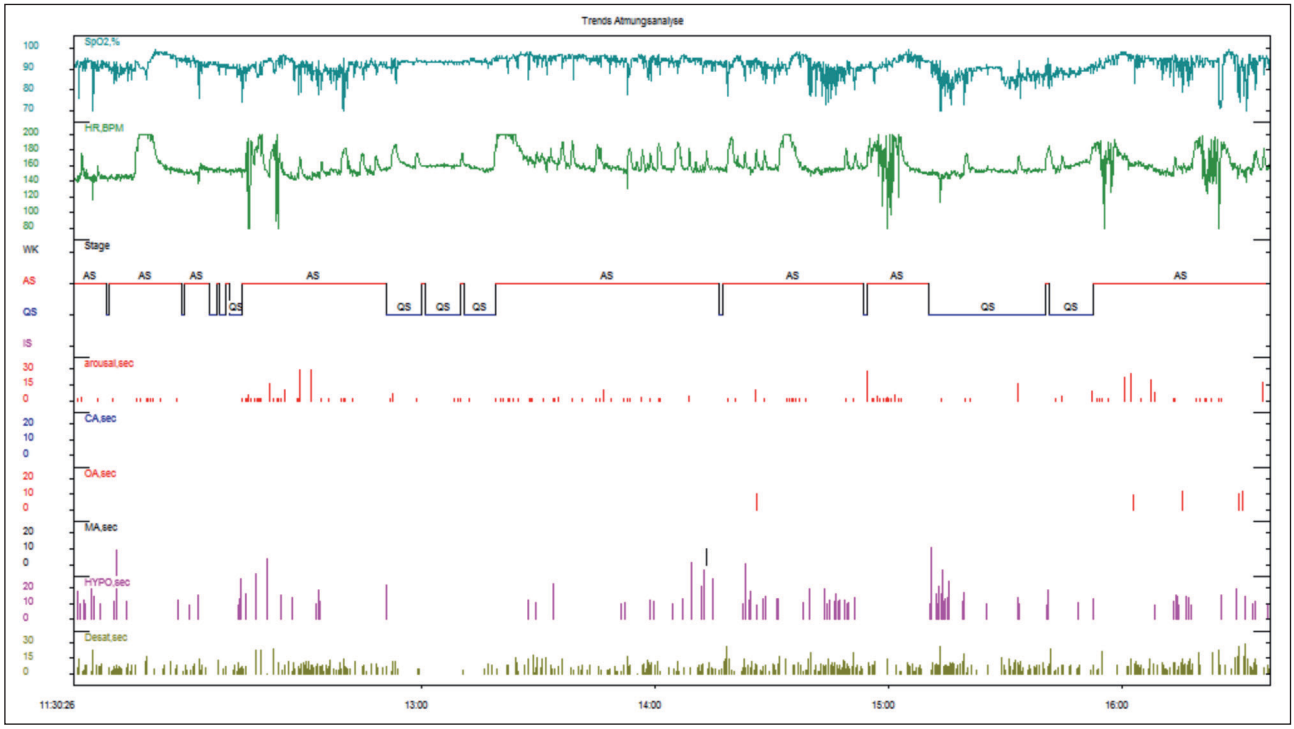

Figure 2. Patient 2, S., female, gestational age (GA) 28 weeks, postmenstrual age (PMA) 36 weeks.
SpO_2, %: level of saturation; HR, BPM: heart rate; Stage: stage of sleep; WK: wake; AS: Active Sleep; QS: Quiet Sleep; IS: Indeterminate Sleep; CA, sec.: central apnea; OA, sec.: obstructive apnea; MA, sec.: mixed apnea; HYPO, sec.: hypopnea; Desat, sec.: desaturation.

was hypoxic-ischemic encephalopathy. The PSG is characterized by regular sleep cycles with changes of AS to QS, short and frequent arousal, absence of CA, 5 episodes of short OA throughout the study, and frequent HYP with desaturations to 65%. According to PSG results the child was recommended to continue receiving methylxanthines for 1 month and periodic PSG recordings.

Discussion

A review of current scientific literature has shown that there is little research on the results of PSG usage in PIs with low and extremely low body weight, including the lack of international and national recommendations on the timing and indications for conducting this investigation in PIs [13]. In our scientific work we present the results of a single-center study of the characteristics of PSG indices in PIs of different GA. This is the first study on this issue conducted in Ukraine.

PSG is one of the components of a comprehensive neuromonitoring program for PIs and children with perinatal pathology who receive treatment at the National Children's Specialized Hospital "OKhMATDYT" (Kyiv, Ukraine). The recording of PSG in neonatal patients is technically difficult, due to the high risk of damage to the fragile skin of newborns during long-term video-PSG recording [13]. However, usage of the video-PSG system does not interfere with the implementation of Newborn Individualized Developmental Care and Assessment Program (NIDCAP) [31]. This enabled us to increase the duration of the PSG recording up to an average of 5.5 hours and, accordingly, to improve the research quality. In research by Miano et al. the average duration of video-PSG recording was 3 hours [32].

One of the peculiarities of our study was that we conducted PSG after standard EEG monitoring. This enabled us to differentiate between paroxysmal states of epileptic and non-epileptic origin, since the majority of PIs do not develop classical clinical signs of seizures.

According to the literature, seizures are one of the most frequent problems in the neonatal period, and are frequently associated with high mortality and morbidity rates [33]. Neonatal seizures may represent a first or even the only sign of central nervous system dysfunction. However, making the diagnosis of neonatal seizures suggests several problems, and clinical observation is not sufficient in many cases. Neonatal PSG is a valuable tool both in the diagnostic and prognostic assessment of neonatal seizures. Oliveira et al. (2000) review some technical aspects related to neonatal PSG, and its usefulness in the area of suspected neonatal seizures. Moreover, some questions arise regarding rhythmic discharges and their significance as a possible ictal and interictal epileptic pattern in the neonate [33].

Glass et al. (2016) noted that seizures are diagnosed in 67% of children born at 28 weeks of gestation or less, in 83% of children born at 28-32 weeks and in 48% of children born at 32-37 weeks [34]. Our results confirm these data and indicate a high frequency of instrumental seizure diagnosis in children with GA of 24-28 weeks and 29-32 weeks. It should be noted that in 1/3 of PIs, born in the GA of 33 weeks and more, electrographic seizures without clinical manifestations were diagnosed using comprehensive neuromonitoring and PSG.

The main goal of PSG is to identify different types of sleep apnea in PIs, which can help to reveal their causes and to develop appropriate management strategies. For example, PIs with CA require caffeine therapy, and for patients with significant OA usage of constant positive airway pressure is indicated [35]. Despite clinical signs of apnea and presence of ICD-10 codes (P28.3-28.4) the diagnosis of this condition in PIs remains difficult.

In our study, in a series of PSG cases in all the gestational groups of PIs, episodes of apnea with significant desaturations and bradycardia were observed, which were not diagnosed in clinical observation and were not recorded by other pulse and respiratory monitors.

AI is one of the PSG study components and is known to have great variability depending on age. According to the American Academy of Sleep Medicine (AASM) guidelines, the physiological level of AI for adults and older children is less than 10-25 [36]. The research by Daftarya et al. (2019) showed that an average value of AI in the healthy term infants is 14.7 episodes per hour in the first 30 days of life [37]. According to Grigg-Damberger et al. (2007), AI is associated with certain physiological features of breathing regulation during sleep in PIs and affects the structure and morphology of sleep. The higher AI rates are associated with deeper sleep fragmentation and higher number of SRBD accompanied by desaturation and arousal. This causes impairment and interruption of the baby's sleep, which interferes with the maturation of sleep stages and depth [25, 38]. Our results showed that the mean values of AI exceeded 20 in all the gestational groups of PIs, with the maximum level detected in children of 24-28 weeks and 29-32 weeks of GA.

The more pronounced hypnotic respiratory disorders were noted in children with signs of inconsistency of hypnogram to age, sleep fragmentation, and frequent arousals. Current literature indicates a close relationship between respiratory disorders and maturation of sleep stages in PIs of all the groups of observation [39-41]. It should be noted that according to the presented results, a statistically significant difference was demonstrated for RDI.QS, the maximum values of which were seen in the PIs of 24-28 weeks' gestation.

According to Mattes et al. (2019), in infants with BPD who receive oxygen therapy at home, SRBD of central genesis is common, but obstructive phenomena are also seen. The authors hypothesize that short breathing pauses in sleep can lead to significant oxygen desaturation in infants with BPD and reduced pulmonary reserve. CA events may also be associated with impaired respiratory control due to altered chemosensitivity [42-44].

Standard monitoring methods in Neonatal Intensive Care Unit (NICU) cannot detect events that are primarily obstructive. The severity of OA is manifested in the occurrence of mixed events in which airflow obstruction leads to a CA pause or vice versa. According to Eichenwald et al. (2016) during continuous recording it is obvious that some PIs continue to have clinically indistinct (subclinical) apnea, bradycardia and oxygen desaturation events even after discharge [8].

During our study respiratory disorders with duration of more than 10 seconds were taken into account, followed by desaturation of less than 89%. Turning to SRBD absolute indicators, the maximum frequency of sleep-related respiratory disorders in the PIs born at 24-28 weeks of gestation was found. It should be noted that these changes were accompanied by the maximum frequency of HYP and OA development in children of this group. There was no statistically significant difference in the incidence of CA and MIXA between the groups of observation. This requires further research with setting filters on shorter episodes duration.

Matlen et al. (2019) found the strongest association between OA and premature birth with a positive correlation between the two ($r = 0.33$, $p < 0.0001$) [45]. In contrast to the results presented by Meerkov et al. (2019) it was found that the majority of SRBD episodes in term and near-term infants receiving treatment in NICU have a central origin [46]. According to the literature, the differences between the nature of PSG indices changes in full-term and PIs are due to the physiological immaturity of brain structures and, accordingly, due to the central mechanisms of respiratory control and sleep maturation [18, 47].

O'Brien et al. (2000) noted that even children born after 37 weeks of gestation have episodes of desaturation (less than 80% SpO_2) with a frequency of 0 per hour (limits: 0-14.7) in the first hour of life up to 4 days of life and 0.9 per hour (limits: 0-15.1) on 39 days of life. At the same time, the average desaturation duration decreased from 5.1 seconds (limits: 4.2-9.9 seconds) on the 4th day to 0.9 seconds (limits: 0.4-1.8 seconds) on the 3rd month [48]. Daftarya et al. (2019) showed that the average SpO_2 value during sleep in healthy term infants is 97.9% with the minimum level of 84.4% [37]. During our research we established a minimum level of oxygen saturation (min SpO_2) during SRBD in children born at 24-28 weeks of gestation. It is noteworthy that even in children of greater GA (29 weeks and older) the manifestations of SRBD were accompanied by a decrease in SpO_2 level below physiological values (89-95%). Episodes of hypoxia of an under-mature brain can lead to impaired maturation processes with further development of pathological consequences. This conclusion is confirmed by the results of Horne et al. (2017), who reported that in those who were born as PIs apnea occurrence at 2-3 and 5-6 months of age is common, and are associated with decreased heart rate and cerebral oxygenation and can contribute to adverse neurocognitive outcomes [49].

The present study has several limitations: first, the inclusion of one center with a low number of participants; second, the absence of a control group with healthy PIs and absence of distribution of PIs according to the main neonatal pathology; third, the presence of repeated PSG recordings was available only in a limited number of children at follow-up.

Prospects for further studies are aimed at conducting large multicenter studies to determine the normal values of PSG indices in PI of different GA and PMA, as well as to study the correlation between changes of PSG indices and development of neonatal and neurological pathology in the future.

Conclusions

The article presents the results of the first single-center 5-year research of PSG indices in PIs of different GA with perinatal pathology conducted in Ukraine.

The most considerable pathological PSG changes were found in infants born at the age of 24-28 weeks of gestation. When an average PMA of 36 weeks was

achieved the maximum levels of RDI.TOT, RDI.AS, RDI.QS, SRBD, OA and HYP were determined in children from this group. Children born in the term of gestation of 29-32 weeks and with an average PMA of 35 weeks developed a statistically more considerable decrease in RDI.QS, with a stable decrease in all other indices. In PIs of 33-36 weeks of GA and an average PMA of the "full-term" 38 weeks, minimum values of all the polysomnographic indices were found respectively. However, it should be noted that in all the groups of observation average values of AI were higher than 20, and min SpO_2 during SRBD was considerably lower than that of the physiological norm.

Peculiarities of the polysomnographic indices found in PIs suffering from various perinatal pathology are indirectly indicative of the dependence of the degree of sleep disturbances and pathological respiratory events during sleep on the baby's GA. The changes detected do not disappear in older infants even after they achieve the "full-term", which requires careful monitoring of the vital functions and differential treatment of various apnea types.

Conducting PSG in PIs allows making individualized correction of respiratory therapy, namely, to determine the need for continuation or discontinuation of oxygen titration, CPAP and/or treatment with methylxanthines.

We realize that our study is, to some extent, restricted and further studies are required with a larger cohort of patients, unification of the insertion criteria and distribution into the groups of investigation, and identification of the control group in order to determine the physiological norm of PSG indices depending on GA and PMA.

Abbreviations

AI: Arousal Index
ALTE: Apparent Life-Threatening Event
AS: Active Sleep
BPD: bronchopulmonary dysplasia
BRUE: Brief Resolved Unexplained Events
CA: central apnea
EEG: electroencephalographic
GA: gestational age
HYP: hypopnea
IQR: interquartile range
IS: Indeterminate Sleep
Lq: lower quartile
Me: median
min SpO_2: minimum pulse oximetry measured oxygen saturation during PSG
MIXA: mixed apnea
NICU: Neonatal Intensive Care Unit
NS: not significant
OA: obstructive apnea
PIs: preterm infants
PMA: postmenstrual age
PSG: polysomnography
QS: Quiet Sleep
RDI.AS: Respiratory Disturbance Index during Active Sleep
RDI.QS: Respiratory Disturbance Index during Quiet Sleep
RDI.TOT: Respiratory Disturbance Index Total
SRBD: Sleep-Related Breathing Disorders
Uq: upper quartile

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Declaration of interest

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