sciendo
ПРИЛОЗИ. Одд. за мед. науки, XLV 3, 2024 МАНУ
CONTRIBUTIONS. Sec. of Med. Sci., XLV 3, 2024 MASA

10.2478/prilozi-2024-0020 ISSN 1857-9345

NEURODEVELOPMENT OF CRITICAL ILL NEONATES AT THE AGE OF 12 MONTHS

Sanja Ristovska[1], Zoran Gucev[2], Valentina Dukovska[2]

[1] University Clinic for Gynecology and Obstetrics, Faculty of Medicine, St. Cyril and Methodius University in Skopje, RN Macedonia
[2] University Clinic for Children's Diseases, Faculty of Medicine, St. Cyril and Methodius University in Skopje, RN Macedonia

Corresponding author: Sanja Ristovska, University Clinic for Gynecology and Obstetrics, Faculty of Medicine, St. Cyril and Methodius University in Skopje, RN Macedonia, email: ivanovska_15_sanja@yahoo.com

ABSTRACT

Critically ill neonates who survive are often left with dire consequences. Cerebral palsy, other neurological and motor deficiencies, intellectual disability, and various degrees of cognitive and behavioral deficiencies all result from neonatal critical diseases. We investigated psychomotor development in 20 children with hypoxic-ischemic encephalopathy (HIE), and as newborns often have multiple comorbidities, the following as well: HIE with respiratory distress syndrome (RDS), infections, hypo and hyperglycemia and hypocalcemia. Socio-demographic, pregnancy and delivery data together with appropriate staging tools in determining the severity of HIE or RDS were utilized in this evaluation. In addition, a physical examination, Apgar score, blood gas analyses, biochemical, microbiological and ultrasound data were also part of this study. A child's psychomotor development includes four main areas: motor skills, language, cognition, and social relationships. The Griffiths Mental Development Scale (GMDS) compares different developmental domains and enables early diagnosis of deficiencies and guidance for appropriate early intervention. Six children (30%) were diagnosed with cerebral palsy. GMDS showed that at the age of one year, 50% of the children had typical development, 5% had mild disability, 20% moderate disability and 25% had severe disability. The severity of HIE, Apgar score, weak muscle tone, seizures, disturbances in glucose homeostasis, comorbidities (sepsis, infection) statistically significantly impacted the outcome. Studies with a greater number of patients are needed to support these findings and enable early interventions to avoid severe consequences of critical illness neonates.

Keywords: critically ill neonates, neurodevelopment, hypoxic-ischemic encephalopathy

INTRODUCTION

Hypoxic-ischemic encephalopathy (HIE), (especially if combined with respiratory distress syndrome (RDS), infection) is a frequent cause of neonatal death. Children who survive are often left with devastating long-term neurological and mental impairment [1, 2]. The incidence of HIE is 1.3 to 1.7 per 1,000 live births, accounting for at least 30% of all cases of neonatal encephalopathy in resource-rich and 60% in resource-poor countries [3]. In addition, the prevalence of neurodevelopmental deficits varies depending on the socio-demographic background of the studied populations [4, 5]. The rate of severe developmental disabilities, which include intellectual disability, cerebral palsy, and/or motor retardation, is proportional to the severity of HIE. Cognitive impairments may be present even without motor disability.

Both high mortality and the impactful consequences of critically ill newborns require tools for precise prediction of outcomes in order to have evidence-based intensive care decisions, for triaging

infants in follow-up programs, and for identifying patients for early interventions [6]. Physical examination, biochemical markers, imaging techniques and psychomotor scales are used to determine the severity of HIE (with or without RDS, sepsis) and to assess the risk of early and late neurodevelopmental outcomes.

A child's psychomotor development includes four main areas: motor skills, language, cognition, and social relationships [7]. The Griffiths Mental Development Scale (GMDS) is an appropriate tool that compares different developmental domains and enables early diagnosis of deficits and guidance towards appropriate early intervention [8].

AIM

The aim of this study is to analyze the neurodevelopmental outcome of critically ill infants with HIE at the age of one year.

PATIENTS AND METHODS

A retrospective-prospective observational study was conducted in critically ill newborns born with HIE at the University Clinic for Gynecology and Obstetrics in Skopje and hospitalized at the Neonatal Intensive Care Unit. This study was conducted in the period from February 2021 to November 2022. Premature (≥26-36 gestational weeks) and term (≥37 gestational weeks) infants with HIE are included in the study. Newborns with congenital anomalies, chromosomal abnormalities, premature newborns <24 weeks of gestation are excluded from the study.

The criteria according to the American College of Obstetricians and Gynecologists (2014) [9] for HIE in acute peripartum or intrapartum change were used to define HIE in term newborns. For premature infants, HIE is defined according to the diagnostic criteria for HIE in premature infants proposed by Gopagondanahalli KR et al. (2016) [10]. A modified Sarnat & Sarnat scale was used for the severity of HIE (2019) [11] and the Thompson score system for the severity of HIE (1997) [12] was used to grade the severity of HIE. Cranial ultrasonography detected intracranial hemorrhages (ICH) in newborns and they are classified from grade I-IV according to the classification by Papile (1978) [13].

Muscle tone, reflexes and seizures were analyzed in the newborns and a comparison with the neurological status at the age of one year was done.

The presence of impaired glucose homeostasis in newborns with HIE in the first 12 hours of birth was analyzed and the influence of hyperglycemia/hypoglycemia on the early neurodevelopmental process in children was evaluated. Hyperglycemia was defined as glucose >150 mg/dl or >8.3 mmol/l [14], and hypoglycemia as glucose ≤40 mg/dl or ≤2.2 mmol/l [15].

The presence of hypocapnia on the first day of birth in newborns with HIE was investigated through the analysis of pCO_2 from the blood gas analyses. Moderate hypocapnia was defined as a pCO_2 less than 3.3 kPa (24.7 mmHg), and severe hypocapnia as a pCO_2 less than 2.6 kPa (19.5 mmHg) [16].

Hypocalcemia was analyzed in all critically ill infants. For term and preterm infants with a BW ≥1500 g, hypocalcemia was defined as ionized Ca <4.4 mg/dL (<1.1 mmol/L) and for preterm very low BW (VLBW; BW 1000 to <1500 g) and extremely low BW (ELBW; BW <1000 g) neonates, hypocalcemia was defined as ionized Ca <4 mg/dL (<1 mmol/L) [17]. Hypomagnesemia was defined as serum Mg < 0.66 mmol/l (< 1.6 mg/dl) [18].

The Apgar score [19] at the first, the fifth, and the tenth minutes was analyzed and compared with the neurodevelopmental outcome at 1 year of age. Sepsis, pneumonia, necrotizing enterocolitis (NEC), RDS and disseminate intravascular coagulation (DIC), as comorbidities in these critically ill infants were considered risk factors.

The Griffiths Mental Development Scale (GMDS) was used for the neurodevelopmental assessment of children aged one year, with analysis of the following subscales: A-locomotor, B-personal-social, C-hearing and speech, D-eye and hand coordination, E-performance [20]. Scores were estimated for each subscale and an overall general quotient (GQ) was calculated. A GQ ≥ 90 was considered normal, 80-89 mild disability, 70-79 moderate disability and <70 severe disability [21]. The neurodevelopmental assessment was conducted by a certified specialist for developmental assessment of high-risk children at the University Clinic for Children's Diseases in Skopje.

STATISTICAL ANALYSIS

The data obtained from the medical history of the newborns were grouped and distributed accordingly in a database in Microsoft Excel. The data were processed with the statistical software programs Microsoft Excel and SSPS 26. A descriptive analysis was carried out and conclusions were obtained. Part of these results are the basis for the calculation of further statistical research. Student's t-test for two dependent samples and Student's t-test for two independent samples were used to determine the significance for testing the alternative hypothesis. With a non-parametric Fisher's Exact Test, the statistical significance/ insignificance of the differences between the frequencies of the dependent samples was determined. Correlation between variables was processed with Pearson's correlation test and Sperman's rank correlation. A p-value less than 0.05 was considered statistically significant.

RESULTS

Twenty critical ill newborns with HIE and common neonatal co-morbidities born at the University Clinic for Gynecology and Obstetrics in Skopje and hospitalized at the Neonatal Intensive Care Unite between February 2021 and November 2022 were examined. The group includes 17 premature (≥25-36 gestational weeks) and 3 term newborns (≥37 weeks of gestation) with HIE (Table 1). The birth weight is 1757.10±745 gr, and the gestational age is 31.89±3.63 gestational weeks. Eleven newborns are boys and nine are girls (Table 1).

Table 1. *Maternal characteristics, comorbidities, pregnancy and birth*

Nationality n(%)	
- Macedonian	11 (55%)
- Albanian	7 (35%)
- others	2 (10%)
Education n(%)	
-tertiary education	7 (35%)
-high school	8 (40%)
-unknown	5 (25%)
Occupation n(%)	
- employee	12 (60%)
-unemployed/housewife	8 (40%)
Mother's age	32.89±4.21
Number of pregnancies n(%)	
- first	9 (45%)
- second	6 (30%)
- third	2 (10%)
- fourth	1 (5%)
- fifth	2(10%)
Pregnancy n(%)	
- spontaneously	17 (85%)
- IVF et ET	3 (15%)
Mode of delivery n(%)	
- vaginal	1 (5%)
- caesarean section	19 (95%)
Infections during pregnancy n(%)	
-colpitis	3 (15%)
-urinary infection	2 (10%)
-chorioamnionitis	1 (5%)
Comorbidities in pregnancy n(%)	
-Preeclampsia	2 (10%)
-Pregnancy induced hypertension	3 (15%)
- DM gestationes	1 (5%)
-Oligohydramnios	1 (5%)
Placenta n(%)	
- placental abruption	9 (45%)
- defective placenta	1 (5%)
Fetal distress n(%)	7 (35%)
Gestational age n(%)	
Extremely preterm (<28 weeks)	4 (20%)
Very preterm (28–<32 weeks)	9 (45%)
Moderate or late preterm (32–<36weeks)	4 (20%)
Term newborn (≥37 weeks)	3 (15%)
Gender n(%)	
Male	11 (55%)
Female	9 (45%)
Birth weight (g) n (%)	
≤1000	3 (15)
1000 – 1500	3 (15)
≥1500	14 (70)
Birth weight (g) (mean ± SD)(min- max)	(1863.5 ± 867.6) (910 – 3885)

The mother's education has no influence on the neurodevelopmental process at the age of one year (p=0.21).

Hypoglycemia was found in 65% of the patients (1.32±0.82 mmol/l), hyperglycemia in 80% (10.71±2.59mmol/l). Disorders of glucose homeostasis were found in 45% of children in the first 24h of life. GMDS found five (55.5%) children with severe locomotor disability and in three (33.3%) patients with severe delay in personal-social development, and in hearing and speech, eye and hand coordination and performance. Four (44.4%) children were diagnosed with cerebral palsy at the age of one year. Total GMDS and the five subscales have an inverse correlation to hyperglycemia (n=15, r=-0.458 p=0.08), Griffiths B (n=15, r=- 0.472, p=0.07), Griffiths C (n=15, r=-0.498 p=0.05), Griffiths E (n=15, r=-0.468 p=0.07). Griffiths A (locomotor) and D (eye and hand coordination) were not significantly correlated with hyperglycemia (fig.1).

Moderate hypocapnia was observed in 40% of patients in the first 24 hours after birth, with 22.68±1.0 mmHg, of which three were HIE

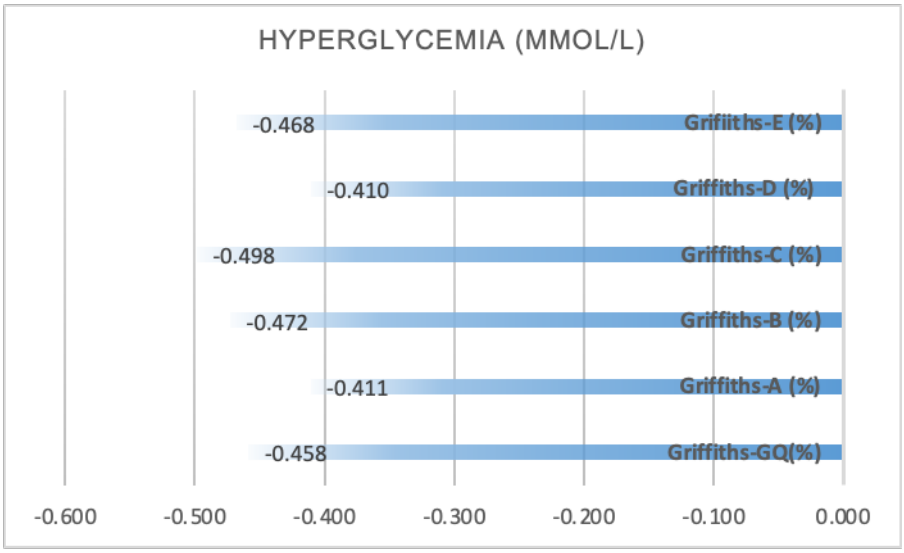

Figure 1. *Correlation between hyperglycemia, total Griffiths score and the five subscales*

grade 1, four with HIE grade 2 and one with HIE grade 3 according to the modified Sarnat & Sarnat severity scale. Half of them (50%) of have cerebral palsy. Linear regression showed that hypocapnia had no significant influence on neurodevelopmental outcome in one-year-old children (p=0.31).

Hypocalcemia was detected in 16 (80%) neonates. At the age of 12 months, GMDS showed five children (31%) with severe, three (18.7%) with moderate and one child (6.2%) with mild developmental affection. Seven patients (44.1%) had typical development.

Hypomagnesemia was not observed in this cohort.

Respiratory distress syndrome (RDS) was detected in 13 (65%) neonates, 53% requiring surfactant application, and 84% required invasive mechanical ventilation. Three (23%) of them had severely affected and four (30%) had moderately affected neurodevelopment. Sepsis, documented by a positive blood culture and elevated inflammatory markers, was present in 40% of infants. In this group there were five children (62.5%) with severely affected and one (12.5%) with moderately affected neurodevelopment. Sepsis was significantly more frequent in infants with a total Griffiths score less than 70 (severe disability) compared to infants with moderate disability, mild disability and children with typical neurodevelopment (p=0.0007). Pearson's correlation test confirmed a direct correlation between the sepsis and neurological outcome at the age of one year (n=8, r=0.579, p=0.007) and an inverse association with total Griffiths score (n=8, r=-0.720, p<0.001) (fig. 2). There was one patient with pneumonia, with typical neurodevelopment at age of 12 months. Necrotizing enterocolitis (NEC) was not observed. DIC associated with sepsis was detected in three (15%) neonates, of whom severe neurodevelopment affection was observed in two patients (15%).

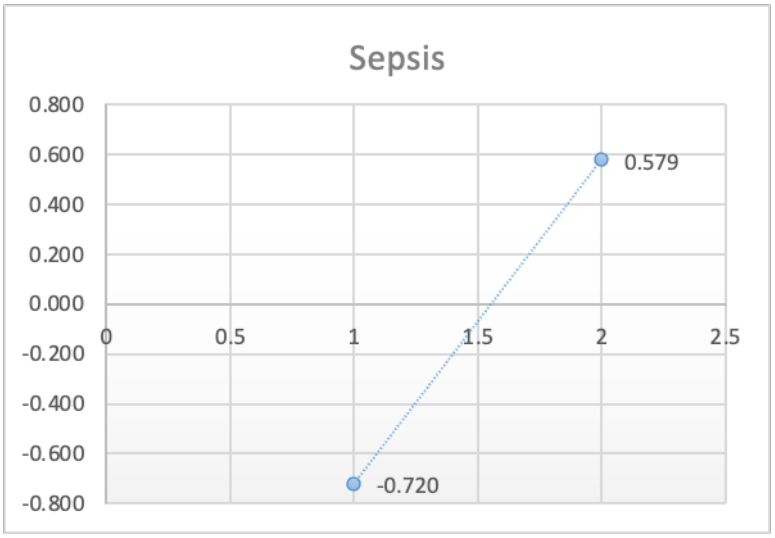

Figure 2. *Correlation between sepsis and total Griffiths score*

An Apgar score of ≤3 in the first and fifth minute was detected in 20% of newborns, and in the tenth minute in 15%. The analyzed correlation between the Apgar score at the 1st, 5th and 10th minutes and the GMDS (all subscales and the total Griffiths score) presents a statistically significant association between the Apgar score at the 10th minute and the locomotor subscale-Griffiths A (p=0.047) and with the total Griffiths score (p=0.046). Spearman's rank correlation coefficient reported both correlations as positive, i.e. direct (R=0.4320 and R=0.40455), respectively for the locomotor subscale and total Griffiths score. Therefore, an increase in the Apgar score increases the values of the Griffiths locomotor subscale and total Griffiths score. Newborns with a higher Apgar score had better neurological development, and vice versa (fig. 3 and 4).

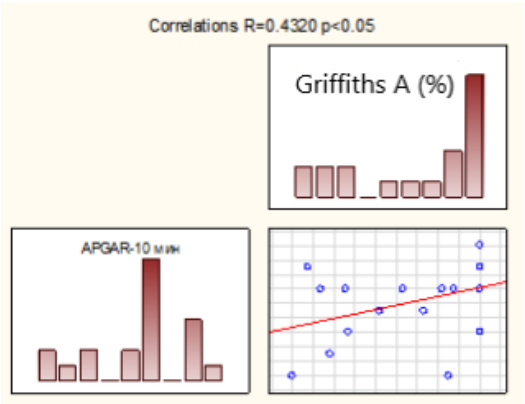

Figure 3. *Correlation between the Apgar score at the 10th minute and the locomotor subscale (Griffiths A)*

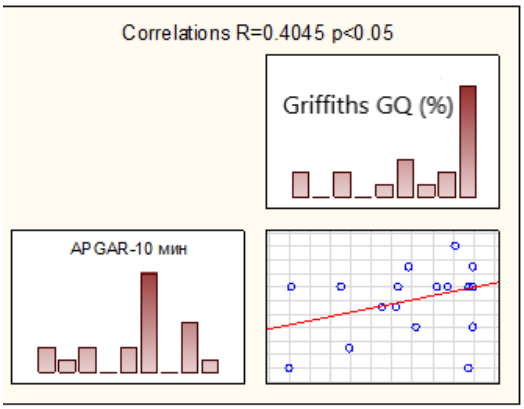

Figure 4. *Correlation between the Apgar score at the 10th minute and total Griffiths score*

In this patient cohort, 70% have a mild HIE, 20% have a moderate HIE, and 10% have a severe HIE (modified Sarnat & Sarnat severity scale). The Thompson score yielded identical results. In children with mild HIE, eight (57.14%) have typical neurologic development and a total Griffiths score ≥90. Neurologic disorders were detected in six (42.89%) children with mild HIE at the age of one year, of which three (21.43%) have cerebral palsy.

Pearson's analysis confirmed that there is a significant statistic correlation between Sarnat & Sarnat score and Griffiths E (abilities) (n=20, r=-0.455, p=0.04)(fig. 5).

Transfontanellar ultrasonography detected intracranial hemorrhage (ICH) in 11 (55%) infants, hemorrhage of first degree in 5%, second degree in 35% and third degree in 15%. The Griffiths scale found that three (27%) of

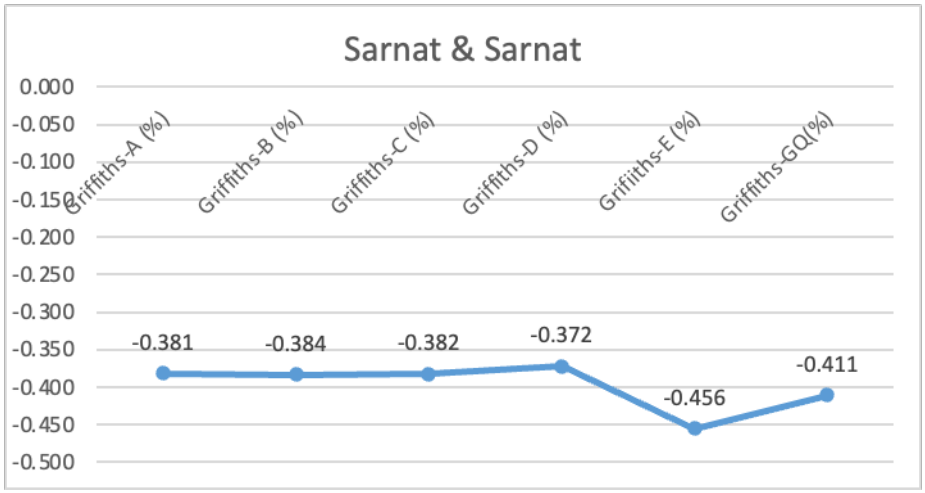

Figure 5. *Correlation between Sarnat & Sarnat score and Griffiths score*

them had severe neurodevelopment damage at the age of one year. In the neonatal period for this group, we observed weak muscle tone in 90%, increased muscle tone in 15%, weak reflexes in 50% and seizures in 10%. Pearson's test showed a statistically significant correlation between week axial muscle tone in children and total Griffiths score (n=17, r=0.65, p=0.002).

Cerebral palsy was diagnosed in six (30%) children at the age of one year, two with spastic quadriplegia, two with hypotonic cerebral palsy and two with spastic diplegia. A direct correlation with weak muscle tone (n=6, r=-0.642, p=0.002), seizures (n=6, r=0.509, p=0.022) in the neonatal period and the development of cerebral palsy at the age of 12 months was confirmed.

The Griffiths Mental Development Scale (GMDS) showed that at the age of one year, 50% of the children have typical development, 5% mild disability, 20% moderate disability and 25% severe disability (table 2). Table 2 shows the values of the GMDS subscales at the age of one year. All five parts in the Griffiths scale were significantly affected (from 76.1 to 79.85 out of 100). The locomotor part of the scale was the most affected, although this was not statistically significant.

The severity of HIE, Apgar score, hypotonia, seizures, disturbances in glucose homeostasis, comorbidities (sepsis, infection) were statistically significant and influenced the neurodevelopmental outcome (p>0.001).

Table 2. *GMDS subscale values at 1 year of age.*

Griffiths subscale 1 year old (n=20)	*Mean*	*SD*	*Min*	*Max*	*median (IQR)*
A-Locomotor	76.1	26.11	29	100	87 (49.5 – 100)
B-Personal-social	79.85	23.54	29	100	83 (70 – 100)
C-Speech and hearing	79.25	23.66	25	100	87 (70 – 100)
D-Eye hand coordination	79.55	23.75	29	100	88 (64.5 – 100)
E-Performance /visual-spacial	79.65	25.15	25	100	88 (70 – 100)
General Griffiths (GQ)	78.2	23.8	29	100	88 (67.5 – 100)

DISCUSSION

The developmental outcome in children with HIE is a spectrum of neurodevelopmental disorders. There is increasing evidence that cognitive deficits can be present in the absence of motor impairment [22]. These problems can be detected in the early years and therefore devel-

opmental follow up of these children is recommended, starting from infancy and continuing further into childhood.

The prevalence of major developmental disabilities increases with the severity of HIE and prematurity. Importantly, moderate to mild neurodevelopmental disorders can occur in the absence of major disability in all developmental domains, including learning disabilities, language delays, motor coordination disorder, and behavioral and social interaction problems. Some problems become apparent during later school age, when more complex academic and cognitive skills develop [23]. Overall, these problems occur in approximately 50% of children with HIE grade 2 and 3 according to Sarnat & Sarnat score in 30-50% of children born under 32 weeks of gestation [24]. We found that in the group of newborns with HIE grade 2 and 3, according to the modified Sarnat & Sarnat score, 66% of the children at the age of 1 year have a severe form of neurodevelopmental disorder as assessed with the GMDS. Correlation analysis between the Sarnat & Sarnat score and the total Griffiths score and the five subscales confirmed that there is statistical significance between the Sarnat & Sarnat score and Griffiths E (performance), regarding the manipulation, speed and precision of the work.

The association of birth asphyxia and cerebral palsy showed a large variation from 3% to 50% [25]. In this study, there was a high prevalence of cerebral palsy (30%). It is of note that all five parts that Griffiths investigates were significantly affected (table 2) (from 76.1 to 79.85 out of 100). Although the locomotor part seemed most affected, this was not statistically significant when compared to the other parts of Griffiths scale. In these children, a direct correlation was confirmed with weak muscle tone and seizures in the neonatal period and the development of cerebral palsy at the age of one year.

We looked further at possible factors influencing the impact on development in those critically ill newborns. Tomilson (2003) [26], cautions that infants live in an environment that is very different from that inhabited by the typical child development researcher. The development of motor skills appears to be differentially influenced by the home environment, with infants from lower socioeconomic groups performing significantly worse than groups with higher socioeconomic status [27]. In this study, unemployed and families with lower education levels have not been found to have worse neurodevelopmental outcomes.

Several studies highlight a favorable outcome in infants with mild HIE. Mendler et al. (2018) [28] showed that a Thompson score ≤10 was associated with normal cognitive function. Higher Thompson scores have been associated with death, development of epilepsy, and abnormalities in amplitude electroencephalography [29, 30]. More recent longitudinal studies in the era of therapeutic hypothermia show that infants receiving therapeutic hypothermia survive without major disability, including those with mild HIE, but may suffer from impairments in memory, intellect, and motor function in later childhood. This can be attributed to specific sites and modalities of brain injury identified in the neonatal period [31]. The Thompson score system for determining the severity of HIE showed that a mild degree of HIE (Thompson score 0-10) was observed in 70% of the examined newborns. This study confirmed that higher Thompson scores predict worse outcomes. In the group of children who have a mild degree of HIE, according to the Thompson score, eight (57.14%) have typical neurological development and a Griffiths score ≥90. In the systematic review by Conway et al. (2018) [32], reports that 22% of infants with mild HIE have an abnormal outcome by age 18 months. They show that approximately one quarter of infants with mild HIE have an abnormal outcome defined as death, motor or developmental delay at the age of 18 months. In our research, six (42.89%) children with mild HIE had neurological disorders at the age of one year, of which three (21.43%) had cerebral palsy.

The American Academy of Pediatrics and the American College of Obstetrics and Gynecology recommend that the Apgar score should not be used as a predictor of neurodevelopmental outcome [33], but several studies have confirmed that a low Apgar score at 10 minutes is significantly associated with death or poor neurodevelopmental outcome at 18-22 months of age and in school age [34, 35, 36]. 75% of newborns who had an Apgar score of 0-3 at 10 minutes die or have disability at the age of 6-7 years [35]. In this study Apgar score ≤3 in the first and fifth minutes was detected in 20% of the newborns, and in the tenth minute in 15%. In this study, a low Apgar score is followed by worse outcomes.

Cerebral palsy and deviations in all five Griffiths subscales were detected in 10%.

pH and pCO_2 are potent modulators of cerebral blood flow in neonates and may contribute to neonatal brain injury with HIE [37]. The CoolCap study confirms that hypocapnia is associated with an increased risk of adverse outcome (death or severe neurodevelopmental disability) at 18 months of age. The probability of an unfavorable outcome increases dose-dependently with decreasing PCO_2, and hypocapnia is associated with a higher probability of an unfavorable outcome in infants with severe HIE, compared to those with moderate HIE [38]. Pappas A et al. (2011) [39] found that a cumulative PCO_2 exposure of less than 35 mm Hg in the first 12 h of life in infants with moderate to severe HIE was associated with death or moderate/severe neurodevelopmental disability at 18–22 months. This study found that both hypocapnia and high Sarnat & Sarnat severity score were found to be linked with less favorable outcomes. Although 50% of children who had hypocapnia on the first day of birth have cerebral palsy at one year of age, there is no statistically significant effect of moderate hypocapnia on neurodevelopmental outcome in these children.

Both hypoglycemia and hyperglycemia during the early postnatal period are associated with adverse outcomes [40, 41]. In patients with HIE, hypoglycemia in the first 24 hours after birth is associated with an increased risk of neurodevelopmental impairment at one-year follow-up [42]. In neonatal hypoxic-ischemic encephalopathy (HIE), hyperglycemia in the first 12 h is associated with poor motor outcome [43]. Postpartum hypoglycemia is associated with the severity of encephalopathy [44] and in the first 24 [42] and 72 hours [45] with adverse neurodevelopmental outcomes. The rate of death or severe neurological disability at 18 months of age is lowest in normoglycemic infants, intermediate in hyperglycemic infants, and highest in hypoglycemic infants [40]. In this study, variations in glucose homeostasis during the first 24 hours in infants with HIE show that 55.5% of infants have severe motor impairment at one year of age. There is an inverse correlation between hyperglycemia and total Griffiths scale, Griffiths B, Griffiths C, Griffiths E.

The incidence of intracranial hemorrhage (ICH) in neonates with HIE varies. Herrera et al. (2018) [46] had published an incidence rate of ICH of 38%, Bashir et al. (2018) [47] had incidence rate of 7.8%. Lakatos et al. (2019) [48] had presented a rate of 36% of ICH in asphyxiated infants and reported that ICH in one third of all cases had no significant effect on neurodevelopmental outcome. In this cohort higher incidence of ICH was found than previously observed. There were 27% of children with severe neurodevelopmental outcome at the age of one year.

Seizures, sepsis, and hypoxic-ischemic encephalopathy had a significant association with adverse outcome [49]. We found that in infants with sepsis there is a high rate of neurodevelopmental impairment. The analysis confirmed a direct correlation between sepsis and the neurological outcome at the age of one year and an inverse correlation with the total GMDS. There is also a direct correlation between convulsions in the neonatal period and the development of cerebral palsy at the age of one year.

CONCLUSION

A high proportion of children (30%) were found to have cerebral palsy at the age of 12 months. Only 50% were unaffected, while among the affected children, all five parts of the Griffiths scale were negatively impacted. Hypocapnia on the first day of birth in these critical infants is crucial for a neurological outcome. The severity scoring systems for HIE (Sarnat & Sarnat, Thompson score) are good predictive tools for early child development. Early assessment of critically ill infants with HIE and comorbidities such as sepsis, RDS, and ICH enables early intervention and early inclusion in follow up programs. Interventions carried out in the first two years of life, when the brain is maturing and there is neurodevelopmental plasticity, are of significant benefits for the future of the patients. The Griffiths scale, neurological assessment and follow up are important tools in the early treatment of the consequences of neonatal critical illness. Taken together with early neonatal treatment, these interventions could bring improvement to the quality of life of the child and the family. This would certainly be of benefit for the society as whole.

REFERENCES

1. Goswami I, Guillot M, Tam EWY. Predictors of Long-Term Neurodevelopmental Outcome of Hypoxic-Ischemic Encephalopathy Treated with Therapeutic Hypothermia. Semin Neurol 2020; 40(3): 322–334.
2. Tagin MA, Woolcott CG, Vincer MJ, Whyte RK, Stinson DA. Hypothermia for neonatal hypoxic ischemic encephalopathy: an updated systematic review and meta-analysis. Arch Pediatr Adolesc Med 2012; 166 (06): 558–566.
3. Kurinczuk JJ, White-Koning M, Badawi N. Epidemiology of neonatal encephalopathy and hypoxic-ischaemic encephalopathy. Early Hum Dev 2010; 86 (06): 329–338.
4. Anderson PJ. Neuropsychological outcomes of children born very preterm. Semin Fetal Neonatal Med 2014; 19 (2): 90–96.
5. Hack M. Survival and neurodevelopmental outcomes of preterm infants. J Pediatr Gastroenterol Nutr 2007; 45 Suppl 3: S141–142.
6. Langeslag JF, Berendse K, Daams JG, Onland W, Leeflang MMG, van Kaam AH, de Haan TR. Clinical Prediction Models and Predictors for Death or Adverse Neurodevelopmental Outcome in Term Newborns with Hypoxic-Ischemic Encephalopathy: A Systematic Review of the Literature. Neonatology 2023; 120 (6): 776–788.
7. Cirelli I, Bickle Graz M, Tolsa JF. Comparison of Griffiths-II and Bayley-II tests for the developmental assessment of high-risk infants. Infant Behav Dev 2015; 41: 17–25.
8. Jacklin, L, K. Cockcroft. The Griffiths Mental Developmental Scales: Psychological Assessment in South Africa 2013; 169–185.
9. Executive summary: Neonatal encephalopathy and neurologic outcome, second edition. Report of the American College of Obstetricians and Gynecologists' Task Force on Neonatal Encephalopathy. Obstet Gynecol 2014; 123(4): 896–901.
10. Gopagondanahalli KR, Li J, Fahey MC et al. Preterm Hypoxic–Ischemic Encephalopathy: Preterm Hypoxic–Ischemic Encephalopathy. Front Pediatr 2016; 4: 114.
11. Power BD, McGinley j, Sweetman D et al. The Modified Sarnat Score in the Assessment of Neonatal Encephalopathy: A Quality Improvement Initiative. Ir Med J 2019; 112(7): 976.
12. Thompson CM, Puterman AS, Linley LL et al. The value of a scoring system for hypoxic ischemic encephalopathy in predicting neurodevelopmental outcome. ActaPediatar 1997; 86(7): 757–761.
13. Inder TE, Perlman JM, Volpe JJ: Preterm intraventricular hemorrhage/posthemorrhagic hydrocephalus. In Volpe's neurology of the newborn, ed 6, Philadelphia, Elsevier 2018; 637–693.
14. Nadeem M, Murray DM, Boylan GB, et al. Early blood glucose profile and neurodevelopmental outcome at two years in neonatal hypoxic-ischaemic encephalopathy. BMC Pediatr 2011; 11: 10.
15. 15. Salhab WA, Wyckoff MH, Laptook AR, et al. Initial hypoglycemia and neonatal brain injury in term infants with severe fetal acidemia. Pediatrics 2004; 114:361–366.
16. Klinger G, Beyene J, Shah P, Perlman M. Do hyperoxaemia and hypocapnia add to the risk of brain injury after intrapartum asphyxia? Arch Dis Child Fetal Neonatal Ed 2005; 90: 49–52.
17. Vuralli D. Clinical Approach to Hypocalcemia in Newborn Period and Infancy: Who Should Be Treated? Int J Pediatr. 2019; 2019: 4318075.
18. Gomella T, Cunningham M, Eyal FG, Tuttle DJ. Magnesium Disorders (Hypomagnesemia, Hypermagnesemia). Neonatology: Management, Procedures, On-Call Problems, Diseases, and Drugs, 7e. McGraw-Hill Education; 2013.
19. Watterberg KL, Aucott S, Benitz WE, Cummings JJ, Eichenwald EC, Goldsmith J et al. The Apgar score. Pediatrics 2015; 136(4): 819–822.
20. Griffiths R. The abilities of young children: A comprehensive system of mental measurement for the first eight years of life. London: ARICD 1984.
21. Ivens J, Martin N. A common metric for the Griffiths Scales. Arch Dis Child 2002; 87: 109–110.
22. Mbatha S, Nakwa FL, Thandrayen K, Velaphi S. Neurodevelopmental outcome in neonates with hypoxic-ischaemic encephalopathy managed with therapeutic hypothermia in a tertiary-level public hospital outside an intensive care unit setting, Paediatrics and International Child Health 2021; 41:3, 171–176.
23. Adams M; Borradori-Tolsa C; Bickle-Graz M; Grunt S; Weber P; Capone Mori A; Bauder F; Hagmann C; Natalucci G; Pfister R E; Latal B. Follow-up assessment of high-risk newborns in Switzerland. Paediatrica 2014; 25(5): 8–10.
24. Latal B. Prediction of neurodevelopmental outcome after preterm birth. Pediatr Neurol 2009; 40 (6): 413–419.
25. Ellenberg JH, Nelson KB. The association of cerebral palsy with birth asphyxia: a definitional quagmire. Dev Med Child Neurol. 2013; 55: 210–6.
26. Tomlinson M. Culture and infancy: A critical examination. South African Journal of Child

and Adolescent Mental Health 2003; 15(1), 45–48.
27. Goyen T, Lui K. Longitudinal motor development of 'apparently normal' highrisk infants at 18 months, 3 and 5 years. Early Human Development 2002; 70(1–2), 103–115.
28. Mendler MR, Mendler I, Hassan MA, Mayer B, Bode H, Hummler HD. Predictive value of Thompson-score for long-term neurological and cognitive outcome in term newborns with perinatal asphyxia and hypoxic-ischemic encephalopathy undergoing controlled hypothermia treatment. Neonatology 2018; 114 (04): 341–347.
29. Thorsen P, Jansen-van der Weide MC, Groenendaal F, et al. The Thompson encephalopathy score and short-term outcomes in asphyxiated newborns treated with therapeutic hypothermia. Pediatr Neurol 2016; 60: 49–53.
30. Horn AR, Swingler GH, Myer L, Linley LL, Chandrasekaran M, Robertson NJ. Early clinical predictors of a severely abnormal amplitude-integrated electroencephalogram at 48 hours in cooled neonates. Acta Paediatr 2013; 102(08): 378–384.
31. Rao R, Trivedi S, Distler A, Liao S, Vesoulis Z, Smyser C, Mathur AM. Neurodevelopmental Outcomes in Neonates with Mild Hypoxic Ischemic Encephalopathy Treated with Therapeutic Hypothermia. Am J Perinatol. 2019; 36(13): 1337–1343.
32. Conway JM, Walsh BH, Boylan GB, Murray DM. Mild hypoxic ischemic encephalopathy and long term neurodevelopmental outcome - A systematic review. Early Hum Dev. 2018; 120: 80–87.
33. American Academy of Pediatrics, Committee on Fetus and Newborn, American College of Obstetricians&Gynecologists, Committee on Obstetric Practice, The Apgar score, Pediatrics 2006; 117: 1444–1447.
34. Laptook AR, Shankaran S, Ambalavanan N, et al; Hypothermia Subcommittee of the NICHD Neonatal Research Network. Outcome of term infants using Apgar scores at 10 minutes following hypoxic-ischemic encephalopathy. Pediatrics 2009; 124(06): 1619–1626.
35. Natarajan G, Shankaran S, Laptook AR, et al; Extended Hypothermia Subcommittee of the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. Apgar scores at 10 min and outcomes at 6- 7 years following hypoxic-ischaemic encephalopathy. Arch Dis Child Fetal Neonatal Ed 2013; 98(06): 473–479.
36. Sarkar S, Bhagat I, Dechert RE, Barks JD. Predicting death despite therapeutic hypothermia in infants with hypoxic-ischaemic encephalopathy. Arch Dis Child Fetal Neonatal Ed 2010; 95 (06): 423–428.
37. Goswami I, Guillot M, Tam EWY. Predictors of Long-Term Neurodevelopmental Outcome of Hypoxic-Ischemic Encephalopathy Treated with Therapeutic Hypothermia. Semin Neurol 2020; 40(3): 322–334.
38. Lingappan K, Kaiser JR, Srinivasan C, Gunn AJ. Relationship between PCO_2 and unfavorable outcome in infants with moderate-to-severe hypoxic ischemic encephalopathy. Pediatr Res 2016; 80(02): 204–208.
39. Pappas A, Shankaran S, Laptook AR, et al. Hypocarbia and adverse outcome in neonatal hypoxic-ischemic encephalopathy. J Pediatr 2011; 158: 752–758.
40. Basu SK, Kaiser JR, Guffey D, Minard CG, Guillet R, Gunn AJ; CoolCap Study Group. Hypoglycaemia and hyperglycaemia are associated with unfavourable outcome in infants with hypoxic ischaemic encephalopathy: a post hoc analysis of the CoolCap Study. Arch Dis Child Fetal Neonatal Ed 2016; 101(02): 149–155.
41. Al Shafouri N, Narvey M, Srinivasan G, Vallance J, Hansen G. High glucose variability is associated with poor neurodevelopmental outcomes in neonatal hypoxic ischemic encephalopathy. J Neonatal Perinatal Med 2015; 8(02): 119–124.
42. Tam EW, Haeusslein LA, Bonifacio SL, et al. Hypoglycemia is associated with increased risk for brain injury and adverse neurodevelopmental outcome in neonates at risk for encephalopathy. J Pediatr 2012; 161(01): 88–93.
43. Spies EE, Lababidi SL, McBride MC. Early hyperglycemia is associated with poor gross motor outcome in asphyxiated term newborns. Pediatr Neurol 2014; 50: 586–90.
44. 44. Basu P, Som S, Choudhuri N, Das H. Contribution of the blood glucose level inperinatal asphyxia. Eur J Pediatr 2009; 168: 833–838.
45. Nadeem M, Murray DM, Boylan GB, Dempsey EM, Ryan CA. Early blood glucose profile and neurodevelopmental outcome at two years in neonatal hypoxic-ischemic encephalopathy. BMC Pediatrics 2011; 11: 10.
46. Herrera TI, Edwards L, Malcolm WF, Smith PB, Fisher KA, Pizoli C, Gustafson KE, Goldstein RF, Cotten CM, Goldberg RN, Bidegain M. Outcomes of preterm infants treated with hypothermia for hypoxic-ischemic encephalopathy. Early Hum Dev 2018; 125: 1–7.
47. Bashir RA, Vayalthrikkovil S, Espinoza L, Irvine L, Scott J, Mohammad K. Prevalence and Characteristics of Intracranial Hemorrhages in Neonates with Hypoxic Ischemic Encephalopathy. Am J Perinatol 2018; 35(7): 676–681.

48. Lakatos A, Kolossváry M, Szabó M, Jermendy Á, Barta H, Gyebnár G, Rudas G, Kozák LR. Neurodevelopmental effect of intracranial hemorrhage observed in hypoxic ischemic brain injury in hypothermia-treated asphyxiated neonates – an MRI study. BMC Pediatr 2019; 19(1): 430.

49. Paul VK, Radhika S, Deorari AK, Singh M. Neurodevelopmental outcome of 'at risk' nursery graduates. Indian J Pediatr 1998; 65(6): 857–862.

Резиме

НЕВРОЛОШКИ РАЗВОЈ НА КРИТИЧНО БОЛНИ НОВОРОДЕНЧИЊА НА ВОЗРАСТ ОД 12 МЕСЕЦИ

Сања Ристовска[1], Зоран Гучев[2], Валентина Дуковска[2]

[1] Универзитетска клиника за гинекологија и акушерство, Медицински факултет, Универзитет „Св. Кирил и Методиј“ во Скопје, РС Македонија

[2] Универзитетска клиника за детски болести, Медицински факултет, Универзитет „Св. Кирил и Методиј“ во Скопје, РС Македонија

Преживеаните критично болни новороденчиња честопати преживуваат со тешки последици. Церебралната парализа, други невролошки и моторни оштетувања, ментална ретардација и различен степен на когнитивни и бихевиорални недостатоци се резултат на неонатални критични болести. Испитани се 20 деца со хипоксично-исхемична енцефалопатија (ХИЕ) и со повеќе коморбидитети: ХИЕ со респираторен дистрес синдром (РДС), инфекции, хипо- и хипергликемија и хипокалциемија. Во анализата на оваа група беа користени социодемографски податоци, податоци за бременоста и за породувањето, заедно со соодветни методи за одредување на стадиумот на тежината на ХИЕ или на РДС. Дополнително, во оваа студија беа користени физикалниот преглед, Apgar score, ацидо-базниот статус, биохемиските и микробиолошките податоци, како и податоците од ултразвучните прегледи. Психомоторниот развој на детето вклучува четири главни области: моторни вештини, јазик, сознание и социјални односи. Griffiths Mental Development Scale (GMDS) е алатка што споредува различни развојни домени и овозможува рана дијагноза на дефицитите и насоки кон соодветна рана интервенција. Кај шест деца (30 %) е дијагностицирана церебрална парализа. GMDS покажа дека на возраст од една година 50 % од децата имаат нормален развој, 5 % имаат лесна попреченост, 20 % умерена попреченост и 25 % имаат тешка попреченост. Резултатите од скалите за тежината на ХИЕ, Apgar score, хипотонијата, конвулзиите, нарушената гликозна хомеостаза, придружните коморбидитети на ХИЕ (сепса, инфекција) покажаа дека тие статистички значајно влијаат на исходот. Потребни се дополнителни студии со поголем број пациенти за да се поддржат овие наоди и да се прецизираат раните интервенции што треба да се преземат за да се избегнат тешките последици кај критично болните новороденчиња.

Клучни зборови: критично болни новороденчиња, невролошки развој, хипоксична-исхемична енцефалопатија