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## PREDICTING NEURO-MENTAL DEVELOPMENT DELAY IN INFANTS WITH HYPOXIC-ISCHEMIC ENCEPHALOPATHY BORN FROM MOTHERS WITH METABOLIC SYNDROME

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### Summary.

Among neonates, 2 per 1,000 experience hypoxia/ischemia at birth, resulting in hypoxic-ischemic encephalopathy (HIE) and subsequent neurodevelopmental disorders, which impose a lifelong burden on families and society. Infants with stage 3 HIE exhibit a high incidence of convulsive syndrome and severe neurodevelopmental delay. Even in the absence of profound impairments, affected children may present with motor, cognitive, or behavioral abnormalities.

**The aim of our study** was to analyze and identify maternal and neonatal risk factors associated with psychomotor developmental delay.

**Materials and methods of the study.** The study enrolled 45 infants born to mothers with metabolic syndrome who were diagnosed with moderate or severe HIE in the early neonatal period; among them, 30 were preterm and 15 were full-term. Follow-up of infants continued until 9 months of age; continued observation was possible in 27 (17 preterm, 10 full-term) of the 45 infants diagnosed with moderate or severe HIE. Statistical analysis was performed using standard descriptive methods and simple and multiple logistic regression, including Poisson regression. The predictive value of maternal history, metabolic parameters, and other variables was evaluated using receiver operating characteristic (ROC) curve analysis with calculation of the area under the curve (AUC) in STATA 14.0.

According to the decision of the Bioethics Commission of Poltava State Medical University No. 217 dated 12.06.2023, the study adhered to ethical standards for the humane treatment of patients, as defined by the Tokyo Declaration of the World Medical Association, the Helsinki Declaration, the Universal Declaration of Human Rights, the Council of Europe Convention on Human Rights and Biomedicine, current Ukrainian legislation, orders of the Ministry of Health, and the Code of Ethics for Physicians of Ukraine. Informed consent was obtained from all parents.

The study was conducted as part of the scientific research project of the Department of Pediatrics No. 1 with Neonatology, Poltava State Medical University, No. 0120U102856: «Development of clinical and laboratory criteria and methods for predicting and preventing metabolic disorders in young children.»

**Research results.** Most infants included in the study were diagnosed with moderate asphyxia at birth. The Apgar scores at 1 and 5 minutes were  $5.83 \pm 0.23$  and  $6.7 \pm 0.14$  points, respectively; in preterm infants, and  $5.8 \pm 0.52$  and  $7.2 \pm 0.34$  points in full-term infants. Mechanical ventilation was required immediately after birth in 16.7% of preterm infants with HIE and 46.7% of full-term infants; the duration of mechanical ventilation was  $4.26 \pm 0.7$  days in preterm infants and  $5.47 \pm 1.26$  days in full-term infants. The most common neurological conditions at 9 months of age were hypoxic-ischemic CNS injury and psychomotor delay. The frequency of hypoxic-ischemic CNS injury was 88.2% in preterm infants and 60% among full-term infants. The incidence of psychomotor delay was 20.0% in preterm infants and 17.6% in full-term infants. Multivariate logistic regression analysis, adjusted for gestational age at birth, was used to develop predictive models for psychomotor delay. The Apgar score and duration of mechanical ventilation were identified as the strongest prognostic factors. The predictive model including the duration of mechanical ventilation demonstrated a reliable predictive coefficient ( $\beta = 0.31$ ; 95% CI, 0.11-0.50) with an area under the ROC curve of 0.9180.

**Conclusion.** Approximately 20% of infants with HIE, both preterm and full-term, exhibited delayed neurodevelopment at 9 months of age. Multivariate logistic analysis identified low Apgar scores and prolonged mechanical ventilation as the most significant prognostic factors, with the predictive model incorporating ventilation duration demonstrating the highest predictive accuracy. These findings highlight the need to optimize medical monitoring and follow-up of infants with HIE born to mothers with metabolic syndrome.

**Key words:** Newborns; Hypoxic-Ischemic Encephalopathy; Neuromental Development Delay; Duration of Mechanical Ventilation.

### Relevanc

Despite advances in perinatal care, asphyxia remains a significant challenge in neonatology and pediatrics. Every two out of 1,000 infants experience hypoxia/ischemia at birth, resulting in hypoxic-ischemic encephalopathy (HIE) and subsequent neuropsychiatric disorders, which impose a lifelong burden on parents and society [1].

Infants with stage 3 hypoxic-ischemic encephalopathy (HIE) demonstrate a high incidence of convulsive syndrome

and severe neurodevelopmental delay. The prognosis of severe asphyxia is further influenced by the involvement of other organs and systems. The timing of spontaneous breathing, as assessed by the Apgar score, represents an additional predictor of adverse outcomes. Mortality among neonates with an Apgar score of 0-3 at 10 minutes is 20%, with 5% subsequently developing cerebral palsy. When the assessment is extended to 20 minutes, mortality increases to 60%, and the incidence of cerebral palsy rises to 55% [2].

In preterm infants, HIE predominantly results in periventricular leukomalacia, whereas in full-term infants, cerebral edema and cortical necrosis involving the basal ganglia are more common. Both conditions may result in cortical atrophy, intellectual disability, and spastic quadriplegia or diplegia [3]. The involvement of nitric oxide (NO) and related metabolites in HIE pathogenesis remains under investigation, as these compounds may function as vasoactive regulators, modulate vascular tone, influence blood-brain barrier permeability, drive neuroinflammation, and trigger apoptotic pathways [4, 5].

Even in the absence of severe neurological deficits, affected children may present with motor, cognitive, or behavioral abnormalities. A recent systematic review reported that a substantial proportion of such children remain at risk for general and domain-specific cognitive impairments, even after therapeutic hypothermia (THT) [6].

Despite the neuroprotective effects of THT, children with a history of HIE who are not subsequently diagnosed with cerebral palsy demonstrate reduced behavioral, cognitive, and motor performance at 6-8 years of age compared with peers, with approximately one-third requiring additional educational support [7].

Mechanical ventilation is an independent risk factor for neurodevelopmental delay in preterm infants. Shorter ventilation duration and noninvasive strategies may reduce the risk of neurodevelopmental impairment [8]. The morphological and functional immaturity of preterm brain increases vulnerability to deleterious factors, including hypoxia, asphyxia, placental dysfunction, and intensive pharmacological therapy, which can impair postnatal nervous system development.

Conversely, modern perinatal technologies and neurodevelopmental care strategies promote effective stimulation of central nervous system maturation through controlled sensory input [9].

Identifying clinically relevant prognostic indicators of neurodevelopmental delay is critical, as understanding long-term outcomes and their progression improves predictive accuracy and informs preventive and therapeutic interventions

**The aim of our study** was to analyze and determine maternal and neonatal risk factors associated with psychomotor developmental delay.

### Materials and methods of the study

The study enrolled 45 infants born to mothers with metabolic syndrome and diagnosed with moderate or severe hypoxic-ischemic encephalopathy (HIE) during the early neonatal period, including 30 preterm and 15 full-term infants. All neonates received care in the neonatal intensive care unit (NICU) of the Perinatal Center. HIE diagnosis was established according to the Sarnat scale. Diagnostic procedures followed the Order of the Ministry of Health of Ukraine dated 28.03.2014, No. 225, «On approval and implementation of medical and technological documents for the standardization of medical care for initial, resuscitation, and post-resuscitation care for newborns in Ukraine.»

The primary diagnostic criteria for inclusion in the HIE group were: evidence of moderate or severe perinatal asphyxia (Apgar score  $\leq 7$  at 1 and 5 minutes and/or umbilical artery blood acidosis); neurological manifestations within the first hours of life persisting for more than 24 hours, including alterations in consciousness (hyperactivity, generalized depression, or comatose state), abnormal muscle tone (hypertonia or hypotonia), diminished or absent primitive reflexes (e. g., sucking and grasping), seizure activity, and indicators of brainstem involvement (abnormal respiration, impaired pupillary light reflex, and other brainstem reflex abnormalities).

Inclusion criteria for newborns comprised maternal diagnosis of metabolic syndrome, presence of clinical signs and laboratory-confirmed HIE according to regulatory healthcare documents, neonatal stay in the post-intensive care unit of the Poltava Regional Clinical Hospital named after M. V. Sklifosovsky, and complete medical documentation on demographic, anamnestic, and clinical characteristics. Exclusion criteria comprised one or more of the following: pronounced dysfunction of vital organs (heart, liver, kidneys) during the perinatal period, hematological diseases or congenital anomalies, convulsive syndrome associated with metabolic disorders (hypocalcemia or hypoglycemia), birth trauma, intrauterine infection, hereditary metabolic disorders or other congenital diseases, and therapy involving controlled hypothermia.

Observation of newborns with HIE continued until 9 months of age. The study was continued in 27 of the 45 infants initially diagnosed with moderate or severe HIE in the early neonatal period. Within this cohort, 17 infants were premature and 10 were full-term.

Statistical analysis was performed using standard descriptive statistics and simple and multiple logistic regression, including Poisson regression. The predictive value of anamnestic, metabolic, and other parameters was evaluated using receiver operating characteristic (ROC) curves, with the area under the curve (AUC) calculated using STATA 14.0 software package.

Ethical approval for the study was granted by the Bioethics Commission of Poltava State Medical University (Decision No. 217, 12 June 2023). The study complied with ethical standards for the humane treatment of patients as defined by the Tokyo Declaration of the World Medical Association, the Helsinki Declaration, the Universal Declaration of Human Rights, the Council of Europe Convention on Human Rights and Biomedicine, current Ukrainian legislation, relevant Ministry of Health orders, and the Code of Ethics of a Doctor of Ukraine. Written informed consent was obtained from all parents.

The study was conducted as part of the scientific research project of the Department of Pediatrics No. 1 with Neonatology at Poltava State Medical University (No. 0120U102856), entitled «Development of clinical and laboratory criteria and methods for predicting and preventing metabolic disorders in young children.»

### Research results

Analysis of maternal risk factors revealed that pregnancy in mothers of infants with HIE was most

frequently complicated by preeclampsia (40% in mothers of both preterm and full-term infants). Anemia was diagnosed in 36.7% of mothers of preterm infants with HIE and in 13.3% of mothers of full-term infants with HIE. Among delivery complications, the most common were weak labor activity (3.3% in mothers of preterm infants with HIE and 26.7% in mothers of full-term infants), placental abruption (16.7% and 13.3%, respectively), the need for amniotomy (6.7% and 13.3%), and cesarean section (73.3% and 40%). Hypoxic episodes during labor could have necessitated urgent cesarean delivery. The association between cesarean section and the development of HIE is supported by other studies [10]. Furthermore, preeclampsia in pregnant

women with overweight or obesity is a recognized risk factor for preterm birth and increased likelihood of neonatal asphyxia [11]. Most infants in the study were diagnosed with moderate asphyxia at birth. The Apgar scores at 1 and 5 minutes were  $5.83 \pm 0.23$  and  $6.7 \pm 0.14$  points in preterm infants, and  $5.8 \pm 0.52$  and  $7.2 \pm 0.34$  points in full-term infants, respectively. Mechanical ventilation was required immediately after birth in 16.7% of preterm infants with HIE and 46.7% of full-term infants. The duration of mechanical ventilation was  $4.26 \pm 0.7$  days in preterm infants and  $5.47 \pm 1.26$  days in full-term infants. Neurosonographic data at birth were analyzed to assess the severity of nervous system changes (Table 1).

**Table 1**

**Frequency of neurosonographic changes among infants with HIE at birth, n (%)**

Indicators	Infants with HIE		p
	Preterm (n=30)	Term (n=15)	
Periventricular edema	6 (20.0)	8 (53.33)	0.067
Subependyma cysts	9 (30.0)	3 (20.0)	0.510
Ventriculodilatation	3 (10)	1 (6.67)	0.593
Hydrocephalic syndrome	4 (13.3)	2 (13.3)	0.429
IVH I-II	6 (20.0)	2 (13.3)	0.458

Periventricular edema was more frequent in full-term infants with HIE than in preterm infants with HIE. No significant differences were observed in the frequency of other conditions between full-term and preterm infants (Table 1) (Table 1).

Analysis of anthropometric parameters revealed a significant difference in birth weight: the median percentile in preterm infants was 94.5% (interquartile range: 68-100), significantly higher than in term infants (61%; 37-80;  $p < 0.001$ ). The mean weight/length ratio at birth did not differ significantly between groups.

At 6 months of age, the interquartile range of the weight/length ratio percentile in preterm infants was broader than

in term infants, reflecting greater variability, including both elevated and reduced values. No significant differences in body weight percentiles were observed between groups. The weight/length ratio may therefore serve as a more precise indicator of physical development in infants with HIE.

Analysis of neurological disorders at 9 months showed that the most frequent conditions were hypoxic-ischemic CNS injury and neurodevelopmental delay. Hypoxic-ischemic CNS injury was observed in 88.2% of preterm infants and 60% of term infants. Neurodevelopmental delay occurred in 20.0% of preterm infants and 17.6% of term infants, with no statistically significant differences between groups (Table 2).

**Table 2**

**Frequency of diagnosed neurological disorders among children with GIE at the age of 9 months, n (%)**

Indicators	Children with HIE after birth		p
	Preterm (n=17)	Term (n=10)	
Hypoxic-ischemic CNS injury	15 (88.24)	6 (60.0)	0.112
Neuromental development delay	3 (17.65)	2 (20.0)	0.628
Epilepsy	0	1 (10.0)	0.393

The data were analyzed considering two aspects. First, the diagnosis of hypoxic-ischemic central nervous system injury may be influenced by a history of moderate or severe hypoxic-ischemic encephalopathy (HIE) in the early neonatal period, since no clearly defined objective markers of this condition currently exist. Second, approximately 20% of children with a history of HIE in the early neonatal period exhibited psychomotor developmental delay at 9 months of age. One

full-term infant was diagnosed with epilepsy. Supervision of these children was performed in accordance with current industry standards, which, however, do not provide specific recommendations for the management of infants with HIE in the early neonatal period. Neurosonographic evaluation at 9 months identified ventriculodilation in two preterm infants and one full-term infant, and hydrocephalic syndrome in one full-term infant (Table 3).

**Table 3**

**Frequency of development of morphological neurological changes among children who had HIE at birth at 9 months of age, n(%)**

Indicators	Preterm (n=17)	Term (n=10)	p
Ventriculodilation	2 (11.76)	1 (10.0)	0.697
Hydrocephalus	0	1 (10.0)	0.393

Among the examined children, up to 20% of both full-term and preterm infants at 9 months of age exhibited neuropsychiatric developmental delay, emphasizing the need to enhance monitoring of infants with HIE born to mothers with metabolic syndrome.

Potential predictors of neuropsychiatric developmental delay at 9 months were assessed using multivariate logistic regression, adjusting for gestational age at birth, which

enabled the development of predictive models for estimating the risk of this outcome. The analysis demonstrated that the Apgar score and the duration of mechanical ventilation had the highest prognostic significance. All children with developmental delay had undergone mechanical ventilation and presented with periventricular leukomalacia, hypertension, and muscular dystonia syndrome; therefore, these indicators were excluded from the predictive models (Table 4)

Table 4

Predictive models of neuro-mental development delay in infants at 9 months of age

Indicators	OR (95% CI)	$\beta$ (95% CI)	p	Area under ROC-curve
<i>I model</i>				
Apgar score on 5 <sup>th</sup> min	0.81 (0.30-2.18)	-0.21 (-1.19-0.78)	0.683	
Mechanical ventilation_duration	1.31 (1.01-1.69)	0.27 (0.01-0.53)	0.039	
_cons	0.06 (0.00001-2220.9)	-2.68 (-10.76-5.39)	0.515	0.9170
<i>II model</i>				
Mechanical lung ventilation_duration	1.35 (1.11-1.65)	0.31 (0.11-0.50)	0.002	
_cons	0.01 (0.002-0.069)	-4.35 (-6.02-(-2.66))	0.000	0.9180

Analysis of predictive factors for psychomotor developmental delay indicated that only the duration of mechanical ventilation demonstrated a reliable predictive coefficient ( $\beta = 0.31$ ; 95% CI, 0.11-0.50), with an area under the ROC curve of 0.9180. Mechanical ventilation in neonates significantly affects the functioning of vital systems, including the cardiovascular, respiratory, and central nervous systems during the first days of life [12]. A complex interaction between supportive therapy and the still-immature organs and systems may disrupt normal neurodevelopment, representing a significant risk factor for adverse neurological outcomes [13]. Moderate sensory and motor impairments, as well as pronounced hearing deficits, have been reported as

potential consequences of various mechanical ventilation modalities [14, 15].

### Conclusion

Approximately 20% of the examined children with HIE, both full-term and preterm, at 9 months of age exhibited delayed neuropsychiatric development. Multivariate logistic analysis confirmed that a low Apgar score and the duration of mechanical ventilation have the greatest prognostic significance, with the predictive model incorporating mechanical ventilation duration demonstrating the highest predictive accuracy. These findings underscore the necessity of enhancing medical supervision for children who experienced HIE and were born to mothers with metabolic syndrome.

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## ПРОГНОЗУВАННЯ ЗАТРИМКИ НЕРВОВО-ПСИХІЧНОГО РОЗВИТКУ У НЕМОВЛЯТ З ГІПОКСИЧНО-ІШЕМІЧНОЮ ЕНЦЕФАЛОПАТІЄЮ, ЯКІ НАРОДИЛИСЯ ВІД МАТЕРІВ З МЕТАБОЛІЧНИМ СИНДРОМОМ

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### Резюме.

Кожні двох немовлят з 1000 піддаються дії гіпоксії/ішемії при народженні, що призводить до розвитку гіпоксично-ішемічної енцефалопатії (ГІЕ) та порушень нервово-психічного розвитку, що, у свою чергу, лягає тягарем на все життя для батьків і суспільства. У дітей, які перенесли 3 стадію ГІЕ, спостерігаються висока частота судомного синдрому й виражена затримка нервово-психічного розвитку. Окремі дослідження демонструють, що навіть за відсутності тяжких порушень діти можуть мати моторні, когнітивні або поведінкові відхилення.

**Метою** нашого дослідження були аналіз та визначення факторів ризику затримки психомоторного розвитку шляхом ідентифікації материнських і дитячих чинників.

**Матеріали та методи дослідження.** У дослідження було включено 45 немовлят, які народилися від матерів з метаболічним синдромом, і у яких у ранньому неонатальному періоді діагностовано помірну або тяжку ГІЕ, із них 30 дітей були передчасно народженими, а 15 дітей – доношеними. Спостереження за дітьми, які перенесли ГІЕ, продовжувалося до 9 місяців їхнього життя. Дослідження продовжено у 27 з 45 немовлят, у яких у ранньому неонатальному періоді діагностовано помірну або тяжку ГІЕ. У цій групі дітей 17 немовлят були передчасно народженими, а 10 немовлят – доношеними.

Статистичну обробку отриманих даних здійснювали за допомогою стандартних методів описової статистики, простого та множинного логістичного регресійного аналізу, в тому числі за Пуасоном. Прогностичну цінність анамнестичних, метаболічних та інших показників оцінювали за допомогою ROC-кривої, визначаючи площу під нею за допомогою пакету прикладних програм STATA 14.0.

Відповідно до рішення комісії з біоетики Полтавського державного медичного університету № 217 від 12.06.2023, матеріали наукового дослідження відповідають етичним вимогам гуманного поводження з пацієнтами, визначеним Токійською декларацією Всесвітньої медичної асоціації, Гельсінкськими міжнародними рекомендаціями, Загальною декларацією прав людини, Конвенцією Ради Європи про права людини та біомедицину, а також чинним законодавством України, наказами МОЗ і положеннями Кодексу етики лікаря України. Усі батьки дали згоду на обстеження.

Дослідження виконано в рамках науково-дослідної роботи кафедри педіатрії № 1 із неонатологією Полтавського державного медичного університету № 0120U102856 «Розробити клініко-лабораторні критерії, методи прогнозування та запобігання метаболічних порушень у дітей раннього віку».

**Результати дослідження.** У більшості немовлят, що були включені у дослідження, була діагностована помірна асфіксія при народженні, оцінка по Апгар на 1 і 5 хвилині у передчасно народжених дітей становила  $5,83 \pm 0,23$  та  $6,7 \pm 0,14$  балів відповідно, у доношених дітей –  $5,8 \pm 0,52$  та  $7,2 \pm 0,34$  балів. 16,7% передчасно народжених дітей з ГІЕ та 46,7% доношених дітей потребували ШВЛ одразу після народження, тривалість ШВЛ становила  $4,26 \pm 0,7$  діб у передчасно народжених дітей з ГІЕ та  $5,47 \pm 1,26$  діб у доношених дітей. Найпоширенішими неврологічними станами у 9-місячному віці виявилися гіпоксично-ішемічне ураження центральної нервової системи (ГІУ ЦНС) та затримка психомоторного розвитку. Частота виявлення ГІУ ЦНС склала 88,2% серед передчасно народжених дітей та 60% – серед доношених. Показники затримки психомоторного розвитку були також подібними у двох групах: 17,6% у доношених і 20,0% – у передчасно народжених. Проведено багатофакторний логістичний регресійний аналіз, з урахуванням гестаційного віку дитини на момент народження, що дозволило створити прогностичні моделі для оцінки ймовірності затримки психо-моторного розвитку. З'ясувалось, що найбільшу прогностичну значущість мають оцінка за шкалою Апгар та тривалість ШВЛ. Прогностична модель, що включає тривалість ШВЛ має достовірний прогностичний коефіцієнт ( $\beta$  0,31 (95% ДІ 0,11-0,50), площа під ROC становить 0,9180).

**Висновок.** Близько 20% обстежених дітей з ГІЕ, як доношених, так і передчасно народжених, у віці 9 місяців демонструють ознаки затримки нервово-психічного розвитку. При проведенні множинного логістичного аналізу було доведено, що найбільшу прогностичну значущість мають низька оцінка за шкалою Апгар та тривалість ШВЛ, а прогностична модель, що включає саме тривалість ШВЛ, має найкращі предиктивні властивості. Це підкреслює необхідність вдосконалення системи медичного нагляду за дітьми, які перенесли ГІЕ та народилися від матерів із метаболічним синдромом.

**Ключові слова:** новонароджені; гіпоксично-ішемічна енцефалопатія; затримка нервово-психічного розвитку; тривалість ШВЛ.

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