ORIGINAL ARTICLE

Prognostic value of colour Doppler brain sonography for the neurodevelopmental outcome in term neonates with hypoxic ischaemic encephalopathy

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ABSTRACT

Aim To determine a prognostic value of cerebral blood flow parameters for the development of neurological sequelae in term neonates with hypoxic ischaemic encephalopathy (HIE).

Methods We reviewed medical records of 47 term neonates with HIE who survived until the age of 12 months of life. According to the Sarnat and Sarnat clinical score, neonates were divided into 3 groups: mild HIE, moderate HIE and severe HIE. All included neonates had the colour Doppler brain sonography performed in the first 24 hours of life. The neurological assessment was done at the age of 12 months of life by using the Denver Developmental Screening Test (DDST). Logic regression analysis was performed using the colour doppler brain sonography parameters with the development of neurological impairment as the primary outcome.

Results Out of 47 neonates, 19 (40.4%) were with mild, 17 (36.2%) with moderate and 11 (23.4%) with severe HIE. The values of cerebral blood flow parameters and resistance index (RI) significantly correlated with the neurological impairment at the age of 12 months of life ($p<0.001$). The limit value of RI indicating the poor neurodevelopmental outcome was 0.81, sensitivity 80%, specificity 85.3%, positive predictive value 52.2% and negative predictive value 95.2%.

Conclusion The cerebral blood flow parameters measured with colour doppler brain sonography are good indicators of the severity of HIE and later neurodevelopmetal outcome.

Key words: asphyxia neonatorum, cerebral blood flow, neurodevelopmental disorders

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INTRODUCTION

Hypoxic ischemic encephalopathy (HIE) represents the most common cause of neonatal morbidity and mortality (1,2). The brain colour doppler ultrasonography (cD-US) allows simultaneous examination of brain parenchymal and vascular structures (3,4). The brain cD-US method enables direct visualization of cerebral blood vessels and their measurement size, and determining the direction and speed of cerebral blood flow (5). Determination of cerebrovascular flow rate (CBFV) is important because it allows the assessment of cerebral circulation in newborns with hypoxic-ischemic and haemorrhagic brain lesions and depends on cerebral blood flow and cerebrovascular resistance (6,7). The cerebral blood flow depends on systemic arterial pressure, central venous pressure and intracranial pressure, while the cerebrovascular resistance depends on vasomotor tone, blood viscosity and the presence of occlusions of cerebral blood vessels (8). By measuring the maximum systolic flow rate (PSV - cm / s), end-diastolic flow rate (EDV - cm / s) and Pursell resistance index (RI), the cerebral perfusion and vascular resistance are assessed and thus, cerebral circulation (9).

Impaired cerebral perfusion has the main role in the pathogenesis of hypoxic-ischemic brain injury in newborns. It is the recommendation of the American Academy of Neurology and the Child Neurology Society (10) to perform measurements of resistive index (RI) and end diastolic flow velocity (EDFV) in the anterior cerebral artery in newborns suffering from perinatal asphyxia as an early indicator of outcome. Still colour doppler ultrasonography (cD-USG), as a diagnostic method, is not widely applied in many countries and has been recently introduced to our department.

The aim of this study was to assess the predictive value of brain CD-US in the early diagnosis of structural brain lesions and cerebral perfusion abnormalities in neonates with HIE that cause neurological sequelae.

PATIENTS AND METHODS

Patients and study design

The medical records of 47 term neonates consecutively treated for hypoxic- ischaemic encephalopathy between January 2017 and January 2021 at the Paediatric Clinic of University Medical Centre Sarajevo, Bosnia and Herzegovina, were reviewed. The inclusion criteria were: term newborns with the presence of diagnostic criteria for hypoxic-ischaemic encephalopathy (HIE) as defined by the American Academy of Pediatrics (11): profound metabolic acidosis (pH<7.0) in umbilical artery blood, Apgar score of 0-3 for longer than 5 minutes, neonatal encephalopathy and multiple organ involvements (e.g. kidney, lungs, liver, heart, intestines) and at least 12 months of neurological follow-up in our or local hospital. Neonates with congenital anomalies, congenital metabolic diseases and neonatal sepsis and/or brain infection were excluded from the study.

All newborns were neurologically assessed according to the Sarnat and Sarnat (12) clinical scoring system and divided into three groups: mild, moderate and severe HIE. The groups were compared according to the gestational age, birth weight, gender, Apgar score, acid-base balance and lactate values in the umbilical arterial blood, resistance index (RI) in the anterior cerebral artery and neurodevelopmental outcome at 12 months of age.

Methods

The brain cD-US was performed in the first 24 hours of life after initial stabilization. During the cD-US examination, neonates were supinated with the head in a horizontal position with minimal handling approach, while avoiding episodes of crying and agitation. Color doppler ultrasound machine (GE Medical System, LOGIQ V5 Expert, Germany), with multifunction convex neonatal probe (7–10 MHz) and the insonation angle less than 30 degrees was used. Anterior cerebral artery (ACA) and its branch artery pericalosis was clearly visualized along the body of the *corpus callosum* at the sagittal section through the great fontanelle.

Cerebrovascular flow rates (end-diastolic velocity (EDV) and peak systolic velocity (PSV)) were determined at the proximal part of the ACA.

Pursell's resistance index RI was calculated by integrated algorithm according to the formula: RI=PSV - EDV/PSV. The RI values in the interval 0.6 – 0.750 were considered as normal.

Neurological assessment was performed at the age of 12 months of life using the Denver Developmental Screening Test (DDST) (13). The

DDST test is a very fast and simple tool for assessing child's neurodevelopment in 4 general areas: 1) personal–social (25 items), 2) fine motor-adaptive (29 items), 3) language (39 items), and 4) gross motor (32 items) (14). Each of the tested items was graded as normal, suspect or non-testable. These items were scored to an age line, which represents the normative data and the percentile ranks. The number of scores a child received below the normal expected range classifies the child as within normal, suspect or delayed (15).

In children with abnormal neurological findings (moderate neurological deviation and suspected cerebral palsy), before making a definitive diagnosis, the test was repeated after 2-3 weeks.

Descriptive statistics of frequencies, percentages (%), mean and standard deviation (SD) were used. For testing of differences between the examined groups Pearson's χ^2 -test, Fisher's exact test, Kruskal-Wallis's test and Wilcoxon test were used. The $p \leq 0.05$ was considered as significant.

RESULTS

This study included 47 term newborns with HIE. The body weight (BW) and weeks of gestation were not significantly different between three different HIE groups. Male gender correlated with HIE severity ($p<0.05$) (Table 1).

Table 1. The correlation between neonatal characteristics with severity of hypoxic-ischemic encephalopathy (HIE) in the first 24 hours of life and neurological outcome at 12 months of age

Parameter	Mild HIE	Moderate HIE	Severe HIE	Infants with neurological sequelae at 12 months of age
Gestational age ($\bar{x}$±SD)	38.1±2.4	37.9±2.9	38.3±2.2	38.4±2.5
Birth weight (g) ($\bar{x}$±SD)	3510±334	3479±285	3580±320	3530±290
Eutrophic (No; %)	25 (86.2)	8 (66.6)	3 (50.0)	10 (66.6%)
Hypotrophic (No; %)	3 (10.3)	2 (16.7)	1 (16.7)	3 (20.0%)
Hypertrophic (No; %)	1 (3.4)	2 (16.7)	2 (33.3)*	2 (13.3%)
Gender (M/F) (%)	52.5/47.8	65.7/34.3	100/0*	66.7/33.3*

*p< 0.05

Twenty-nine (61.7 %) neonates had mild, 12 (25.5%) moderate and 6 six (12.8%) had severe HIE. The Apgar score values ($p<0.01$), pH values ($p<0.001$), base excess (BE) and lactate ($p<0.05$) from umbilical arterial blood were correlated with HIE severity (Table 2).

Table 2. The correlation between neonatal vitality assessment parameters with the severity of hypoxic-ischemic neuropathy (HIE) and neurological sequelae at 12 months of age

Parameter (mean±SD)	Mild HIE	Moderate HIE	Severe HIE	Infants with neurological sequelae at 12 months of age
1-minute Apgar score	4.0±1.0	2.5±1.3	1.2±0.6	2.4±1.5*
5-minute Apgar score	5.5±0.4	4.4±1.2	2.5±1.0	3.7±1.7*
pH	7.15±0.03*	7.01±0.2*	6.90±0.09*	6.98±0.13*
Base excess (mmol/L)	-10.0±1.5*	-15.0±3.5*	-19.5±3.7*	-15.9±4.9*
Lactate (mmol/L)	5.3±2.7*	9.3±4.7*	13.5±3.5*	10.9±4.9*

*p<0.05;

The pH values from arterial blood had the greatest predictive value for later occurrence of neurological sequelae ($W=815$; $p<0.001$). RI values in ACA in neonates with HIE during the first 24 hours correlated with the severity of HIE ($p<0.0001$) (Table 3). The limit value for RI in ACA indicating severe HIE and neurological impairment at the age of 12 months of life was 0.81, sensitivity 80%, specificity 85.3%, positive predictive value 52.2% and negative predictive value 95.2%.

Table 3. The correlation of cerebral anterior artery resistance index (RI-ACA) in neonates with hypoxic-ischemic encephalopathy (HIE) measured in the first 24 hours of life with the severity of HIE and the neurological sequelae at 12 months of age

RI-ACA	Mild HIE	Moderate HIE	Severe HIE	Infants with neurological sequelae at 12 months of age
$\bar{x}$±SD	0.68±0.11*	0.75±0.24	1.2±0.8*	0.88±0.24*
Normal (No; %)	14 (48.3)*	2 (16.7)	1 (16.6)*	2 (13.3)
Low (No; %)	10 (34.4)*	3 (33.3)	0	3 (20.0)
High (No; %)	5 (17.2)*	6 (50.0)*	5 (83.3)*	10 (66.8)*

*p<0.05;

Neurological findings at the 12 months of age correlated with severity of HIE at birth (Table 4).

Table 4. The neurological findings in neonates at the 12 months of age and a correlation with severity of hypoxic-ischemic encephalopathy (HIE) at birth

Neurological findings	No (%) of neonates		
	Mild HIE	Moderate HIE	Severe HIE
Normal	Absolute No. 26 (89.7)*	7 (58.3)*	0
Moderate delay	2 (6.9)	4 (33.3)*	0
Severe delay	1 (3.4)	1 (8.3)	4 (66.7)*
Epilepsy	0	1 (8.3)	2 (33.3)*

*p<0.05;

DISCUSSION

The results of our study showed male gender was as a significant risk factor for neonatal morbidity and mortality. Many studies indicated sex differences in brain structure and immunology status, which make male newborns less resistant to perinatal asphyxia (16).

As the only criterion, Apgar score (AS) has poor predictive significance for the assessment of neurological outcome and the occurrence of late neurological sequelae (11). In our study it was confirmed that persistently low AS (AS ≤3 at 5 min) and profound metabolic acidosis at birth (pH <7.0, BE> 16 mmol/L, and lactate >11 mmol/L) indicate a severe, irreversible brain damage, due to perinatal asphyxia which later leads to neurological impairment. Disorders of cerebral perfusion and cerebral autoregulation are the most important pathophysiological mechanism of neuronal damage in HIE (3). It was assumed that changes in cerebral blood perfusion could indicate the severity of brain damage. This led to introducing the brain cD-US as a useful diagnostic method which by measuring cerebral blood flow could be used as an early prognostic indicator of neurodevelopmental and general outcome following perinatal asphyxia. In our study the increasing blood vessel resistance index (RI) in the first 24 h of life following perinatal asphyxia had the highest correlation with the severity of HIE and the neurodevelopmental outcome at 12 months of age.

The main limitation of our study is a relatively small sample since the brain cD-US is a newly introduced method in our Clinic.

Our results are in line with other studies and confirm the importance of cD-US for the decision making in early management of asphyxiated newborns, as well as its prognostic value for the neurodevelopmental outcome.

In conclusion, colour doppler neurosonography is a very safe, accurate and simple diagnostic method for early assessment of HIE severity and subsequent occurrence of neurological impairment.

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TRANSPARENCY DECLARATION

Conflict of interest: None to declare.

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