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Original Research Article

The value of ultrasonography and Doppler sonography in prognosticating long-term outcomes among full-term newborns with perinatal asphyxia

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ARTICLE INFO

Article history:
Received 1 December 2013
Accepted 9 May 2014
Available online 27 June 2014

Keywords:
Ultrasonography
Doppler sonography
Hypoxic-ischemic encephalopathy
Mental development
Neuromotor development

ABSTRACT

Background and objective: The aim of the study was to determine the correlation of hypoxic-ischemic (HI) brain injury in full-term neonates detected via ultrasonography (USG) and blood flow parameters evaluated via Doppler sonography (DS) with long-term outcomes of mental and neuromotor development at the age of 1-year.

Materials and methods: In total, 125 full-term neonates (78 subjects of case group and 47 subjects of control group) were studied. During the first five days of life, the subjects daily underwent cerebral USG and DS. At the age of 1-year the neuromotor condition and mental development was evaluated.

Results: The HI injury groups detected during USG significantly correlated with the mental development groups ($r = 0.3$; $P = 0.01$) and the neurological evaluation groups ($r = 0.3$; $P < 0.001$). In the presence of brain swelling (edema) and thalamus and/or basal ganglia (E/T/BG) injury, USG demonstrated high accuracy values when prognosticating spastic quadriparesis and severe mental development impairment in 1-year-old subjects: sensitivity – 100%, specificity – 93–100%, positive predictive value (PPV) – 60–100%, and NPV – 100%.

In subjects with spastic quadriparesis, mean end-diastolic velocity (Vd) values were significantly higher ($P \le 0.05$), and mean resistive index (RI) values were significantly lower

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Peer review under responsibility of Lithuanian University of Health Sciences.

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http://dx.doi.org/10.1016/j.medici.2014.06.007

($P < 0.05$) than those in subjects with normal neuromotor development. In subjects with severe mental retardation, mean Vd values in ACA were statistically significantly higher, and mean RI values in ACA and ACM were statistically significantly lower than those in subjects with normal mental development.

Conclusions: Hypoxic-ischemic brain changes detected during ultrasonography and cerebral blood flow parameters associated with long-term outcomes of mental and neuromotor development at the age of 1-year.

1. Introduction

Perinatal asphyxia is one of the most common causes of neonatal morbidity and mortality in most countries of the world. Perinatal asphyxia results in hypoxic-ischemic brain injury, whose long-term outcomes include severe disability (impaired mental and motor development, cortical blindness, sensorineural hearing loss, epilepsy, and cerebral palsy) and death. Early diagnostics of hypoxic-ischemic brain injury would help to identify neonates who require early rehabilitation for the improvement of long-term outcomes and the reduction of disability. In clinical practice, hypoxic-ischemic brain injury in neonates is usually diagnosed via ultrasonography. Nevertheless, data on the associations between hypoxic-ischemic brain injury detected via ultrasonography (USG) in full-term neonates and late psycho-motor development outcomes are scarce [1,2]. Literature for the last 5-years recommends magnetic resonance tomography and spectrography as the principal techniques for the diagnostics of hypoxic-ischemic brain injury in full-term neonates [3–6]. However, a number of researchers indicated that in daily practice, less sophisticated and more readily available radiological examination techniques – ultrasonography and Doppler sonography – should be used, although the prognostic abilities of these techniques are under-researched [7–9]. It has been proven that impaired cerebral blood circulation plays the main role in the pathogenesis of hypoxic-ischemic brain injury in neonates, yet studies conducted so far have been insufficient to explain how changes in blood circulation parameters are related to long-term outcomes. The aim of the study was to determine the correlation of hypoxic-ischemic (HI) brain injury in full-term neonates detected via ultrasonography (USG) and blood flow parameters evaluated via Doppler sonography (DS) with long-term outcomes of mental and neuromotor development at the age of 1-year.

2. Materials and methods

This prospective case–control study was conducted at the Clinic of Neonatology, Hospital of Lithuanian University of Health Sciences, from April 2008 to June 2011. The studied group consisted of 78 full-term (≥37 weeks of gestation) neonates who suffered from hypoxia or asphyxia during birth. The control group consisted of healthy full-term neonates born at the Clinic of Obstetrics and Gynecology, Hospital of Lithuanian University of Health Sciences.

The inclusion criteria for the case group neonates were as follows: full-term (≥37 weeks of gestation) neonates born with perinatal hypoxia or asphyxia required resuscitation, Apgar score at 5 min after birth ≤7 points, fetal acidosis (umbilical artery blood pH < 7.2) [10] or neonatal acidosis (capillary blood pH within the first hour after birth < 7.3) [11].

The exclusion criteria for the case group neonates were as follows: full-term (≥37 weeks of gestation) neonates with congenital developmental or chromosome abnormalities, hemolytic disease of the newborn, congenital brain infection or severe sepsis with hemodynamic disturbances, or suspected metabolic diseases.

The inclusion criteria for the control group neonates were as follows: full-term (≥37 weeks of gestation) neonates who did not require resuscitation, Apgar score on the first and the fifth minute of life ≥8 points, and no neonatal pathologies.

The structure of the study is presented in Fig. 1. The characteristics of the subjects are presented in Table 1.

2.1. *Hypoxic-ischemic encephalopathy (HIE) clinical evaluation*

The neurological status was evaluated every day for the first three days of life. The HIE stage was evaluated using the modified Sarnat and Sarnat scale [12].

2.2. *Brain ultrasonography*

During the first days of life, every subject underwent once-daily brain scanning conducted by an experienced sonographer operating a digital ultrasound device Xario SSA-660A (Toshiba) with a sector 5–9 mHz transducer, and a linear 7–14 mHZ transducer. Brain structures were visualized using acoustic windows: the frontal, the occipital, the temporal, and the mastoid fontanelles. The brain was evaluated in the anterior, the posterior, the lateral, the diagonal, and the axial planes. In this study, we evaluated anatomical brain structures, brain maturity, echogenicity ratio between the cortex and the white matter, echogenicity of the cortex, echogenicity and homogeneity of the white matter, echogenicity and homogeneity of the basal nuclei (thalamus and basal ganglia), the ventricle system (size, contour, and echogenicity of the cerebrospinal fluid), subarachnoid space width, midline position, structures of the posterior cranial fossa and their

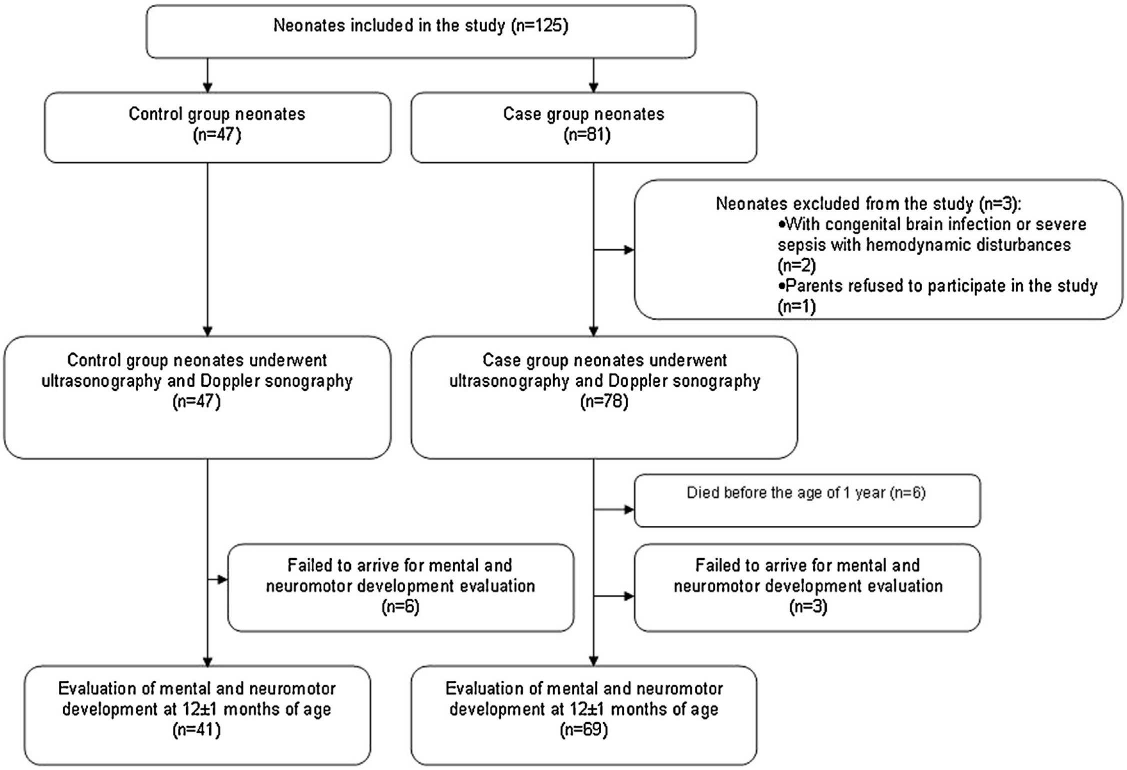

Fig. 1 – The structure of the study.

echogenicity and homogeneity (cerebellum and cerebral peduncles), and pathological findings (calcification or bruises).

Literature indicates that brain alterations detected via ultrasound during the first days following an ischemic stroke may be very mild [13,14], and therefore we presumed that HI is present in a neonate when the detected alterations persisted for over two days. In the case group neonates, single HI injuries or various variants of HI injuries were detected, which were distributed into five groups: watershed border-zone (WB) injury, WB and/or thalamus and/or basal ganglion injury (WB/T/BG), brain edema and/or thalamus and/or basal ganglion injury (E/T/BG), brain edema and/or thalamus and/or basal ganglion injury along with cerebellum and brainstem injury (E/T/BG/C/B), intraventricular hemorrhage, and bleeding into the parenchyma.

Doppler sonography was conducted simultaneously with USG. In all subjects, cerebral blood flow parameters – peak systolic velocity (Vs), end-diastolic velocity (Vd), and resistive index (RI) – were measured in the anterior cerebral arteries (ACA) (the right and the left one) and the medial cerebral arteries (ACM) (the right and the left one). Imaging of the anterior cerebral arteries was bilaterally conducted on the parasagittal planes, obtaining the image through the anterior fontanelle. Blood flow velocity parameters in all subjects were measured in the branch of the anterior artery located in front of the genus of corpus callosum. Imaging of the medial cerebral arteries was bilaterally conducted through the right and the left temporal bones on axial planes, at the level of cerebral peduncles. Blood flow velocity parameters in all subjects were measured in the proximal branch of the medial cerebral artery, in the lateral sulcus (the fissure of Sylvius). We tried to keep the angle of insonation as close to 0° as possible (not more than 15°). In total, 5 cardiac cycles were measured on spectrograms. The exposure time of intravascular Doppler sonography (DSG) was ≤60 s so as not to exceed the safety margin – 100 mW/cm^2. The neonates' examination was performed at rest or during sleep.

2.3. *Evaluation of neuromotor and mental development*

Case and control group neonates at the age of 12 ± 1 months the neuromotor condition and mental development was evaluated. The pediatric neurologist evaluated the children's neuromotor condition by applying the standard neuromotor evaluation scale [15]. Neuromotor development was evaluated by assessing children's posture, gait, muscle tone, reflexes, and cranial nerve function. By their neuromotor development, the subjects were distributed into 6 groups: normal neurological status; slight changes in muscle tone or reflexes; slight changes in muscle tone and reflexes; changes in muscle tone, reflexes, or both, and reduced power in the body and the extremities; any motor changes and cranial nerve damage; and spastic quadriparesis. The pediatric psychologist evaluated the children's mental development by using the mental scale of the Bayley Scale for Infant Development, 2nd ed. (BSID-II) [16]. Mental development was considered to be normal when the mental development index was >85; slight mental retardation was diagnosed when the mental development index was 70–85 (−1 SD); and marked mental retardation was diagnosed when the mental development index was <70 (−2 SD).

Table 1 – Characteristics of the subjects.

Characteristics	Case group N = 78	Control group N = 47
Sex, *n* (%)		
Boys	35 (44.9)	21 (44.7)
Girls	43 (55.1)	26 (55.3)
Body weight, mean (SD), g	3553 (512)	3513 (511)
Body weight, *n* (%)		
<4000 g	68 (87.2)	38 (80.9)
>4000 g	10 (12.8)	9 (19.1)
Gestation age, mean (SD), weeks	40 (1.1)	39 (1.2)
Gestation age, weeks, *n* (%)		
37	4 (5.1)	4 (8.5)
38	7 (9)	9 (19.1)
39	15 (19.2)	11 (23.4)
40	34 (43.6)	14 (29.8)
41	18 (23.1)	9 (19.1)
Mode of birth, *n* (%)		
Via naturalem	39 (50)	6 (12.8)
Cesarean section	32 (41)	41 (87.2)
Vacuum extraction	7 (9)	0 (0)
Hypoxic-ischemic brain injury, *n* (%)		
Not detected	14 (18)	47 (100)
HIE stage I	31 (39.7)	
HIE stage II	27 (34.6)	
HIE stage III	6 (7.7)	
Outcomes, *n* (%)		
Survived	72 (92.3)	47 (100)
Died total	6 (7.7)	0 (0)
Died on the first day	1 (1.3)	0 (0)
Died during the first week	3 (3.8)	0 (0)
Died during the first month	1 (1.3)	0 (0)
Died during the first year	1 (1.3)	0 (0)

V (SD), mean (standard deviation); HIE, hypoxic-ischemic encephalopathy.

2.4. *Methods of statistical data analysis*

Statistical analysis was conducted by applying computer software package SPSS 13.0 for Windows. During data analysis, we calculated descriptive statistics and verified logistic hypotheses about differences between frequencies of mean values. When verifying statistical hypotheses, the level of significance was set at 0.05.

Interdependence of qualitative attributes was evaluated by applying the chi-square (χ^2) criterion (the precise Fisher or Monte Carlo criterion (for small samples)) and Kendall rank correlation criterion. To determine the correlation of Doppler sonography with neuromotor and mental development outcomes in 1-year-old subjects, the control and the case groups were compared on the basis of the parametric Student's *t* test and the non-parametric Mann–Whitney test. To compare the studied case groups, the parametric ANOVA analysis and the non-parametric Kruskal–Wallis (χ^2 chi-square) criterion were applied. In order to determine which mean values differed statistically significantly from each other, the least significant difference (LSD) multiple comparison post hoc criterion was applied. We determined the sensitivity (the probability of a positive test for an ill person) and specificity (the probability of a negative test for a healthy person) of the blood flow parameters evaluated during USG and DS, and also determined the values of the positive and the negative tests.

2.5. *Ethical considerations*

This study was approved by the decision of Kaunas Regional Biomedical Research Ethics Committee passed at Committee session on February 19, 2008 (protocol No. BE-2-12). The representatives of all subjects (mothers and/or fathers) gave written consent to participate in the study after they were familiarized with its aim and methods.

3. Results

3.1. *Correlation of ultrasonography with long-term outcomes of neuromotor and mental development in 1-year-old subjects*

In total, 68% of the case group subjects were found to have impaired neuromotor and mental development (Fig. 2).

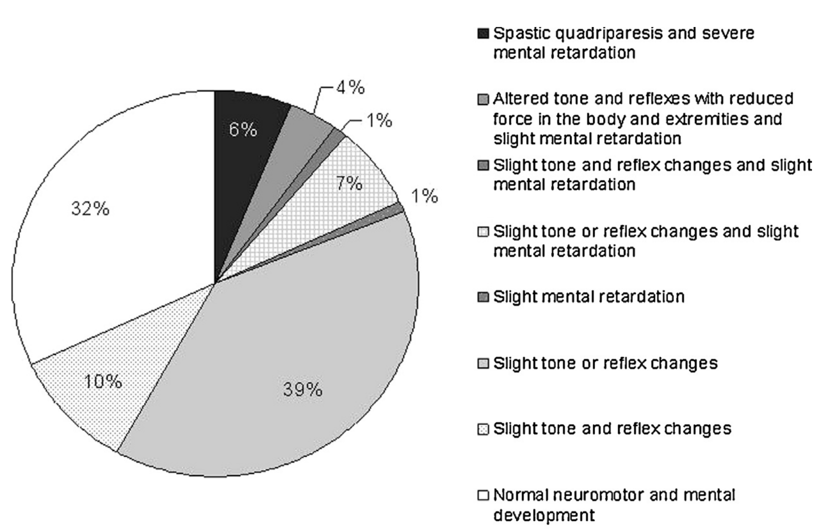

Fig. 2 – Long-term outcomes in case group subjects at the age of 1-year.

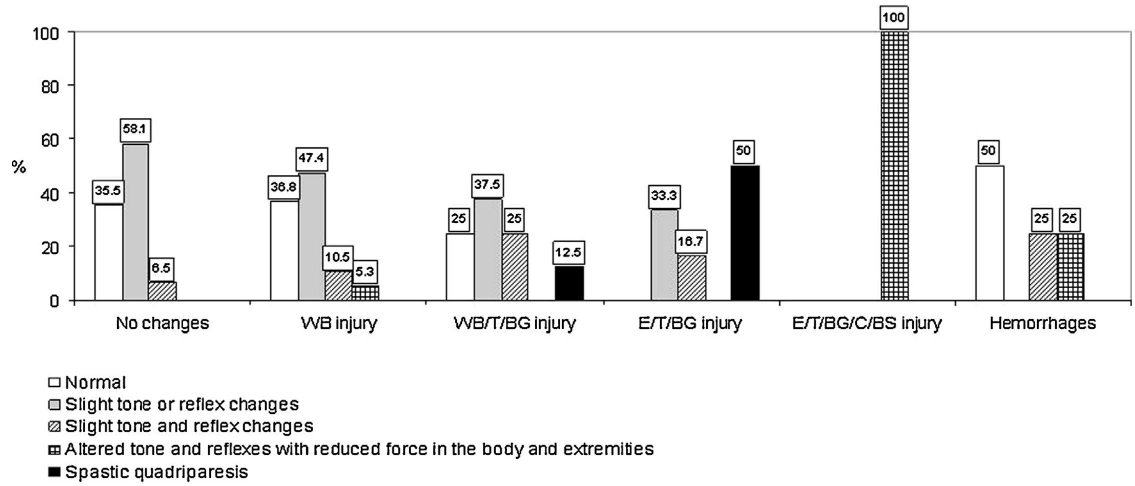

Fig. 3 – Percentage distribution of HI brain injury in case group subjects with respect to the neurological evaluation groups. $\chi^2 = 60.5$; $df = 20$; $P < 0.001$. WS, watershed injury; WS/T/BG, WS and thalamus and/or basal ganglia injury; E/T/BG, brain swelling (edema) and thalamus and/or basal ganglia injury; E/T/BG/C/BS, brain swelling (edema), thalamus and/or basal ganglia, cerebellum, and brainstem injury.

HI injury groups detected on ultrasonography significantly correlated with neuromotor ($r = 0.3$; $P < 0.001$) and mental ($r = 0.3$; $P = 0.01$) development groups. Six subjects in the case group were found to have brain swelling (edema), thalamus, basal ganglia, cerebellum, and brainstem injury (E/T/BG/C/BS). Five subjects (83.3%) died before the age of 1-year, and one who survived was found to have altered muscle tone and reflexes, and slight mental retardation. The percentage distribution of HI brain injury with respect to the neurological evaluation groups is presented in Fig. 3. The percentage distribution of HI brain injury with respect to the mental development groups is given in Fig. 4.

3.2. *Prognostic value of USG in predicting long-term outcomes among 1-year-old subjects*

We evaluated the accuracy of USG in the prognostication of long-term outcomes of neuromotor and mental development in subjects with detected hypoxic-ischemic brain injury.

We compared the accuracy of the results of USG examination of HI brain injuries conducted during the first 5 days of life, and found that the specificity of HI brain injuries detected via USG in the prognostication of long-term neuromotor development outcomes was 61–100%. In the presence of WB/T/BG injury, the sensitivity of USG in predicting spastic quadriparesis was 100%, specificity – 85%, PPV – 33%, and NPV – 100%. In

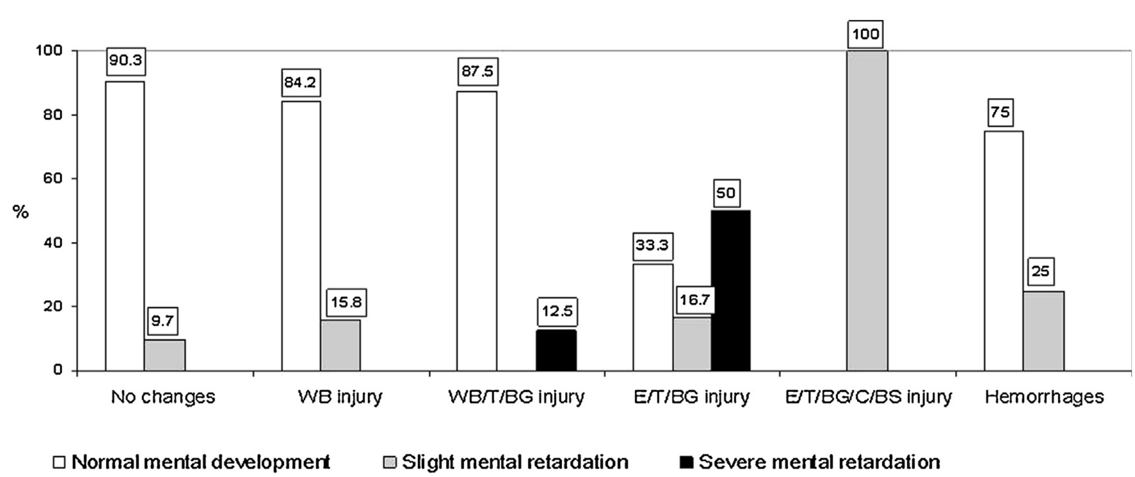

Fig. 4 – Percentage distribution of HI brain injury in case group subjects with respect to the mental development evaluation groups. $\chi^2 = 34.7$; $df = 10$; $P < 0.001$. WS, watershed injury; WS/T/BG, WS and thalamus and/or basal ganglia injury; E/T/BG, brain swelling (edema) and thalamus and/or basal ganglia injury; E/T/BG/C/BS, brain swelling (edema), thalamus and/or basal ganglia, cerebellum, and brainstem injury.

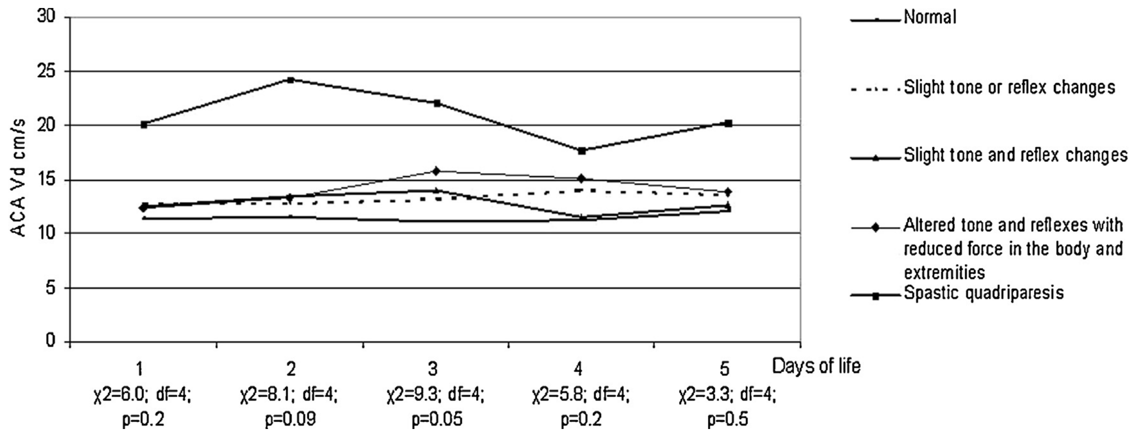

Fig. 5 – Blood flow Vd values in the anterior cerebral artery among case group subjects on days 1–5 of life, with respect to neuromotor development.

the presence of brain swelling, thalamus, and basal ganglia (E/T/BG) injury, the sensitivity of USG in predicting spastic quadriparesis was 100%, specificity – 100%, PPV – 100%, and NPV – 100%.

The specificity of HI brain injuries detected via USG in the prognostication of long-term mental development outcomes was 64–100%. In the presence of WB/T/BG injury, the sensitivity of USG examination when predicting a severe mental developmental disorder was 100%, specificity – 80%, PPV – 31%, and NPV – 100%. In the presence of E/T/BG injury, the sensitivity of USG examination in the prognostication of a severe mental developmental disorder was 100%, specificity – 93%, PPV – 60%, and NPV – 100%.

3.3. *Correlation of Doppler sonography with long-term outcomes of neuromotor and mental development in 1-year-old subjects*

We found no statistically significant differences in mean peak systolic velocity (Vs) values registered in ACA and ACM on the first–fifth days of life between neuromotor and mental development groups in the case subjects. There was no statistically significant difference in mean end-diastolic velocity (Vd) values registered in ACM between mental development groups of the case subjects.

Mean ACA Vd values between neuromotor development groups of the case group subjects differed statistically significantly on the third day of life, and mean ACM Vd values on the second day of life. In subjects with spastic quadriparesis, mean Vd values were statistically significantly higher ($P = 0.05$; $P = 0.04$) than those in the other groups (Figs. 5 and 6).

The difference in mean RI values registered in ACA between neuromotor development groups of the case group subjects differed statistically significantly on the third day of life, and mean ACM RI values on the second and third days of life. In subjects with spastic quadriparesis, mean RI values were statistically significantly lower than those in subjects with normal neuromotor development (Figs. 7 and 8).

In subjects with severe mental retardation, mean Vd values in ACA on the first, second, and third days of life were statistically significantly higher than those in subjects with normal mental development (Fig. 9). Mean RI values registered

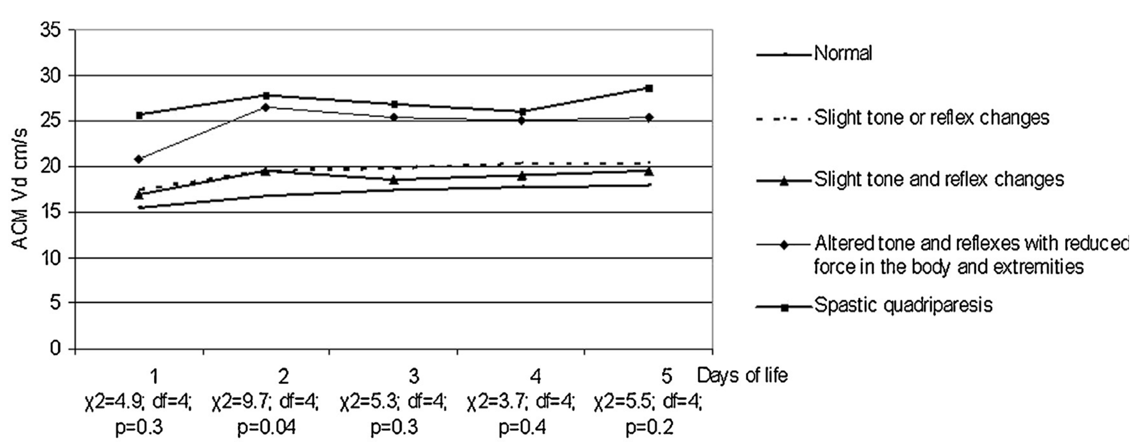

Fig. 6 – Blood flow Vd values in the medial cerebral artery among case group subjects on days 1–5 of life, with respect to neuromotor development.

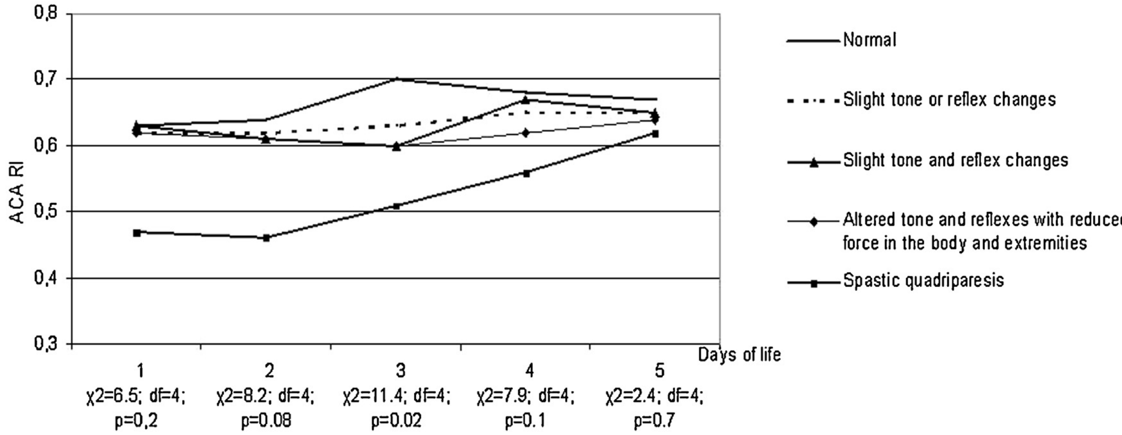

Fig. 7 – RI values in the anterior cerebral artery among case group subjects on days 1–5 of life, with respect to neuromotor development.

in ACA and ACM were significantly lower than those seen in subjects with normal or slightly impaired mental development (Figs. 10 and 11).

3.4. *Intercorrelation between ultrasonography and Doppler sonography*

The study showed that ACA Vs < 20 cm/s and ACA Vs > 40 cm/s statistically significantly positively correlated with USG examination groups on day 1 (Kendall's correlation coefficient $r = 0.3$; $P = 0.025$ and $r = 0.3$; $P = 0.002$), and was significantly more frequently found in subjects with E/T/BG/C/BS injury detected during USG.

ACA Vd > 20 cm/s statistically significantly positively correlated with USG examination groups on day 1 ($r = 0.3$; $P = 0.03$), day 2 ($r = 0.4$; $P < 0.001$), day 3 ($r = 0.3$; $P = 0.006$), day 4 ($r = 0.3$; $P = 0.009$), and day 5 ($r = 0.4$; $P = 0.001$), and was significantly more frequently found in subjects with E/T/BG and E/T/BG/C/BS injury detected during USG. ACA Vd < 5 cm/s statistically significantly positively correlated with USG examination groups on day 2 ($r = 0.3$; $P = 0.02$) and day 4 ($r = 0.3$; $P = 0.02$), and was significantly more frequently found in subjects with E/T/BG/C/BS injury detected during USG.

RI ≤ 0.55 in ACA and ACM statistically significantly positively correlated with USG examination groups on day 1 ($r = 0.3$; $P = 0.04$ and $r = 0.2$; $P = 0.04$), day 2 ($r = 0.3$; $P = 0.01$ and $r = 0.3$; $P = 0.003$), day 3 ($r = 0.3$; $P = 0.02$ and $r = 0.4$; $P < 0.001$), day 4 ($r = 0.3$; $P = 0.003$ and $r = 0.3$; $P = 0.01$), and day 5 ($r = 0.4$; $P = 0.003$ and $r = 0.3$; $P = 0.003$). The study showed that RI ≤ 0.55 (significantly reduced) on days 1–5 was significantly more frequently detected in subjects with WB/T/BG, E/T/BG, and E/T/BG/C/BS injury.

4. Discussion

Prognostication of long-term outcomes is one of the main objectives in USG and Doppler sonography of the brain of full-term neonates who experienced perinatal asphyxia (PA). This is important for devising the follow-up plan for such neonates during the postnatal period and later.

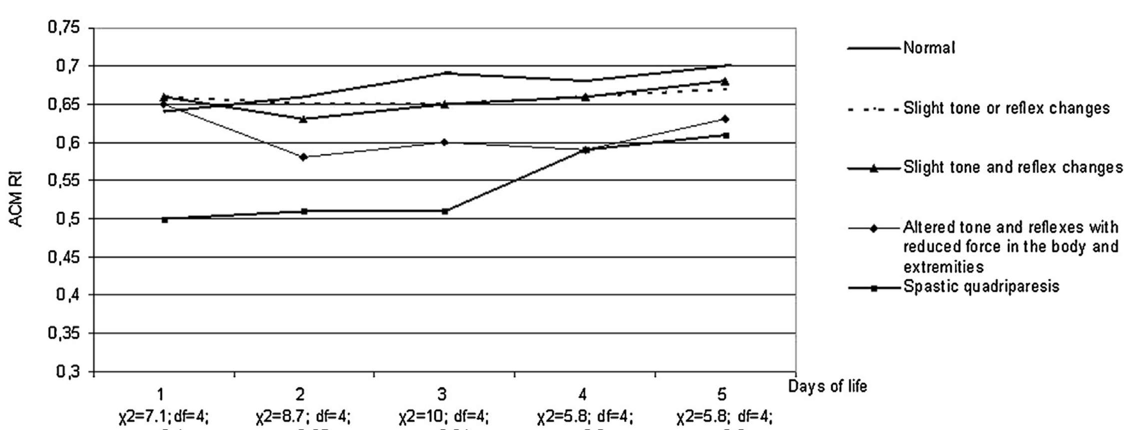

Fig. 8 – RI values in the medial cerebral artery among case group subjects on days 1–5 of life, with respect to neuromotor development.

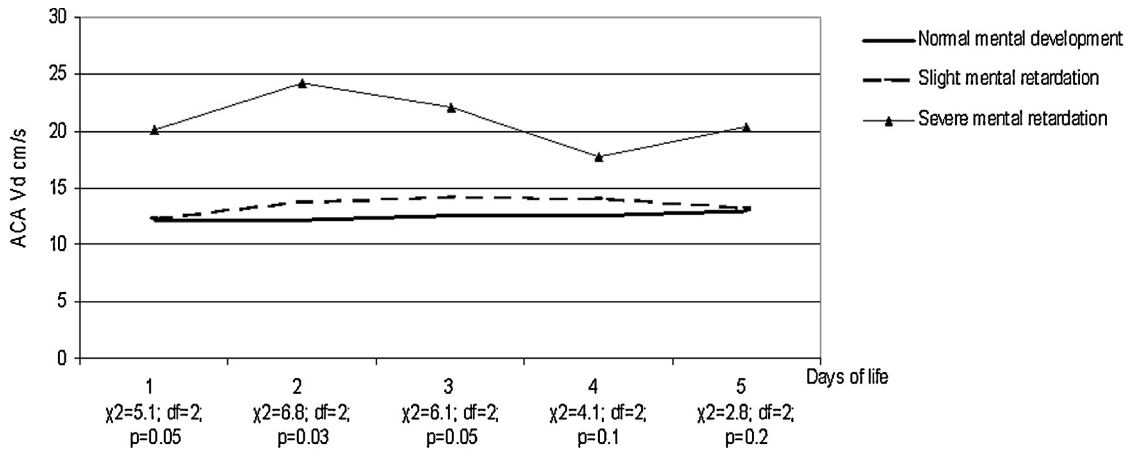

Fig. 9 – Vd values in the anterior cerebral artery among case group subjects on days 1–5 of life, with respect to mental development.

Our study analyzed how HI brain injury detected via USG during the first days of life is related to long-term (1-year after the birth) outcomes of neuromotor and mental development, and revealed a significant relationship with neuromotor ($P < 0.001$) and mental ($P = 0.01$) development. All neonates with extensive brain injuries (brain swelling (edema), thalamus, basal ganglia, cerebellum, and brainstem injury) demonstrated poor outcomes. At the age of 1-year, one-half of the subjects with brain swelling and injuries of the thalamus and basal ganglia were diagnosed with spastic quadriparesis and severely impaired mental development. Other researchers who analyzed the associations of USG findings with long-term outcomes also presented similar results. They found a significant association between HI brain injury detected via USG and long-term outcomes [17–20]. In the presence of signs of brain swelling, severe neuromotor and mental development impairment was detected in 33% [21] to 92.3% of the subjects [22]. According to the data of the study conducted in 2000 in the USA, 33% of full-term neonates with PA in whom HI changes were detected during ultrasonography had neuromotor and mental development impairment during their second year of life [21]. In 2000, Boo et al. detected severe neuromotor development impairment at the age of 1-year in 56.8% of the subjects in whom diffuse increase in parenchyma echodensity (brain edema) was detected via USG ($P < 0.05$) [18]. In Australia, a retrospective study of 3-year-old children conducted by Jongeling et al. showed that poor outcomes (death or diagnosed cerebral palsy (CP)) were detected in 65% of the subjects with marked brain swelling on the first day of life and in 49% of the subjects in whom this condition was observed on the second–third days of life [23].

Our study analyzed the indices of the accuracy of USG in prognosticating long-term neuromotor and mental development outcomes. The study showed that the accuracy of USG in prognosticating spastic quadriparesis and severe impairment of mental development is high in neonates who within the first 5 days of life are found to have brain swelling with HI injury to the thalamus and basal ganglia, and WB injury with damage to the thalamus and basal ganglia although the PPV of the latter injury is low. Several researchers analyzed the accuracy indices of USG conducted during the first hours of life, and found that they were poor [22,24]. The results of the study conducted in 2002 in Australia have shown that in cases when USG detects signs of marked cerebral edema, the probability of

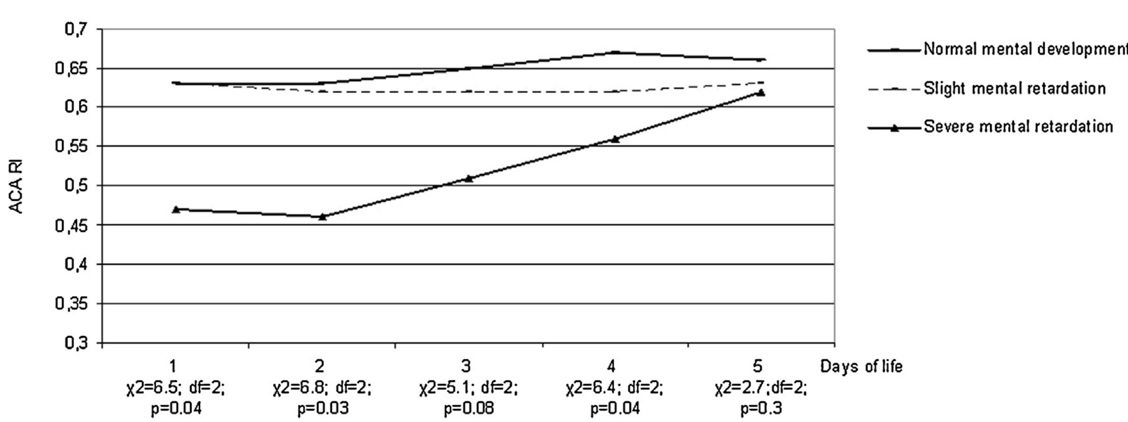

Fig. 10 – RI values in the anterior cerebral artery among case group subjects on days 1–5 of life, with respect to mental development.

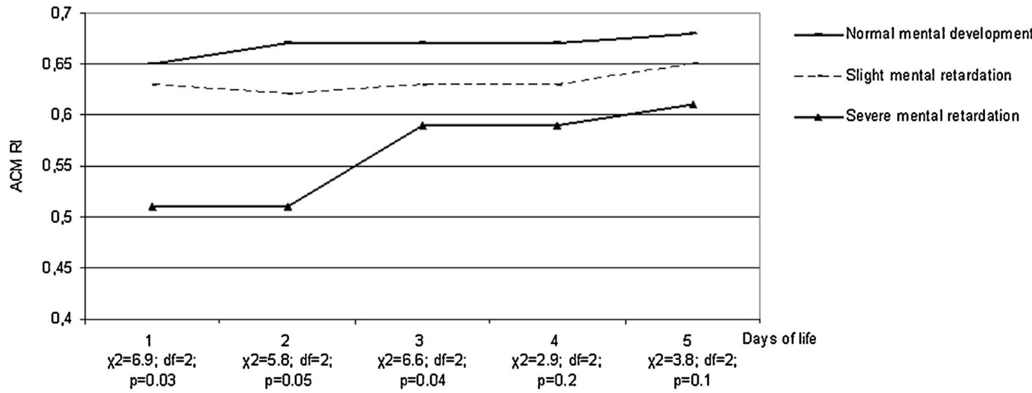

Fig. 11 – RI values in the medial cerebral artery among case group subjects on days 1–5 of life, with respect to mental development.

a poor outcome (CP or death) in 3-year-old children increases by 11-fold [23]. According to the data of two studies conducted in Belgium by Himpens et al. and published in 2010, any brain injury detected via USG (white matter injury, cerebral infarction, bruising, gray matter injury, or parasagittal white matter injury) increases the probability of CP by 7-fold. By applying the logistic regression model, the researchers found that HI injury to the thalamus and basal ganglia detected via USG increased the probability of spastic cerebral palsy by 31-fold ($P < 0.001$) [25,26].

Compared to the results obtained by other researchers, the accuracy indices of our study are relatively high because we chose to conduct USG evaluation of HI brain injury during the first 5 days of life.

In our study, we analyzed the relationship of cerebral blood circulation parameters Vs, Vd, and RI evaluated 12–24 h after birth with neuromotor and mental development of 1-year-old children. The study showed that subjects who on the first day were found to have significantly higher Vd values and lower RI values demonstrated severe impairment of mental development ($P < 0.05$). A number of researchers analyzed associations between blood flow parameters measured via Doppler sonography on the first days of life and long-term outcomes [23,24,27–29]. Some researchers analyzed the significance of blood flow parameters measured during the first 12 h of life. They found that the accuracy indices of blood circulation parameters are low [24,28]. That the accuracy of blood circulation parameters improved when the examination was performed in the second half of the first day and on subsequent days [8,23,28]. Kirimi et al. investigated the relationship of blood flow parameters registered during the first 12 h after birth with neuromotor and mental development of 1-year-old children. They found that neonates whose Vs and Vd of cerebral blood flow were significantly lower, and R was significantly higher, were found to have cerebral palsy (CP) and impairment of the mental and neuromotor development ($P < 0.003$) [29]. Ilves et al. found that in children with poor outcomes (death or marked disability), blood flow Vs and Vd values in the anterior and medial cerebral arteries recorded 12 ± 2 h after birth were significantly higher than those in the control group ($P < 0.005$). In children whose psychomotor development at the age of 18 months was unaltered or only slightly impaired, blood flow Vs and Vd values in the anterior and medial cerebral arteries recorded 12 ± 2 h after birth were significantly lower than those in the group of healthy full-term neonates ($P < 0.05$). According to the researchers, the sensitivity of changes in cerebral blood flow velocity (Vs and Vd) measured within 12 ± 2 h after asphyxia for the prognostication of poor long-term outcomes in 18-month-old subjects was 92%, specificity – 84%, PPV – 80%, and NPV – 94% ($P < 0.05$) [28]. Fukuda et al. in their study conducted in 2005 in Japan found that in subjects with perinatal asphyxia (PA) followed by asymptomatic HIE, who at the age of 1-year were diagnosed with CP, cerebral blood flow Vm on the first day after birth was significantly lower (ischemia) than in subjects without HIE or CP. According to the researchers, a higher Vm in subjects with HIE resulted from unstable hemodynamics, and a low Vm in the absence of clinical signs of HIE allows for prognosticating long-term outcomes [27].

According to the results of a retrospective study by Jongeling et al. in Australia, low RI (<0.56) on the first day after birth was associated with poor outcomes (death or CP) by 23.4-fold more often, compared to RI 0.57–0.8. The specificity of RI < 0.56 in prognosticating long-term outcomes was 95%, sensitivity – 53%, PPV – 90%, and NPV – 72% ($P < 0.002$) [23].

Our study showed that on the second day after birth, in children who were found to have severe mental development impairment at the age of 1-year, blood flow Vd value in the anterior cerebral arteries was significantly higher, and RI was lower, and in those who at the age of 1-year had severe mental development impairment and spastic quadriparesis, RI in the medial cerebral artery was significantly lower ($P < 0.05$). In children who at the age of 1-year had severe mental development impairment and spastic quadriparesis, Vd in the anterior cerebral artery measured on the third day of life was significantly higher, and RI was lower, and RI in the medial cerebral artery was significantly lower ($P < 0.05$). Jongeling et al. presented similar results: if RI remains low (<0.56) during the first 72 h of life, poor outcomes in 3-year-old children are found by 8.8-fold more frequently than in cases when RI is normal. According to the researchers, the specificity of RI < 0.56 in prognosticating long-term outcomes was 95%, sensitivity – 33%, PPV – 71%, and NPV – 78% ($P < 0.001$) [23].

Thus, the obtained findings confirm that cerebral blood flow parameters Vd and RI registered on the first, second, and third days of life may help to predict long-term outcomes. The accuracy indices of cerebral blood flow parameters measured by Doppler sonography for the prognostication of long-term outcomes are high when this examination is performed during the first three days of life.

Several researchers noticed that full-term neonates with PA are found to have 2 types of blood circulation disorders. Some neonates are diagnosed with reduced or absent blood perfusion (ischemia) during diastole – Vd 0 cm/s or negative RI – 1.0, while others demonstrate hyperperfusion (hyperemia) – elevated Vd and significantly reduced RI [8,30]. In our study, one group of subjects with severe HIE also demonstrated reduced end diastolic velocity (Vd < 5 cm/s) and elevated RI (0.8) in the anterior and the medial cerebral arteries during the first three days of life. Another group of subjects with severe HIE had significantly higher Vd and significantly lower RI (≤0.55) (signs of hyperemia), compared to controls or subjects with mild to moderate HIE ($P \leq 0.05$).

Our study analyzed the relationship of cerebral blood flow parameters (Vs, Vd, and RI) registered in the anterior and medial cerebral arteries with HI brain injury detected via USG. Some subjects in whom USG detected cerebral edema and hypoxic-ischemic injury to the thalamus, basal ganglia, cerebellum, and brainstem, demonstrated blood flow deceleration in the anterior cerebral artery on the first and the second days of life, while in others, the blood flow was accelerated. Literature indicates that RI may be elevated because of reduced brain perfusion in the presence of cerebral edema. A direct linear relationship was found between RI and elevated intracranial pressure [31,32]. According to the findings of Pinto et al. published in 2011 in the US, full-term neonates who had experienced PA significantly more frequently demonstrate absent cortico-medullar differentiation (a sign of cerebral edema, detected via USG) and significantly reduced RI, compared to the control group subjects [33].

The generalized survey of the results of our study suggests that HI brain injury detected by timely and properly conducted ultrasonography (USG) is related to changes in cerebral blood circulation detected vial Doppler sonography, and helps to prognosticate long-term outcomes of neuromotor and mental development in full-term neonates who experienced perinatal asphyxia/hypoxia.

Our study has several limitations. The study was conducted at a University hospital – a hospital providing tertiary healthcare services, and thus there was a higher probability that women who arrived for childbirth there ran a higher risk of their newborns having perinatal asphyxia, compared to those delivering in hospitals providing lower-level services; for this reason, the obtained data may not reflect the situation in the general population of neonates. Inaccuracies in cerebral blood flow parameters are possible because on the first day (within 12–24 h after birth) and on the subsequent four days, the neonates' blood flow was evaluated at any time of the day rather than at a fixed hour: within 12–24 h after birth on the first day, and within the period of 24 h on the subsequent days. This could have skewed mean values of cerebral blood flow parameters.

5. Conclusions

Hypoxic-ischemic brain changes detected during ultrasonography and cerebral blood flow parameters evaluated via Doppler sonography were statistically significantly associated with neuromotor and mental development in 12 ± 1 month-old subjects: in the presence of more extensive hypoxic-ischemic brain injury and statistically significantly higher end-diastolic velocity (Vd) and lower resistive index (RI) in the anterior and medial cerebral arteries, the neuromotor and mental development outcomes were poorer (spastic quadriparesis and severe mental retardation).

Conflict of interest

The authors state no conflict of interest.

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