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ORIGINAL RESEARCH

The value of ultrasonography in predicting outcomes at an early school age among individuals with perinatal hypoxic-ischemic encephalopathy

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Abstract

Neurosonography (NSG) is a readily available non-invasive radiological examination technique that assesses brain damage in neonates who experienced perinatal hypoxia. The aim of the study was to determine the relationship between hypoxic-ischemic (HI) brain injuries in full-term neonates detected during ultrasonography and mental and neuromotor development outcomes at an early school age. We evaluated 8–9-year-old children (n = 32) who had experienced hypoxia at birth with mild to moderate hypoxic-ischemic encephalopathy (HIE) and hadn't undergone therapeutic hypothermia. The control group consisted of 8–9-year-old children (n = 16) who were born healthy. During the first five days of life, the newborns underwent cerebral ultrasonography. The HIE stage was evaluated according to the Sarnat and Sarnat scale. Neuromotor and neurological outcomes were assessed using the Gross Motor Function Classification System, the Health Utilities Index (HUI) questionnaire, the Wechsler Intelligence Scale for Children WISC-III, and structured neurological examination. In the case of moderate brain edema and/or thalamus and/or basal ganglion injuries along with cerebellum and brainstem (E/T/BG/C/B) injuries compared to other injuries, the following abnormalities were statistically significantly more common: hearing disorders (100%, p = 0.03), cerebellar dysfunction (60%, p = 0.02), epilepsy (60%, p = 0.01), a lower Working Memory Index (median, 82.0, p = 0.015). In case of moderate brain swelling (edema) and thalamus and/or basal ganglion (E/T/BG) injuries, the sensitivity and specificity of the ultrasound examination when predicting epilepsy, hearing disorders, lower full IQ, and the Perceptual Organization Index were 100%. Neurosonography helps predict the outcomes of mental and neuromotor development at an early school age in full-term neonates who experienced perinatal asphyxia/hypoxia. Moderate hypoxic-ischemic brain changes detected during ultrasonography were statistically significantly associated with hearing disorders, cerebellar dysfunction, epilepsy, and a lower Working Memory Index in children at an early school age.

Keywords

Neurosonography; Hypoxic ischemic encephalopathy; Long-term outcomes; Early school age

1. Introduction

Hypoxic-ischemic encephalopathy (HIE) after perinatal asphyxia is one of the leading causes of death or long-term neurological disorders. Early predictive indicators of neurological outcomes in infants with HIE are very important when compiling a developmental monitoring and early habilitation plan. The results of a number of systematic reviews, meta-analysis, and studies suggest that Magnetic resonance imaging (MRI), Electroencephalography (EEG), and Amplitude-integrated electroencephalography (aEEG) findings were useful predictors of adverse outcomes [1–4]. In clinical work, ultrasound examination (US) is the most common method used for the detection of hypoxic-ischemic brain injuries in neonates. This study is non-invasive and readily available at any time of the day. A number of researchers analyzed the association of hypoxic ischemic brain injuries detected via ultrasonography with early long-term outcomes. Research has shown that severe abnormal cranial US findings at birth were associated with long-term neuromotor outcomes at the age of 6 months–2 years [5–7]. The outcomes in full-term neonates with hypoxic-ischemic encephalopathy are often assessed in infancy or early childhood, but data on the outcomes in childhood and adolescence are limited [8]. There are insufficient

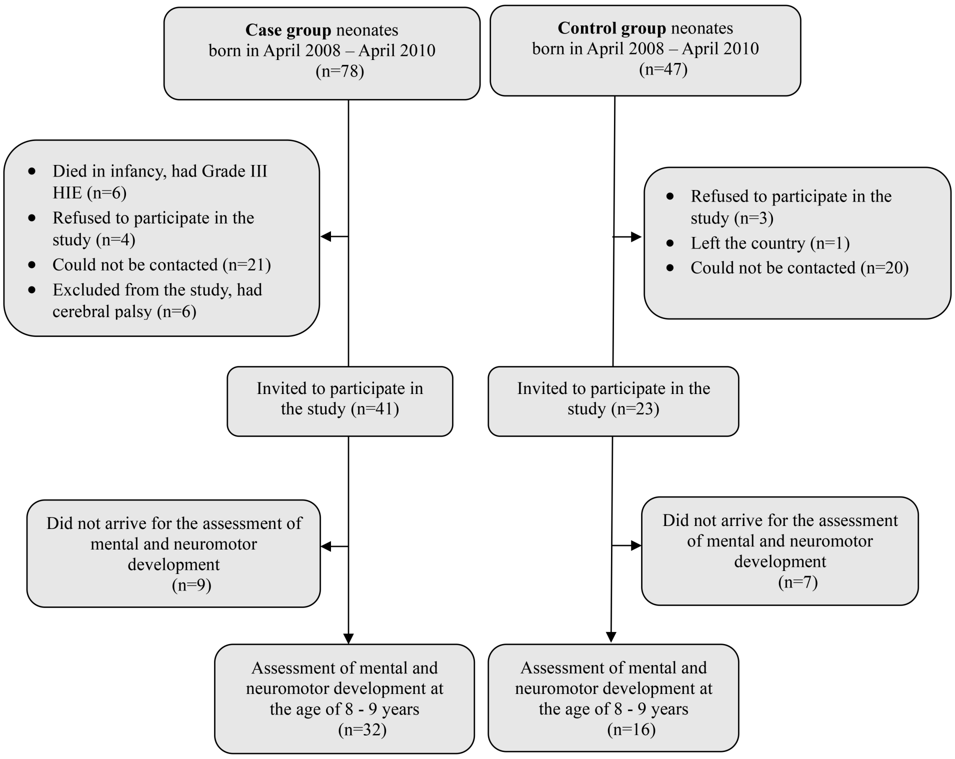

FIGURE 1. The course of the study.

data on the association of hypoxic-ischemic brain injuries in full-term neonates detected via ultrasonography with psychomotor developmental outcomes at school age or about the value of the injuries detected via US in predicting long-term outcomes at an early school age.

The aim of our study was to determine the relationship between hypoxic-ischemic brain injuries in full-term infants found during US and mental and neuromotor developmental outcomes at an early school age.

2. Methods

A prospective case-control study was performed at the Clinical Department of Neonatology of the Lithuanian University of Health Sciences (LSMU) from April 2008 to April 2019. The aim of the study was to determine the prognostic value of ultrasonography in predicting early and late long-term outcomes in full-term neonates with perinatal asphyxia. In this study, we analyzed the predictive value of ultrasonography in predicting long-term outcomes at an early school age.

Inclusion criteria for the case group subjects were the following: full-term ($\geq$ 37 weeks of gestation) neonates who required resuscitation, Apgar score at 5 minutes after birth $\leq$ 7 points, fetal acidosis (umbilical artery blood pH $<$7.2), or neonatal acidosis (capillary blood pH within the first hour after birth $<$7.3). Parental agreement for their child's participation in the study.

The exclusion criteria for the case group neonates were the following: full-term ($\geq$ 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.

Inclusion criteria for the control group subjects were the following: full-term ($\geq$ 37 weeks of gestation) neonates who did not require resuscitation, Apgar score on the 1st and the 5th minute of life $\geq$ 8 points, and no neonatal pathologies. Parental agreement for their child's participation in the study.

The study included children with mild to moderate HIE. Six children with severe HIE died during the neonatal period, and 6 early school-age children had cerebral palsy and were excluded from the study. The course of the study is presented in Fig. 1 . The characteristics of the subjects are presented in Table 1. Long-term outcomes of perinatal asphyxia/hypoxia are presented in Table 2.

2.1 Cranial ultrasound

For the first five days of life, the same ultrasonographer once daily examined the brain in all subjects, using a digital ultrasound machine Toshiba Xario SSA-660A, Otawara, Japan, a sector 5-9 MHz transducer, and a linear 7-14 MHz transducer. Brain structures were visualized through the anterior, the posterior, the sphenoid, and the mastoid fontanelles. The brain was assessed in the coronal, sagittal, parasagittal, and axial planes. The examination was carried out to assess anatomical brain structures and their maturity, the difference in the echogenicity between the cortex and the white matter, the echogenicity and homogeneity of the cortex and the white matter, the echogenicity and homogeneity of the nuclei of the cerebral base (thalami and basal ganglia), the ventricular system (size, contour, and the echogenicity of the cerebrospinal fluid), the width of the subarachnoid space, the position of the midline, the structures of the posterior cranial fossa (cerebellum and cerebral peduncles) and their echogenicity and homogeneity, and pathological findings (calcinates or

TABLE 1. Characteristics of the subjects.

Characteristics	Case group	Control group	p
	n = 32	n = 16	
Sex, n (%)			
boys	13 (40.6)	7 (43.8)	$p = 0.836$
girls	19 (59.4)	9 (56.3)	
Age (years)			
Min.	8.03	8.05	$p = 0.629$
Max.	9.08	9.09	
Mean (SD)	8.8 (0.417)	8.7 (0.45)	
Birth weight (g), n (%)			
<3500	16 (50)	5 (31.25)	$p = 0.457$
>3501	16 (50)	11 (68.75)	
Mean (SD)	33.3 (10.05)	33.7 (8.12)	
Gestational age at birth, weeks, n (%)			
37	2 (6.3)	1 (6.3)	
38	3 (9.4)	0 (0)	
39	8 (25.0)	5 (31.3)	$p = 0.464$
40	13 (40.6)	5 (31.3)	
41	6 (18.8)	5 (31.3)	
Mean (SD)	39.56 (1.105)	39.81 (1.109)	
Delivery, n (%)			
natural	17 (53.1)	1 (6.3)	$p = 0.004$
cesarean section	14 (43.8)	15 (93.8)	
vacuum extraction	1 (3.1)	0 (0)	
HIE, n (%)			
Not detected	5 (15.6)	16 (100)	$p < 0.05$
mild	15 (46.9)	0 (0)	
moderate	12 (37.5)	0 (0)	

HIE—hypoxic-ischemic encephalopathy.

bruises). We divided the HI injuries found in the neonates of the case group into 4 groups according to the location of the injuries: watershed border-zone (WB) injuries, WB and/or thalamus and/or basal ganglion injuries (WB/T/BG), brain edema, and/or thalamus and/or basal ganglion injuries (E/T/BG), brain edema and/or thalamus and/or basal ganglion injuries along with cerebellum and brainstem injuries (E/T/BG/C/B). Hypoxic-ischemic brain injuries were classified by severity into normal-mildly abnormal and moderate abnormal ones using the cerebral ultrasound scoring system by L. M. Leijser and A. Vein's classification [9] adapted from the classification by Mercuri *et al.* [10].

2.2 Assessment of intellectual abilities at an early school age

The intellectual abilities of all subjects were assessed using a standardized methodology validated in Lithuania: the Wechsler Intelligence Scale for Children (WISC-III^{LT}). Different aspects of the functioning of the intellect were assessed, determining the total, verbal, and nonverbal intelligence quotient (IQ). Qualitative data interpretation was used to assess the children's abilities (Table 3) [11]. All subjects were evaluated by the same specialist, a child psychologist, who did not know to which group the subject belonged.

2.3 Special neurological examination and assessment of the development of motor functions at an early school age

The studied early school-age children underwent a special structured neurological examination to assess the function of the cranial nerves and the cerebellum, changes in upper and lower extremities and muscle tone, and gait disorders. The neuromotor function of the children was assessed with the Gross Motor Function Classification System (GMFCS). The assessment was performed between the 8th and the 9th birthday. Scores on the two assessments ranged from 1 to 5. A higher score meant a greater impairment [12]. Scoring on the Gross Motor Function Classification System is as follows:

TABLE 2. Long-term outcomes of perinatal asphyxia or hypoxia.

	Case group	Control group	p
One-year outcomes			
Mental development, n (%)			
normal mental development	27 (87.1)	14 (100)	$p = 0.16$
slight mental retardation	4 (12.9)	0 (0)	
Neurological examination, n (%)			
No abnormality	10 (32.3)	12 (85.7)	
Slight changes in tone or reflexes	16 (51.6)	1 (7.1)	$p = 0.07$
Slight changes in tone and reflexes	2 (6.5)	1 (7.1)	
Altered tone and reflexes	3 (9.7)	0 (0)	
Early school-age outcomes			
Intellectual abilities (The Wechsler Intelligence Scale for Children), Mean (SD)			
Full IQ	87.07 (16.86)	107.24 (12.15)	$p < 0.001$
Verbal IQ	89.07 (17.45)	105.33 (11.55)	$p = 0.002$
Verbal Comprehension Index	88.87 (17.36)	105.06 (10.74)	$p = 0.002$
Working Memory Index	88.80 (15.68)	103.82 (11.84)	$p = 0.002$
Performance IQ	86.53 (16.51)	108.36 (15.48)	$p < 0.001$
Perceptual Organization Index	84.60 (15.71)	105.36 (15.93)	$p < 0.001$
Evaluation of health-related quality of life (Health Utilities Index-3 questionnaire), n (%)			
Ambulation	8 (25.0)	1 (6.3)	$p = 0.12$
Dexterity	2 (6.3)	0 (0)	$p = 0$
Hearing disorders	1 (3.1)	0 (0)	$p = 0.48$
Speech disorders	2 (6.3)	1 (6.3)	$p = 1.0$
Vision disorders	4 (12.5)	2 (12.5)	$p = 1.0$
Neuromotor function (Gross Motor Function Classification System), n (%)			$p = 0.55$
No abnormality	24 (75)	14 (87.5)	
Level I	7 (21.9)	2 (12.5)	
Level II/III	1 (3.1)	0 (0)	
Neurological examination, n (%)			
Changes in upper and lower limbs	13 (40.6)	2 (12.5)	$p = 0.05$
Changes in cerebellar function	5 (15.6)	0 (0)	$p = 0.1$
Gait disorders	3 (9.4)	0 (0)	$p = 0.2$
Epilepsy	4 (12.5)	0 (0)	$p = 0.14$
Muscle tone disorders	3 (9.4)	0 (0)	$p = 0.2$
Other abnormalities (tics, myoclonus, tremor, muscle atrophy)	6 (18.8)	1 (6.3)	$p = 0.21$
Mental and behavioral disorders	4 (12.5)	1 (6.3)	$p = 0.5$
Learning problems	7 (21.9)	1 (6.3)	$p = 0.17$

IQ—intelligence quotient. SD—standard deviation.

level 1—children can perform usual activities such as running and jumping; level 2—able to walk in most settings but have difficulty with uneven surfaces, inclines or in crowds; level 3—children walk with assistive mobility device indoors and outdoors. Children may propel a manual wheelchair (may require assistance for long distances or uneven surfaces); level 4—children use methods of mobility that require physical assistance or powered mobility most of the time; they may participate in standing transfers; level 5—children are transported in a manual wheelchair in all settings, they are limited

TABLE 3. Qualitative description of composite scores.

Composite score	Classification	Theoretical Normal Curve
130 and above	Very superior	2.2
120–129	Superior	6.7
110–119	High average	16.1
90–109	Average	50
80–89	Low average	16.1
70–79	Borderline	6.7
69 and below	Extremely low	2.2

in their ability to maintain antigravity head and trunk postures and control arm and leg movements. For all the early school-age children, the neurological examination was performed by one specialist, a pediatric neurologist, who did not know which group the subject was assigned to.

2.4 Evaluation of health-related quality of life (HRQL) at an early school age

Parents completed the Health Utilities Index (HUI) questionnaire on behalf of their children [13]. The HUI questionnaire helps to assess overall health status. It consists of two questionnaires: HUI2 and HUI3. The HUI3 questionnaire contains questions about eight attributes: vision, hearing, speech, ambulation, dexterity, emotion, cognition, and pain. The HUI2 questionnaire has questions about six attributes: sensation, mobility, emotion, cognition, self-care, and pain. As the HUI3 questionnaire contains a more detailed description of the general health status, HUI3 was used here and is the preferred measure. We used HUI2 for further analysis.

For each question in the HUI3 questionnaire, the respondents chose one of the many descriptions provided, which covered different levels of abilities, from best or normal (level 1) to the most severe impairment (level 2, 3, 4, 5, or 6 depending on the attribute and the scoring system). For example, there were 6 questions for the assessment of vision, which described the level of visual ability: from "Able to see well enough to read ordinary newsprint and recognize a friend on the other side of the street, without glasses or contact lenses" (level 1) to "Unable to see at all" (level 6).

2.5 Statistical methods of data analysis

Statistical analysis of the data was performed using the IBM SPSS 27.0 software (IBM, Armonk, NY, USA), package for data storage and analysis. All parametric data were expressed as means and standard deviations. The Kolmogorov-Smirnov test was used for the determination of quantitative data distribution. When the distribution of the variables was normal, Student's *t-test* was used to compare the quantitative sizes of two independent samples. The Mann-Whitney U test was used to compare non-normally distributed variables. The Kruskal-Wallis test was used to compare non-normally distributed variables. The Kruskal-Wallis test was also used for comparing more independent samples of equal or different sizes. The interdependence of qualitative evidence was evaluated by using the chi-squared (χ^2) test (the exact and Monte Carlo methods). When determining sensitivity, specificity, and predictive values, differences between the groups were considered statistically significant when the level of significance was $p < 0.05$.

3. Results

3.1 Findings of ultrasound examinations obtained during the first five days after birth in study group subjects who experienced perinatal hypoxia or asphyxia

Ultrasound examinations of the control group subjects did not reveal any brain injuries. In the case group, hypoxic-ischemic changes were found in 50% of the subjects (n = 16). The assessment of the severity of hypoxic-ischemic changes according to the cerebral ultrasound scoring system showed that all the detected hypoxic-ischemic changes emerged, on average, on the 3rd–the 5th days of life (Fig. 2).

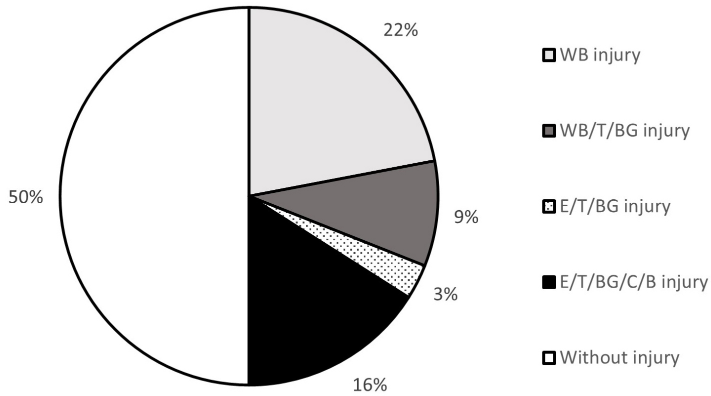

FIGURE 2. Percentage distribution of hypoxic-ischemic brain injuries detected by ultrasound in the case group. WB injury—watershed border-zone injury; WB/T/BG injury—watershed border-zone and/or thalamus and/or basal ganglion injury; E/T/BG injury—brain edema and/or thalamus and/or basal ganglion injury; E/T/BG/C/B injury—brain edema and/or thalamus and/or basal ganglion injury along with cerebellum and brainstem injury.

3.2 The relationship of ultrasonography findings with long-term outcomes of neuromotor and mental development at an early school age

Subjects with moderate E/T/BG injuries on ultrasound were significantly more likely to have hearing disorders requiring a hearing aid at an early school age, while E/T/BG/C/B injuries were associated with a higher incidence of cerebellar dysfunction and epilepsy (Table 4).

Subjects with moderate E/T/BG/C/B injuries were found to have a significantly lower Working Memory Index than the other subjects with other injuries did and were within the low average range (Table 5).

TABLE 4. Percentage distribution of hypoxic-ischemic brain injuries in the study group according to the evaluation of the health-related quality of life, neurological examination, and other neurological disorders.

Long-term outcomes	No changes detected on US	Groups of hypoxic-ischemic brain injuries, %				
	n = 16	WB injury n = 7	WB/T/BG injury n = 3	E/T/BG injury n = 1	E/T/BG/C/B injury n = 5	χ^2; df; p
Evaluation of health-related quality of life						
Speech disorders	6.3 (n = 1)	0	0	0	20.0 (n = 1)	χ^2 = 2.347; df = 4; p = 0.67
Orientation disorders	12.5 (n = 2)	42.9 (n = 3)	0	0	60.0 (n = 3)	χ^2 = 7.124; df = 4; p = 0.1
Dexterity disorders	0	0	0	0	40.0 (n = 2)	χ^2 = 11.52; df = 8; p = 0.2
Hearing disorders	0	0	0	100 (n = 1)	0	χ^2 = 32; df = 4; p = 0.03
Vision disorders	12.5 (n = 2)	14.3 (n = 1)	0	0	20.0 (n = 1)	χ^2 = 0.849; df = 4; p = 1.0
Neurological examination						
Cerebellar dysfunction	0	28.6 (n = 2)	0	0	60.0 (n = 3)	χ^2 = 12.1; df = 4; p = 0.02
Changes in upper and lower limbs	31.3 (n = 5)	57.1 (n = 4)	33.3 (n = 1)	0	60.0 (n = 3)	χ^2 = 2.9; df = 4; p = 0.6
Gait disorders	0	14.3 (n = 1)	0	0	40.0 (n = 2)	χ^2 = 7.8; df = 4; p = 0.1
Muscle tone disorders	0	14.3 (n = 1)	0	0	40.0 (n = 2)	χ^2 = 7.8; df = 4; p = 0.1
Tics, myoclonus, tremor, muscle atrophy	12.5 (n = 2)	14.3 (n = 1)	0	0	60.0 (n = 3)	χ^2 = 7.01; df = 4; p = 0.1
Others						
Neuromotor function (GMFCS)	18.8 (n = 3)	42.9 (n = 3)	0	0	40.0 (n = 2)	χ^2 = 5.5; df = 8; p = 0.7
Epilepsy	0	14.3 (n = 1)	0	0	60.0 (n = 3)	χ^2 = 13.2; df = 4; p = 0.01
Mental and behavioral disorders	6.3 (n = 1)	28.6 (n = 2)	0	0	20.0 (n = 1)	χ^2 = 4.03; df = 4; p = 0.4
Learning problems	6.3 (n = 1)	28.6 (n = 2)	0	0	20.0 (n = 1)	χ^2 = 4.03; df = 4; p = 0.4

χ^2—Chi-squared criterion; df—number of degrees of freedom; WB injury—watershed border-zone injury; WB/T/BG injury—watershed border-zone and/or thalamus and/or basal ganglion injury; E/T/BG injury—brain edema and/or thalamus and/or basal ganglion injury; E/T/BG/C/B injury—brain edema and/or thalamus and/or basal ganglion injury along with cerebellum and brainstem injury.

TABLE 5. Mean IQ of the subjects depending on the type of hypoxic-ischemic brain injuries.

IQ	Groups of hypoxic–ischemic injuries and median IQ with [25–75] percentiles					
	No changes n = 16	WB injury n = 7	WB/T/BG injury n = 3	E/T/BG injury n = 1	E/T/BG/C/B injury n = 5	χ^2; df = 4; p
Full IQ	104.5 [93.25–119.5]	102.00 [89.00–114.00]	105.00 [100.00–.]	65.0	78.00 [63.50–106.00]	$\chi^2 = 5.8$; $p = 0.118$
Verbal IQ	104.5 [93.25–119.5]	105.00 [92.00–110.00]	100.00 [98.00–.]	62.0	82.00 [66.00–102.50]	$\chi^2 = 6.8$; $p = 0.126$
Performance IQ	100.00 [92.5–115.00]	103.00 [85.00–113.00]	99.00 [94.00–.]	69.0	81.00 [64.5–109.00]	$\chi^2 = 3.9$; $p = 0.317$
Verbal Comprehension Index	104.00 [92.00–116.75]	105.00 [90.00–113.00]	100.00 [96.00–.]	60.0	85.00 [66.50–103.00]	$\chi^2 = 6.96$; $p = 0.117$
Working Memory Index	104.00 [100.00–114.25]	98.00 [82.00–106.00]	100.00 [98.00–.]	79.0	82.00 [60.00–102.00]	$\chi^2 = 8.36$; $p = 0.015$
Perceptual Organization Index	98.50 [80.00–114.75]	98.00 [83.00–111.00]	98.00 [94.00–.]	63.0	83.00 [66.50–108.00]	$\chi^2 = 3.8$; $p = 0.375$

IQ—Intelligence quotient; χ^2—Chi-squared criterion; df—number of degrees of freedom; WB injury—watershed border-zone injury; WB/T/BG injury—watershed border-zone and/or thalamus and/or basal ganglion injury; E/T/BG injury—brain edema and/or thalamus and/or basal ganglion injury; E/T/BG/C/B injury—brain edema and/or thalamus and/or basal ganglion injury along with cerebellum and brainstem injury.

3.3 Prognostic value of ultrasound examination in predicting late outcomes at an early school age

In case of a moderate E/T/BG/C/B injuries, the sensitivity of ultrasonography in predicting epilepsy and hearing disorders at an early school age was 60%, positive predictive value (PPV)—100%, specificity—100%, and negative predictive value (NPV)—89%.

In case of a moderate E/T/BG injuries, the sensitivity of ultrasonography in predicting hearing disorders at an early school age was 100%, PPV—100%, specificity—100%, and NPV—100%.

The value of ultrasonography in predicting intellectual abilities at an early school age in groups of subjects with previously detected moderate HI injuries are presented in Table 6.

4. Discussion

One of the main tasks in ultrasound examination of the brain in full-term neonates who experienced perinatal hypoxia is to predict early and late outcomes. This is important in developing a plan for further child monitoring and complementary education. In this study, we analyzed the association of premature neonatal hypoxic-ischemic (HI) injuries found via ultrasonography (US) performed during the first days of life with mental and neuromotor developmental outcomes at an early school age.

The study showed that in 50% of the subjects with mild (46.9%) or moderate (37.5%) HIE, ultrasonography revealed moderate hypoxic-ischemic changes in the brain. Of these, 22% of the subjects had WB injuries, 16% had E/T/BG/C/B injuries, 9% had WB/T/BG injuries, and 3% had E/T/BG injuries. Similar results were obtained by B. Guan and co-authors and by S. Narayan *et al*. [5] in their studies, changes of moderate severity were detected in 36.7% [14] and 64.3% [5] of cases, respectively. However, subjects in these studies were found to have not only mild to moderate but also severe HIE. The results of a study by C.J. Tann and co-authors showed that significantly fewer 23.3% (10.3% BGT and 13% WM) moderate HI changes were detected via neurosonography, even though the study group also included subjects with mild, moderate, and severe HIE [15].

The results of a number of studies suggest that the presence of abnormal changes detected on neurosonography during the first week after birth are reliable predictors of early adverse outcomes at the age of 6 months–2 years. S. Narayan *et al*. [5] found a significant association with abnormalities detected on cranial US and poor neuromotor outcomes at the age of 6 months. The results of one part of our study also showed that the HI injury groups detected during cranial US significantly correlated with the mental development groups (r = 0.3; p = 0.01) and the neurological evaluation groups (r = 0.3; $p <$ 0.001) at the age of 1 year [6]. Other researchers who analyzed the value of cranial ultrasonography in predicting long-term outcomes at the age of 2 years found that all sonographic signs of HI injury were found 3 to 7 days after birth (cerebral edema and injuries to the thalamus, putamen, periventricular white matter, and subcortical white matter) were significant predictors of an adverse outcome at the age of 2 years [7]. Severe HI injuries detected via neurosonography were significantly associated with poor motor function outcomes, but normal or mildly abnormal neuro-imaging findings did not mean a favorable outcome [9]. Our study showed that subjects with moderate E/T/BG/C/B injuries detected via neurosonography significantly more commonly had hearing disorders requiring hearing aids, cerebellar dysfunction, and epilepsy at an early school age. Subjects with moderate E/T/BG/C/B injuries were found to have a significantly lower Working Memory Index (which was in the low average range) than subjects with other groups of injuries did. The decreased Working Memory Index reflects problems with attention and short-term memory (the subjects forgot what they wanted to say and how to perform the explained task, did not complete the started task, and had more difficulty solving arithmetic tasks, performing tasks in the required order, and planning) [16].

One part of his study analyzing the value of ultrasonography in predicting spastic quadriparesis and severe mental developmental impairment in 1-year-old subjects revealed that neurosonography was a sensitive and specific examination method when WB/T/BG and E/T/BG injuries were found [6]. According to the data from two studies by Himpens and co-authors, any brain damage detected by ultrasound (white matter injury, cerebral infarction, bruising, grey matter injury, or parasagittal white matter injury) increases the likelihood of cerebral palsy in children sevenfold. Using the logistic regression model, the researchers found that HI injury to the thalamus and basal ganglia detected via US increased the probability of spastic cerebral palsy 31-fold ($p < 0.001$) [17, 18]. The analysis of the value of ultrasonography in predicting long-term outcomes at an early school age showed that neurosonography is a sensitive and specific examination technique for the prediction of epilepsy, hearing disorders, and lower (low average) IQ in the presence of previously detected moderate E/T/BG/C/B injuries.

Our study has several limitations. One of the limitations of our study is a small sample size in both the case and the control groups. When assessing long-term outcomes at school age, a large proportion of the respondents are lost for a variety of reasons. We were unable to evaluate a large proportion of the subjects due to personal data (telephone number and/or place of residence) changes that occurred over such a long period of time. A large proportion of the parents of healthy early school-age children refused to come for their children's assessment. Due to difficulties in conducting the study, we had to exclude patients with severe HIE, which reduced the sample size.

In conclusion, our study showed that neurosonography helps to predict the outcomes of mental and neuromotor development at an early school age in full-term infants who have experienced asphyxia/hypoxia at birth. Moderate-severity hypoxic-ischemic brain injuries detected during ultrasonography were statistically significantly associated with hearing disorders, cerebellar dysfunction, epilepsy, and a lower Working Memory Index in early school-age children.

TABLE 6. The value of ultrasonography in predicting intellectual abilities at an early school age in groups of subjects with previously detected moderate HI injuries.

Groups of hypoxic-ischemic injuries	Intellect quotient	Sensitivity	Specificity	PPV	NPV
WB/T/BG injury	Full IQ	0	100	-	84
	Verbal IQ	67	69	29	92
	Performance IQ	0	81	0	81
	Verbal Comprehension Index	67	69	29	92
	Working Memory Index	33	81	25	87
	Perceptual Organization Index	0	100	-	84
E/T/BG injury	Full IQ	100	100	100	100
	Verbal IQ	100	69	17	100
	Performance IQ	100	81	25	100
	Verbal Comprehension Index	100	69	17	100
	Working Memory Index	100	81	25	100
	Perceptual Organization Index	100	100	100	100
E/T/BG/C/B injury	Full IQ	60	100	100	89
	Verbal IQ	80	69	44	92
	Performance IQ	60	81	50	89
	Verbal Comprehension Index	80	69	44	92
	Working Memory Index	60	81	50	87
	Perceptual Organization Index	20	100	100	80

IQ—Intelligence quotient; PPV—positive predictive value; NPV—negative predictive value; WB/T/BG injury—watershed border-zone and/or thalamus and/or basal ganglion injury; E/T/BG injury—brain edema and/or thalamus and/or basal ganglion injury; E/T/BG/C/B injury—brain edema and/or thalamus and/or basal ganglion injury along with cerebellum and brainstem injury.

AUTHOR CONTRIBUTIONS

Conceptualization, RD, RT, and AK; methodology, AK, SL, VM, JL; software, RD, AK and IN; validation, AK, RT, SL; formal analysis, RD, AK, IN; investigation, RD, AK, VM, IN, and JL; data curation, RD, AK, IN; writing—original draft preparation, RD, AK; writing—review and editing, RT, SL; visualization, RD, AK, RT; supervision, RT, SL; project administration, RT, AK and SL. All authors have read and agreed to the published version of the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by the decision of the Kaunas Regional Biomedical Research Ethics Committee passed at Committee sessions on 8 February 2008 (protocol No. BE-2-12) and on 4 April 2017 (protocol No. BE-2-13). 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.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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