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Ultrasonography and Magnetic Resonance Imaging of the Brain in Hypoxic Full-Term Newborns

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Key Words: *hypoxic-ischemic encephalopathy; radiological investigations; neurodevelopmental outcome.*

Summary. *The aim of this article was to review the studies on diagnostic and prognostic value of radiological investigations (cranial sonography, Doppler ultrasonography, and magnetic resonance imaging) in the detection of hypoxic-ischemic brain injuries in full-term newborns.*

Materials and Methods. A systematic search of studies on the diagnostic and prognostic possibilities of radiological investigations for the detection of hypoxic-ischemic injuries in full-term newborns was performed.

Results. A total of 13 prospective and 4 retrospective studies that analyzed the incidence of hypoxic-ischemic cerebral injuries, determined by means of cranial sonography, Doppler sonography, and magnetic resonance imaging, and associations with the stages of hypoxic-ischemic encephalopathy and long-term neurodevelopmental outcomes were included in this systematic review.

Conclusions. Magnetic resonance imaging detects lesions in 75%–100% of cases. Magnetic resonance imaging performed at the age of 7–11 days demonstrated a high sensitivity (100%) and negative predictive value (100%) to predict unfavorable outcomes at 4 years of age. In newborns with hypoxic-ischemic encephalopathy, substantial cerebral hemodynamic alterations are detected after birth. The sensitivity and negative predictive value of cerebral blood flow velocities (peak systolic flow velocity, end-diastolic flow velocity) changes at 12±2 hours of age to predict the severity of hypoxic-ischemic encephalopathy and unfavorable outcomes at 18 months of age were found to be high (90% and 94%, respectively). A low resistive index (<0.56) at the age of 1–3 days had a specificity of 95% to predict unfavorable outcomes at 3 years of age. The data on the diagnostic and prognostic potential of cranial sonography are limited scarce and contrary.

Introduction

Perinatal asphyxia (PA) remains one of the main causes of mortality and morbidity among newborns, with an estimated incidence of 1–8 per 1000 live births according to different studies (1).

The clinical evaluation of a newborn with signs of encephalopathy during the first days of life is not always feasible, and its differentiation from other possible causes of encephalopathies, such as trauma, developmental disorders, infection, and coagulopathy, is necessary (2). In order to identify hypoxic injuries, it is necessary to evaluate the findings suggestive of asphyxia and perform neuroradiological investigations. Ideally, neuroradiological investigations should depict cerebral injuries and prompt the initiation of necessary neuroprotective treatment. In case of cerebral affection, the prognosis of long-term neurodevelopmental outcome must be carried out, as well as necessary rehabilitation means should be applied as soon as possible (2).

The main methods of investigation of cerebral injuries in a full-term newborn are cranial sonography (CS), Doppler sonography (DS), magnetic resonance imaging (MRI), and in some cases, computed tomography (CT) (2–4).

CS examination of a newborn is an effective, noninvasive, and portable method of investigation, especially useful in severe cases (3). Based on the studies published between 1994 and 2002, the potential of CS for the evaluation of hypoxic lesions in full-term newborns is rather low, but the majority of these studies were retrospective where CS and MRI were performed with a long time interval between them (3). According to Daneman et al., CS and MRI have a strong correlation if performed with a minimum time interval between these 2 investigations (3). The results of ultrasound investigation de-

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pend on various factors such as technical characteristics of a CS unit, application of optimal scan planes, acoustic windows, and skills of the investigator (5).

DS performed in full-term newborns on the first day of life may have an important prognostic value, regarding cerebral hypoxic-ischemic injuries (6). A decreased resistive index (RI) and elevated end-diastolic flow velocity (EDFV) are the main alterations of cerebral blood flow in case of asphyxia (6). According to the recommendations of the American Academy of Neurology and the Practice Committee of the Child Neurology Society, the measurements of RI and EDFV in the anterior cerebral artery are performed in order to assess cerebral perfusion and early predict an outcome (2). An increase in EDFV indicates local or diffuse vasodilatation, caused by increased pCO_2 in case of asphyxia and accumulation of metabolites (3, 6). However, in many countries, Doppler sonography is not widely applied in daily practice (3), and data on its diagnostic and prognostic potential remain scarce.

Based on the recent 5-year publications, MRI is the most important method of investigation in case of hypoxic-ischemic cerebral injuries in full-term newborns. The following aspects contribute to a high prognostic value of cerebral MRI in newborns: an early evaluation of infarction, hemorrhage, injuries of prematurity, and myelination is possible, white and gray matter differentiation abnormalities etc. can be detected (4). Yet, CS and DS are simple and inexpensive methods of investigation with not fully established potential. CT was one of the main methods of investigation of neonatal brain for about 30 years. Despite the effect of ionizing radiation in some situations, it is still considered a very important diagnostic method (2).

The aim of this systematic literature review was to survey the studies on the diagnostic and prognostic possibilities of cerebral radiological investigations (CS, DS, and MRI) in full-term newborn with hypoxic-ischemic injuries, evaluate methods of investigation, and compare the results of their application.

Material and Methods

The inclusion criteria were as follows: data on application of radiological investigations (CS, DS, MRI) in case of full-term newborn hypoxic-ischemic cerebral injuries; correlation of data of radiological investigations (CS, DS, MRI) with severity of hypoxic-ischemic encephalopathy (HIE), and long-term neurodevelopmental outcome.

The following bibliographic databases were searched: Medline, Springer Link Information Service, Science Direct, Lippincott Williams & Wilkins, and EBSCO Publishing. The following key words were employed to identify the relevant articles: asphyxia and cerebral blood flow velocity and Doppler sonography; hypoxic-ischemic encephalopathy and brain sonography; hypoxic-ischemic encephalopathy and MRI; and neurodevelopmental outcomes. The articles published between 1998 and 2008 were included.

The criteria to evaluate the quality of publications were as follows: 1) indication of the beginning and end of a study; 2) population selection criteria defined; 3) exclusion criteria defined; 4) indication of radiological method; 5) time of performance of radiological investigation indicated; 6) radiological findings indicated; and 7) information about methods of evaluation of long-term outcomes indicated.

The study was considered as "good quality" if it could be evaluated by 6 and more criteria; "fair," by 4–5 criteria; and "insufficient," by 3 and fewer criteria.

The data from the selected publications on the detection of hypoxic-ischemic injuries by means of CS, DS, and MRI, associations with long-term neurodevelopmental outcomes, and evaluation criteria of radiological investigation methods (specificity, sensitivity, negative and positive predictive values) were summarized.

Results

General Characteristics

The search revealed 57 studies carried out during the 1998–2008 period. Forty studies did not meet the inclusion criteria: 11 studies presented the comparison of MRI sequences, 6 analyzed lesions of definite cerebral structures, 5 assessed the correlation of long-term HIE outcomes with MRI findings, 2 reported MRI findings after the application of hypothermia, 4 reported the findings of MRI performed during 1–24 years of life or radiological-pathological correlation, 4 included preterm newborns, and 8 studies were not associated with the problem at all.

Table 1 presents the general characteristics of the studies included. All the studies included the data of one or more hospitals. The size of study populations ranged from 17 to 500 cases.

Evaluation of Quality of Studies

The quality of nearly 60% of all studies was considered as methodologically "good" (Table 2). The duration of the study and the method of population selection were indicated in 65% and 76% of studies, respectively. All the studies indicated the used radiological methods, evaluation criteria of radiological findings, and the methods of evaluation of long-term outcomes.

Discussion

The data in the literature on the prognostic possibilities of radiological investigation methods (US, Doppler sonography, MRI) for the detection of hy-

Table 1. General Characteristics of Included Studies

Study	Country	Type of Study	n	Method of Sample Selection	Gestational Age, Selection Criteria
Boo et al., 2000 (7)	Malaysia	Prospective cohort	104	Random	⩾37 weeks, PA and HIE
Blankenberg et al., 2000 (8)	USA	Prospective cross-sectional	47	Random	28–41 weeks, suspected HIE
Okereafor et al., 2008 (9)	UK	Retrospective correlational	500	Random	⩾37 weeks, PA and suspicion of HIE
Boichot et al., 2006 (10)	France	Retrospective correlational	30	Random	⩾37 weeks, PA and severe HIE
Jyoti et al., 2006 (11)	Australia	Prospective correlational	20	Random	⩾37 weeks, PA and suspicion of HIE
Fukuda et al., 2005 (12)	Japan	Prospective cross-sectional	127	Random	Full-term newborns, PA
Miller et al., 2005 (13)	USA	Prospective correlational	173	Random	⩾37 weeks, PA and HIE
Belet et al., 2004 (14)	Turkey	Prospective correlational	24	Not indicated	⩾37 weeks, PA and HIE
Nishimaki et al., 2008 (15)	Japan	Prospective case-control	17	Not indicated	⩾37 weeks, PA
Liu et al., 2007 (16)	China	Prospective case-control	40	Random	⩾37 weeks, PA and HIE
Liu et al., 2007 (17)	China	Prospective case-control	40	Random	37–40 weeks, PA and HIE
Ilves et al., 2004 (18)	Estonia	Prospective case-control	60	Random	37–42 weeks, PA
Kirimi et al., 2002 (19)	Turkey	Prospective case-control	23	Random	⩾37 weeks, PA and medium or severe HIE
Pezzati et al., 2002 (20)	Italy	Prospective cross-sectional	120	Random	24–41 weeks, healthy newborns
Jongeling et al., 2002 (21)	Australia	Retrospective case-control	276	Random	⩾37 weeks, PA and HIE
Meek et al., 1999 (22)	UK	Prospective correlational	27	Random	36–44 weeks, PA and HIE
Ilves et al., 1998 (23)	Estonia	Prospective case-control	39	Not indicated	37–42 weeks, PA

PA, perinatal asphyxia; HIE, hypoxic-ischemic encephalopathy.

Table 2. Evaluation of Quality of Included Studies

Study	Indication of Duration of Study	Method of Sample Selection	Characteristics of Population	Indication of Radiological Method	Time of Radiological Investigation	Method of Evaluation of Long-Term Outcomes	Description of Radiological Findings*	Evaluation of Quality of Study
Boo et al., 2000 (7)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Blankenberg et al., 2000 (8)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Okereafor et al., 2008 (9)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Boichot et al., 2006 (10)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Jyoti et al., 2006 (11)	Yes	Yes	No	Yes	Yes	Yes	Yes	Good
Fukuda et al., 2005 (12)	Yes	Yes	No	Yes	Yes	Yes	Yes	Good
Miller et al., 2005 (13)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Belet et al., 2004 (14)	No	No	Yes	Yes	Yes	Yes	Yes	Medium
Nishimaki et al., 2008 (15)	No	No	Yes	Yes	Yes	Yes	Yes	Medium
Liu et al., 2007 (16)	Yes	Yes	No	Yes	Yes	Yes	Yes	Medium
Liu et al., 2007 (17)	No	Yes	No	Yes	Yes	–	Yes	Medium
Ilves et al., 2004 (18)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Kirimi et al., 2002 (19)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Pezzati et al., 2002 (20)	No	Yes	No	Yes	Yes	–	Yes	Medium
Jongeling et al., 2002 (21)	Yes	Yes	No	Yes	Yes	Yes	Yes	Good
Meek et al., 1999 (22)	No	Yes	Yes	Yes	Yes	Yes	Yes	Good
Ilves et al., 1998 (23)	No	No	Yes	Yes	Yes	Yes	Yes	Medium

*Radiological findings were indicated in all the studies included in this systematic review: type of lesions (magnetic resonance imaging), parameters of blood flow velocities (Doppler sonography), etc.

poxic-ischemic injuries in newborns are scarce and the methods applied are different; therefore, this limits the comparison of findings across studies.

Diagnostic Potential of Cranial Sonography in the Evaluation of Hypoxic-Ischemic Cerebral Injuries in Full-Term Newborns

Our search found only 3 studies that analyzed neurosonographic findings and their associations with HIE stages and long-term neurodevelopmental outcomes in asphyxiated newborns (7, 19, 21). One study evaluated neurosonographic findings within the first 12 hours (19); the second study, within the first 24 hours (7); and the last study, within the first 24 and 72 hours after birth (21). A study by Blankenberg et al. compared CS and MRI findings for the detection of intracranial ischemia or hemorrhage in newborns with suspected HIE (8).

Early neurosonography (12 hours after birth) revealed specific pathological findings, such as increased echodensity of periventricular zones and diffuse increase of parenchymal echodensity (edema), in 47.7% of cases; intraventricular hemorrhage, in 8.6% of cases; and no any pathological findings, in 43.7% of cases (19).

According to the findings of the study by Boo et al., early CS (at 24 hours of life) showed abnormal changes in 79.8% of asphyxiated term infants and 39.5% of control infants ($P<0.0001$). The main CS findings in the asphyxiated term infants were

Table 3. Accuracy of Radiological Methods

Radiological Method of Investigation	Detection Time	Prognosis of Unfavorable Outcomes	Specificity, %	Sensitivity, %	PPV, %	NPV, %	*P*	Study
Cranial ultrasonography	Cerebral edema, 24 h of life	Bad outcomes at 3 years of life*	93	65	87	79	<0.001	Jongeling et al., 2002 (21)
	Cerebral edema, 72 h of life	Bad outcomes at 3 years of life*	92	49	71	82	<0.001	Jongeling et al., 2002 (21)
Doppler ultrasonography	Evaluation of cerebral blood flow velocity at 12±2 hours after asphyxia	Severe HIE	65	90	60	94	<0.005	Ilves et al., 2004 (18)
	Evaluation of cerebral blood flow velocity at 12±2 hours after asphyxia	Bad outcomes at 18 months of life**	84	92	80	94	<0.05	Ilves et al., 2004 (18)
	RI<0.56 at 24 hours of age, with signs of HIE	Bad outcomes at 3 years of life*	95	53	90	70	0.002	Jongeling et al., 2002 (21)
	RI<0.56 at 72 hours of age, with sings of HIE	Bad outcomes at 3 years of life*	95	33	71	78	<0.001	Jongeling et al., 2002 (21)
MRI	Periventricular and gray matter injuries at the 11th day of life	Bad outcomes at 4 years of life***	44.4	100	75	100	Not indicated	Belet et al., 2004 (14)
	Encephalomalacia, periventricular leukomalacia and cerebral atrophy at 4 months of life	Bad outcomes at 4 years of life***	100	86.7	100	81.8	Not indicated	Belet et al., 2004 (14)
	Encephalomalacia, periventricular leukomalacia and cerebral atrophy at 4 years of life	Bad outcomes at 4 years of life***	100	91.7	100	90	Not indicated	Belet et al., 2004 (14)

*Cerebral palsy or death. **Death or severe disability. ***Cerebral palsy, developmental delay, epilepsy, death.

as follows: a general increase in echodensity of cerebral parenchyma (38.7%), increased periventricular echodensity (61.5%), loss of corticomedullary differentiation (26%), compressed lateral ventricles (44.2%), and echogenic thalamus (30.8%). However, based on the results, the authors concluded that these early cranial ultrasound changes on the first day of life were not significant predictors of long-term unfavorable outcomes at 1 year of age (7).

A study by Jongeling et al. showed that newborns with CS findings of cerebral edema in the first 24 hours of life were 24.1 times more likely to have unfavorable long-term outcomes at 3 years of age (death or cerebral palsy) (CS sensitivity, 65%; specificity, 93%; positive predictive value [PPV], 87%; negative predictive value [NPV], 79%; $P<0.001$) (Table 3). The authors reported that in case of presence of all 3 parameters (RI of <0.56, cerebral edema, and clinical manifestation of HIE) in the first 24 hours of life, PPV to detect the unfavorable outcomes by means of CS increased up to 80%; specificity, to 95%; sensitivity, to 53%; and odds ratio, up to 20 ($P<0.001$) (21). Newborns with the signs of cerebral edema at 71 hours of life were 11.2 times more likely to develop long-term unfavorable outcomes at 3 years of age (CS sensitivity, 49%; specificity, 92%; PPV, 71%; NPV, 82%; $P<0.001$) (Table 3). Based on the results of these studies, the most optimal time and modality of CS investigation remains unclear in order to more accurate detect hypoxic-ischemic cerebral injuries in full-term newborns.

Diagnostic and Prognostic Possibilities of Magnetic Resonance Imaging in the Evaluation of Hypoxic-Ischemic Injuries in Full-Term Newborns

Our search revealed 7 studies that analyzed cerebral MRI findings and their associations with long-term neurodevelopmental outcomes in asphyxiated newborns with HIE. One study presented the comparison of a diagnostic potential of CUS and MRI in case of hypoxic-ischemic cerebral injuries in full-term newborns.

According to the recommendations of the American Academy of Neurology and the Practice Committee of the Child Neurology Society published in 2002, MRI in the neonate should be performed at the end of the first week of life in order to predict long-term neurodevelopmental outcomes (2). The time of MRI investigation in all included studies was the end of first or the beginning of the second week of life. In one study, MRI scans were performed at the 5th-19th day, 4 months, and 4 years of life with the interpretation of late signs of HIE.

According to the data reported by different studies, alterations on MRI performed at the end of the first week or the beginning of the second week of life are evident in 75%–100% of patients with stage I-III HIE (9, 11, 13, 14). The main types of lesions include a watershed pattern of injury and an isolated or concomitant basal ganglia/thalamus pattern (4). The injuries of the cortical gray matter or internal capsula posterior limb are documented to be less frequent.

The authors of the studies analyzed reported that the predominance of watershed injury was evident in 23%–70.8% of studies, and predominant or isolated basal ganglia/thalamus injury, in 26% of studies (9, 11, 13, 14). Diffuse injuries of the basal ganglia, thalami, hemispheric white and gray matter, and posterior limb of internal capsula were found in 14%–45% of cases (9, 11, 13).

According to Belet et al., in newborns who had HIE in the neonatal period, encephalomalacia, periventricular leukomalacia, and cerebral atrophy were the most common lesions documented at 4 months and 4 years of age (14).

A US study by Miller et al. evaluated the associations between the pattern of brain injury and prenatal risk factors, extent of resuscitation at birth, and severity of encephalopathy and seizures. The study reported that prenatal risk factors, such as maternal substance use, gestational diabetes mellitus, preterm rupture of membranes, preeclampsia, and retardation of intrauterine growth, did not predict the pattern of cerebral injury (13).

A study by Miller et al. found a weak correlation between the intensity of newborns' resuscitation at birth (correlation coefficient, ϱ=0.21; P<0.006), severity of HIE (ϱ=0.32; P<0.0001), and severity of seizures (ϱ=0.29; P<0.0001) and the watershed score; the correlation between the same parameters and the basal ganglia/thalamus score was found to be slightly stronger (ϱ=0.32; P<0.0001; ϱ=0.42, P<0.0001; ϱ=0.41, P<0.0001, respectively) (13).

One of the challenges of radiological investigations is to predict adverse long-term neurodevelopmental outcomes. One study analyzed long-term outcomes at 12 and 30 months of age; 3 studies, at 12 months of age; and 1 study, at 4 years of age. In the studies included in this systemic review, neurological status and mental development were evaluated according to the Griffiths (11, 22), Bayley (7, 13, 14), and Denver (19) scales and the World Health Organization (WHO) criteria (10).

Cerebral injuries in newborns with HIE are associated with different clinical and neurodevelopmental outcomes (13). Based on the studies carried out in the United Kingdom, Australia, and Turkey, all newborns without lesions or with only mild periventricular white matter injuries on MRI at the end of the first week or the beginning of the second week of life had favorable neurodevelopmental outcomes at 12 months and 4 years of life (9, 11, 14).

According to the studies included into this systematic review, favorable outcomes were documented in 25%–55% of neonates, while unfavorable, in 40%–62.5% of neonates (9–11, 14). In case of unfavorable outcomes, Belet et al. documented cerebral palsy in 58.3%, mental retardation in 50%, and epilepsy in 33.3% of cases (14). Miller et al. reported that in case of the predominant watershed pattern of injuries, 18% of patients had mental retardation and 11% had motor impairment (spastic quadriparesis, hemiparesis, or triparesis) (13).

A French study by Boichot et al. showed that cerebral edema on MRI was detected at the same frequency in the groups of favorable and unfavorable outcomes (81% vs. 86%); the isolated basal ganglia/thalamus injury was more common among cases with unfavorable outcomes (94% vs. 57%, P=0.018) (10). Newborns with predominant basal ganglia/thalamus injury at 30 months of age had cognitive (P=0.0007) and motor (P=0.0001) impairment more frequently than those with watershed zone injuries (13).

In newborns with an isolated basal ganglia/thalamic injury accompanied by the white matter injury of medium severity, neurodevelopmental retardation or diplegic cerebral palsy was apparent at the first year of life (9). In newborns with a predominant basal ganglia/thalamus injury, spastic quadriparesis was detected in 56% of live patients at 30th month of age, while in 50% of cases, mental retardation was documented (mental development index, <70) (13).

According to Jyoti et al., all newborns with diffuse basal ganglia/thalamus injury accompanied by white matter injury detected on MRI on the 7th–10th day of life (cerebral palsy, mental retardation) had unfavorable outcomes at the first year of life (PPV, 90%) (11). However, Miller et al. failed to determine a significant difference in the mental development index and the neuromotor assessment score between newborns with diffuse cerebral injury and those with predominant basal ganglia/thalamus injury (P>0.1) (13).

Cortical lesions (mostly in the frontal lobes and precentral gyrus), along with basal ganglia/thalamus injury, were detected in 81% of cases with unfavorable outcomes and in 21% of cases with favorable outcomes (P=0.011). This combination of lesions is typical of severe perinatal asphyxia (10). Jyoti et al. reported that unfavorable outcomes were evident in all patients with injuries of the posterior limb of the internal capsule (11).

Okereafor et al. detected injuries of the posterior limb of the internal capsule in 93% of newborns with basal ganglia/thalamus injury and white matter lesions of different severity; 86% of patients developed unfavorable outcomes (death or cerebral palsy) (9). However, according to Biochot et al., there was no significant difference in the frequency of injuries of the posterior limb of the internal capsule between the groups of favorable and unfavorable outcomes (10).

Table 3 shows the accuracy of radiological methods across different studies. MRI findings in the neonatal period showed a higher NPV in determin-

ing long-term outcomes at 4 years of life (14). MRI performed at 4 months and 4 years of age showed that patients with HIE had leukomalacia, encephalomalacia, and cerebral atrophy, and outcomes were unfavorable in all cases (14). According to the authors of this study, MRI findings at 4 months of age (sensitivity, 86.7%; specificity, 100%; PPV, 100%; NPV, 81.8%) and 4 years of age (sensitivity, 91.7%; specificity, 100%; TPV, 100%; NPV, 90%) had a greater PPV than MRI findings in the neonatal period (sensitivity, 100%; specificity, 44.4%; PPV, 75%; and NPV, 100%) (14).

Only one study compared the potential of CS and MRI in the detection of cerebral injuries in newborns with suspected HIE: MRI was more precise in detecting hypoxic-ischemic cortical lesions compared with CS ($P<0.001$), but the absence of lesions on neurosonograms/MRI does not mean that no unfavorable outcomes will develop. The NPV of CS and MRI to predict unfavorable outcomes at 2 years of life was found to be low (58.8%) (8).

Diagnostic and Prognostic Possibilities of Doppler Sonography in the Evaluation of Hypoxic-Ischemic Cerebral Lesions in Full-Term Newborns

Based on the studies included this analysis, Doppler sonographic findings could be valuable for the prognosis of HIE severity and the evaluation of possible long-term outcomes in newborns who suffered perinatal hypoxia.

A total of 10 studies that investigated cerebral blood flow velocity of full-term newborns with perinatal hypoxia were included into analysis. Six studies evaluated cerebral blood flow during the first day of life (16– 20, 22), 1 study during the first and second days of life (20), and 2 studies during the first-third days of life (12, 21, 23).

Changes in Blood Flow Velocity After Asphyxia and Associations With the Stage of HIE and Long-Term Outcomes

An increase in blood flow velocity during the first hours after birth indicates a normal reaction to the postnatal environment (22). Pezzati et al. evaluated cerebral blood flow in the anterior and medial cerebral arteries of healthy preterm and full-term newborns (gestational age, 24 to 41 weeks) and showed that blood flow velocity at 2–8 hours after birth increased significantly with increasing gestational age and birthweight ($P<0.0001$) (20).

Newborns with perinatal asphyxia and HIE had significantly lower peak systolic flow velocity (PSFV) and EDFV in the anterior and medial cerebral arteries at 12 hours of life as compared with control newborns ($P<0.05$) (16, 19). Ilves et al. reported that cerebral blood flow velocities (PSFV and EDFV) measured up to 6 hours after asphyxia are not specific and not suitable for the prediction of HIE severity and long-term unfavorable outcomes such as death and severe disability (sensitivity, 78% and 78%; specificity, 44% and 37%; PPV, 58% and 50%; NPV, 66% and 66%, respectively) (18). At the age of 2–6 hours, there was no significant difference in PSFV and EDFV between newborns with mild-to-moderate HIE and those with severe HIE. Moreover, no significant difference in PSFV and EDFV was found between newborns with a poor outcome (death or severe disability) and newborns with normal development/mild impairments (18).

The evaluation of cerebral blood flow within 12±2 hours has a greater prognostic value. Cerebral blood flow velocities differ depending on the severity of HIE. Ilves et al. reported that increased blood flow velocities of more than 3 SD at the age of 12±2 hours showed an early onset of severe vasoparalysis of the brain and were found to be associated with severe HIE and unfavorable outcomes (23). Cerebral blood flow velocities in the anterior, medial, and basilar cerebral arteries at 12±2 hours of life were significantly greater in newborns with severe HIE ($P<0.005$) and significantly lower in newborns with mild-to-moderate HIE ($P<0.05$) compared with the control group (18).

Newborns with normal or mild neurological symptoms at the age of 18 months had significantly lower cerebral blood flow velocities at 12±2 h of life in the anterior, medial and basilar cerebral arteries as compared with control newborns ($P<0.05$) (18). The sensitivity, specificity, PPV, and NPE of mean cerebral flow velocity changes at the age of 12±2 hours to predict the development of severe HIE were 90%, 65%, 60%, and 94%, respectively ($P<0.005$). The sensitivity, specificity, PPV, and NPE of mean cerebral flow velocity changes at the age of 12±2 hours to predict a poor prognosis at the age of 18 months were 92%, 84%, 80%, and 94%, respectively ($P<0.05$) (18) (Table 3).

A study by Meek et al. reported that cerebral blood volume on the first day after asphyxia was significantly higher in newborns with severe HIE than newborns with moderate HIE ($P=0.003$). An increase in cerebral blood flow volume on the first day of life was found to be a very sensitive indicator (sensitivity, 86%) for the prediction of unfavorable outcomes (22).

The high velocities of cerebral blood flow recorded in asphyxiated newborns at 24–48 hours of life are prognostically important as well, enabling to predict the severity of HIE and unfavorable prognosis. Ilves et al. reported that cerebral blood flow normalized in newborns with mild and moderate encephalopathy as well as with normal or slightly impaired psychomotor development by the age of

24–36 hours. The infants with severe HIE and unfavorable long-term neurodevelopmental outcomes showed significantly higher blood flow velocities in the anterior, medial, and basilar cerebral arteries than those with mild-moderate HIE or the control group infants ($P<0.001$) (18).

A study by Nishimaki et al. showed that the median end-diastolic cerebral blood flow velocity in the anterior cerebral arteries was significantly higher in the severely asphyxiated newborns than in the healthy or mildly asphyxiated newborns (19.8 vs. 10.2 and 10.4 cm/s, respectively; $P<0.05$). However, the authors failed to detect the significant differences in the peak systolic blood flow velocity comparing the groups of severely and mildly asphyxiated or healthy newborns (15).

Fukuda et al. investigated cerebral blood flow velocity in the anterior and internal carotid cerebral arteries of asphyxiated newborns on days 1–3. They reported that newborns with perinatal asphyxia but without HIE symptoms at birth and with cerebral palsy at 1 year showed significantly lower time-averaged mean flow velocity compared with those without cerebral palsy at 1 year ($P<0.05$). No significant difference in time-averaged mean flow velocity was recorded in the newborns with HIE regarding the presence/absence of cerebral palsy (12).

Alterations of Resistive Index After Asphyxia and Association With HIE Stage and Unfavorable Long-Term Outcomes

The RI is a very important parameter for the evaluation of cerebral perfusion and predicting the HIE stage, as well as long-term neurodevelopmental outcome. According to Liu et al., a low RI (<0.55) with decreased cerebral blood flow velocity observed on the first day after birth indicates cerebral hypoperfusion, and these alterations are more common among patients with mild HIE. Meanwhile, a low RI (<0.55) with significantly increased cerebral blood flow (>normal mean values plus double standard deviation) indicates cerebral hyperperfusion, and these alterations are more common in patients with moderate and severe HIE (17).

Ilves et al. did not detect any significant differences in RI between newborns with severe encephalopathy and those with mild-to-moderate encephalopathy and between newborns with poor neurodevelopmental outcome and those with normal outcome/mild impairments at the postnatal age of 2–6 and 12 hours. However, by the age of 24 hours, differences were documented in the anterior, medial, and basilar cerebral arteries. In newborns with severe HIE or with poor outcome, lower RI was recorded as compared with the control group at the age of 2–6 hours in the basilar artery, at the age of 12 hours in the medial and internal carotid arteries, and from the age of 24 hours in all investigated vessels ($P<0.05$) (18). However, the studies by Liu et al. and Kirmi et al. revealed that at the age of 12 hours, the RI was significantly higher in the newborns with HIE as compared with healthy newborns ($P<0.05$) (16, 19).

Jongeling et al. reported that the newborns with a low RI (0.56) detected in the first 24 hours after birth were 23.6 times more likely to have unfavorable outcomes (death or cerebral palsy) at the age of 3 years than the newborns with a normal RI. The authors reported a specificity of 95%, a sensitivity of 53%, a PPV of 90%, and a NPV of 72% ($P<0.002$) (21) (Table 3). The analysis by Nishimaki et al. revealed that the median RI in the anterior cerebral arteries at 24–48 hours of life was significantly lower in the patients with severe asphyxia as compared with the control patients (0.52 and 0.7, $P<0.001$) and patients with mild asphyxia (0.52 and 0.65, $P<0.001$) (15). The abovementioned study by Jongeling et al. showed that the newborns with a low RI (<0.56) detected on the first 72 hours of life were 8.8 times more likely to develop unfavorable outcomes at 3 years of age (specificity, 95%; sensitivity, 33%; PPV, 71%; NPV, 78%; $P<0.001$) (21) (Table 3).

The low RI may be present for a longer period depending on the severity of asphyxia (3), but there are no studies reporting how the low RI remaining for a longer period is associated with HIE and long-term outcomes.

Conclusions

The comparison of data in the literature about the diagnostic and prognostic possibilities of radiological methods (cranial sonography, Doppler sonography, and magnetic resonance imaging) in the evaluation of cerebral hypoxic ischemic injuries in full-term newborns is limited as different methods for the evaluation were applied. Moreover, these data are not sufficient and contrary.

Magnetic resonance imaging detects lesions in 75%–100% of cases. The main injuries detected with the help of magnetic resonance imaging are white-matter watershed injuries and basal ganglia/thalamus lesions. They appear to be isolated or concomitant. The lesions of the cortical gray matter and injuries of the posterior limb of the internal capsule are detected more rarely. Magnetic resonance imaging performed at the age of 7–11 days demonstrated a high sensitivity (100%) and negative predictive value (100%) to predict unfavorable outcomes at 4 years of age.

In newborns with hypoxic-ischemic encephalopathy, significant cerebral hemodynamic alterations are detected after birth. The sensitivity and negative predictive value of cerebral blood flow velocities (peak systolic flow velocity, end-diastolic flow

velocity) changes at 12±2 hours of age to predict the severity of hypoxic-ischemic encephalopathy and unfavorable outcomes at 18 months of age were found to be high (90% and 94%, respectively). A low resistive index (<0.56) at the age of 1–3 days had a specificity of 95% to predict unfavorable outcomes at 3 years of age.

Statement of Conflict of Interests

The authors state no conflict of interest.

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