PROGNOSTIC ROLE OF EARLY MRI IN NEONATAL HYPOXIC ISCHEMIC ENCEPHALOPATHY

PhD thesis

Andrea Lakatos, MD

János Szentágothai PhD School of Neurosciences
Semmelweis University

Supervisor: Lajos R. Kozák, MD, Ph.D

Official Reviewers: Gábor Nagy, MD, Ph.D
Erzsébet Mária Babity-Botos, MD, Ph.D

Chair of the Final Examination Committee:
Kinga Karlinger, MD, C.Sc

Members of Final Examination Committee:
Zoltán Harkányi, MD, C.Sc
Dávid László Tárnoki, MD, Ph.D

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„If we do not honour our past,
we lose our future.
If we destroy our roots,
we cannot grow.”
Friedensreich Hundertwasser

To my parents

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Abbreviations

ADC	apparent diffusion coefficient
aEEG	amplitude integrated electroencephalography
aOR	adjusted odds ratio
ASL	arterial spin labelling
BGT	basal ganglia - thalamus
BSID-II.	Bayley Scales of Infant Development
BW	body weight
CT	computed tomography
DTI	diffusion tensor imaging
DWI	diffusion weighted imaging
EDH	epidural hemorrhage
EEG	electroencephalogram
FA	fractional anisotropy
GMH	germinal matrix hemorrhage
HIE	hypoxic ischemic encephalopathy
ICE	Infant Cooling Evaluation Collaboration (trial)
ICH	intracranial hemorrhage
iSORT	intelligent structured online reporting tool
IVH	intraventricular hemorrhage
LAC	lactate
LOC	level of consciousness
MDI	mental developmental index
MRI	magnetic resonance imaging
MRS	magnetic resonance spectroscopy
MTI	magnetization transfer imaging
NAA	N-acetylaspartate
NE	neonatal encephalopathy

NICHD	National Institute of Child Health and Human Development (study)
NO	nitric oxide
OR	odds ratio
P	intraparenchymal hemorrhage
PC-MRA	phase contrast magnetic resonance angiography
PDI	psychomotor developmental index
PLIC	posterior limb of the internal capsule
ppm	parts per million
PRESS	Point RESolved Spectroscopy
SAH	subarachnoid hemorrhage
SDH	subdural hemorrhage
SR	structured reporting
SV-MRS	single voxel magnetic resonance spectroscopy
SWI	susceptibility weighted imaging
T1	T1 weighted imaging
T2	T2 weighted imaging
TE	echo time
TOBY	Total Body Hypothermia for Neonatal Encephalopathy (trial)
TOF-MRA	time-of-flight MR angiography
TR	repetition time
WM	white matter

1. Introduction

The two studies introduced in this thesis build on each other. Structured reporting provided a framework to investigate neonatal hypoxic ischemic encephalopathy from the imaging point of view.

1.1. Structured reporting

The radiology report is fundamental in the clinician-radiologist communication. Standardized reports with higher quality and reproducibility allow for better clinical and scientific workflow, therefore facilitate the optimization of individualized patient care, and improve the exploration of possible novel prognostic factors. The term structured reporting (SR) is used to describe a wide range of concepts in the literature. It can mean a simple template or macro, or a more complex system with „controlled terminology". A radiology report communicates important information about the patient to the referring physician and also serves as a legal record, so it should be comprehensive, consistent, „re-readable" for comparison or searchable for scientific purposes [1-3]. Although the traditional free text reporting affords the radiologist with latitude [4], it does not always address key clinical questions, and may also contain clinically relevant errors, omissions and ambiguous terms [3, 5]. Structured reports have the benefit of reducing the incidence of errors, making it easier to extract and compare information, and reducing possible ambiguity (hence misunderstanding) by encouraging the use of a standard lexicon [3, 4, 6]. Creating a structured reporting template in complex modalities, such as magnetic resonance imaging (MRI) meets several challenges which need to be handled. Compared to other imaging modalities there is more variability in the MR image quality, sequence types and the acquisition parameters. Besides, there are remarkable inter-observer differences in image interpretation [7]. Our intent was to troubleshoot the above mentioned potential problems and create a clear and consistent reporting template in a user friendly format, providing detailed information and the possibility of easy data extraction. Hypoxic ischemic

encephalopathy (HIE) was chosen as the target of our template-building efforts as the long-range plan of our workgroup of radiologists, neonatologists and information technologists was to build an “asphyxia database”. The goal of such database was to include all relevant data of affected neonates for immediate clinical use while fostering research, as well.

1.2. Hypoxic ischemic encephalopathy

1.2.1. Hypoxic ischemic encephalopathy – the beginning

Sixty years ago, experiments have demonstrated that perinatal asphyxia could induce brain injury in primates [8]. Since then, different patterns of hypoxic ischemic encephalopathy (HIE) have been established, which were dependent on the severity and duration of the hypoxic-ischemic insult [9]. These findings in animal studies were comparable with postmortem findings in asphyxiated human neonates. During the 1960s and 1980s, imaging of brain injury in human neonates was performed by mainly ultrasound or computer tomography. Since the introduction of MRI, the knowledge of localization and severity of HIE in surviving neonates has expanded tremendously [10-12]. Diffusion-weighted MRI has enabled radiologists to diagnose a lesion much earlier than conventional MRI. In addition, proton magnetic resonance spectroscopy (MRS) provided the detection of metabolic changes in the neonatal brain following asphyxia [13, 14].

1.2.2. Incidence of hypoxic ischemic encephalopathy

HIE is a paramount problem worldwide being the major cause of neurologic disability in term neonates despite the recent widespread use of hypothermic therapy. The incidence ranges from 1 to 8 per 1000 live births in developed countries to as high as 26 per 1000 live births in undeveloped countries [15]. 10% to 60% of the affected infants die, and at least 25% of survivors have long term neurodevelopmental sequelae [16].

1.2.3. Pathophysiology of hypoxic ischemic encephalopathy

Cerebral blood flow delivers oxygen and glucose to the fetal brain. Adequate blood flow helps fetal brain maintain homeostasis and meet cellular energy demands. A variety of conditions can decrease placental perfusion or disrupt the delivery of oxygen and glucose in the umbilical cord, including placental abruption, prolapse of the umbilical cord and uterine rupture. The hypoxia eventually leads to a decrease in fetal cardiac output, which reduces cerebral blood flow. If the decrease in cerebral blood flow is moderate, the cerebral arteries shunt blood from the anterior circulation to the posterior circulation to maintain adequate perfusion of the brainstem, cerebellum and basal ganglia [17]. As a result, damage is restricted to the cerebral cortex and watershed areas of the cerebral hemispheres. Acute profound hypoxia causes an abrupt decrease in cerebral blood flow, which produces injury to the basal ganglia and the thalami [17].

Decreased cerebral perfusion leads to an injury with a temporal "evolution", which clinicians have divided into distinct phases (**Figure 1**). In the acute phase, the decreased cerebral blood flow reduces the delivery of oxygen and glucose to the brain, which leads to anaerobic metabolism. As a result, production of adenosine-triphosphate (ATP) decreases and that of lactic acid increases. The depletion in ATP reduces transcellular transport and leads to intracellular accumulation of sodium, water and calcium [18]. When the membrane depolarizes, the cell releases glutamate (excitatory amino acid), and calcium flows into the cell via N-methyl-D-aspartate-gated channels. This cascade of events perpetuates injury in a process termed excitotoxicity. The peroxidation of free fatty acids by oxygen free radicals leads to more cellular damage [19]. The culmination of energy failure, acidosis, glutamate release, lipid peroxidation, and the toxic effects of nitric oxide leads to cell death via necrosis and activates apoptotic cascades [19].

Depending on the timing of injury and the degree of medical intervention, a partial recovery occurs during the 30 to 60 minutes after the acute insult or the primary phase of injury. This partial recovery ushers in a latent phase of injury [20]. The latent phase may last from 1 to 6 hours and is characterized by recovery of oxidative metabolism, inflammation, and continuation of the activated apoptotic cascades [18].

The latent phase is followed by a secondary deterioration in neonates with moderate to severe injury. The secondary phase of injury occurs within approximately 6 to 15 hours after the insult. Cytotoxic edema, excitotoxicity, and secondary energy failure with nearly complete failure of mitochondrial activity characterize this secondary phase, which leads to cell death and clinical deterioration [20]. Seizures typically occur in the secondary phase [21]. A tertiary phase occurs during the months after the acute insult and involves late cell death, remodeling of the injured brain, and astrogliosis [22].

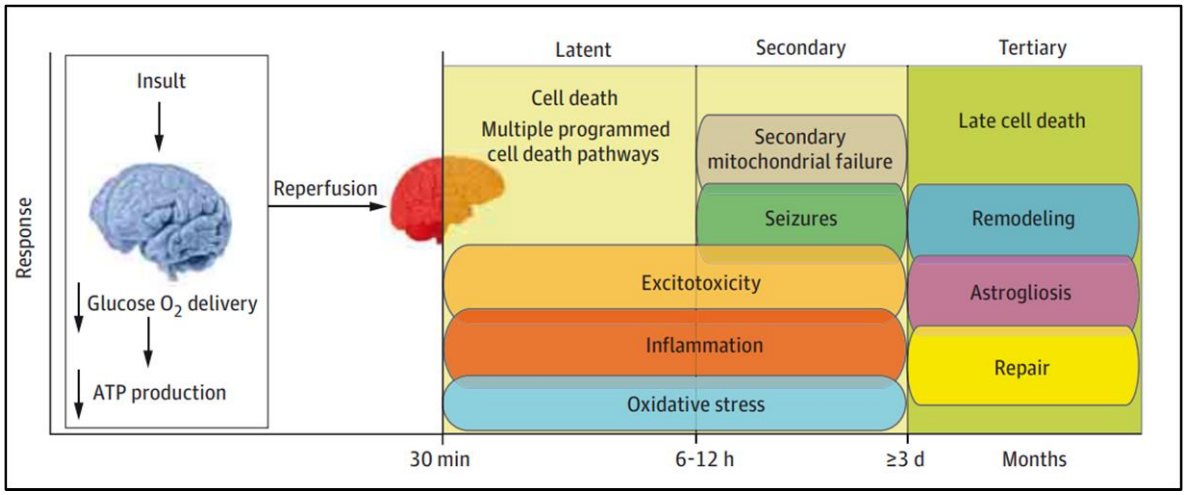

Figure 1 Schematic overview of the pathophysiological features of hypoxic-ischemic encephalopathy [23]

1.2.4. Diagnostic considerations of hypoxic ischemic encephalopathy

1.2.4.1. Clinical diagnosis

The main purpose of the clinical scoring of asphyxiated infants is to assess the severity of HIE in order to find those neonates with moderate to severe encephalopathy who may benefit from hypothermia treatment. These clinical grading systems also have a prognostic value.

1.2.4.1.1. Clinical signs and symptoms

Apgar score

In 1953, Virginia Apgar published what was later named Apgar score to assess newborn infants in the first minutes after birth [24]. Its ability to assess the need for, and response to resuscitation has led it being incorporated into neonatal guidelines and WHO policy [25, 26]. The Apgar score comprises five components: 1) color, 2) heart rate, 3) reflexes, 4) muscle tone and 5) respiration, each of which is given a score of 0, 1 or 2. Thus, the Apgar score quantifies clinical signs of neonatal depression such as cyanosis or pallor, bradycardia, depressed reflex response to stimulation, hypotonia and apnea or gasping respirations. The score is reported at 1 minute and 5 minutes after birth for all infants, and at 5-minute intervals thereafter until 20 minutes for infants with a score less than 7 [27]. The Apgar score is an expression of the infant's physiologic condition at one point in time, which includes subjective components. There are numerous factors that can influence the score, including maternal sedation or anesthesia, congenital malformations, gestational age, trauma and interobserver variability [28]. The isolated use of Apgar score for defining perinatal asphyxia has been discontinued over the years in developed countries. The American Academy of Pediatrics and the American College of Obstetrics and Gynecology's definition stipulates that other evidences of hypoxemia such as acidemia, encephalopathy, and multiorgan dysfunction should be present before the diagnosis could be made [29].

Sarnat and Sarnat classification of HIE

The Sarnat and Sarnat staging system classifies the degree of encephalopathy. Affected infants are assigned into one of the three categories: mild (stage 1), moderate (stage 2) and severe (stage 3) [30].

Sarnat stage 1 is characterized by hyperalertness, uninhibited Moro and stretch reflexes, sympathetic effects and normal electroencephalogram (EEG).

Sarnat stage 2 is marked by obtundation, hypotonia, strong distal flexion, and multifocal seizures. The EEG shows a periodic pattern sometimes preceded by continuous delta activity.

Sarnat stage 3 infants are stuporous, flaccid, and brain stem and autonomic functions are suppressed. The EEG is isopotential or has infrequent periodic discharges.

Thompson score

The HIE scoring system named after Thompson consists of the clinical assessment of nine signs: tone, level of consciousness, clinically apparent seizures, posture, primitive reflexes (Moro, grasp and suck), respiratory pattern, and the fontanelle tension [31].

1. **Tone** progresses from normal and slightly increased peripheral tone in the mildly affected infant to general hypotonia or complete flaccidity in the more severely affected infant.
2. The **level of consciousness** (LOC) is assessed as described by Sarnat and Sarnat [30]. The mildly affected infant has a normal LOC or is hyperalert and staring with normal and decreased spontaneous movement and exaggerated responses to minimal stimuli. The more severely affected infant progresses through lethargy to complete unresponsiveness.
3. The **clinically apparent seizures** are given higher scores with increasing frequency of seizures.
4. The **posture** is assessed as described by Sarnat and Sarnat [30], except for a difference that an intermediate score of 1 is given to the infant who has mild to moderate HIE and shows intermittent bicycling movements of the limbs together with fisting (thumbs flexed, adducted and opposed across palms).
5-7. The **primitive reflexes (Moro reflex, palmar grasp, suck reflex)** are normal in the mildly affected infant, poor or partial in moderate HIE and absent in severe HIE.
8. The **respiratory pattern**: In mild HIE the infant breathes normally or hyperventilates. More severely affected infants have episodes of apnea and may require ventilation.
9. The more severely the infant is affected, the more full or tense (bulging) **fontanelle** is seen.

Each sign is scored from 0-2 or 0-3 and the final score sums the individual points. The higher the score, the more severely affected the infant. The score is equally applicable in a ventilated infant, but cannot be applied in a paralyzed infant.

1.2.4.1.2. Laboratory findings

There are no specific tests to confirm or exclude HIE, as the diagnosis is made on the basis of the history, physical, neurologic examinations, and laboratory evidence. Many of these tests are performed to assess the likelihood of severe brain injury and to monitor the functional status of the organ systems. The results should be interpreted in conjunction with the clinical history and findings from the physical examination.

In neonatal encephalopathy (NE) basic tests allow calculation of the anion gap ((serum sodium + potassium)-(serum bicarbonate + chloride)), with the normal value being <16. Where a clear history of an antenatal/intrapartum event exists, and the clinical presentation, course and first time investigations point towards HIE, no further etiological investigations are required, although neuroimaging will provide prognostic information [32].

Full blood count: May suggest infection, hemorrhage and thrombocytopenia.

Clotting: Clotting disorders may be seen in HIE and sepsis, but should also lead the clinician to think about anemia secondary to inherited coagulation disorders and intracranial hemorrhage.

Direct Coombs test: Detects evidence of hemolysis.

Liver function test: May be abnormal in HIE but is usually transient until severe insult to the liver has occurred. Abnormal liver function tests can be a feature of bilirubin encephalopathy, metabolic conditions, congenital infections, and acute sepsis with bacteria and viruses, including herpes virus.

Urea and electrolytes: May be impaired if the kidneys have had an ischemic insult but usually improves, unless severe ischemic injury has occurred. May also be impaired in congenital abnormalities of the kidneys, metabolic conditions.

Whole blood glucose: Hypoglycemia may be seen following HIE, but is usually correctable with appropriate treatment. Persistently low glucose requires further evaluation.

Arterial blood gas: Blood gas monitoring is used to assess acid-base status and to avoid hyperoxia and hypoxia as well as hypercapnia and hypocapnia. Lactate is often measured on the blood gas, and may increase rapidly to high levels following HIE, but usually falls within days and returns to normal. A persistently high lactate should trigger further investigations.

1.2.4.1.3. Amplitude-Integrated Electroencephalography (aEEG)

Seizures are a common feature of HIE; however, it should be noted that around 34% of neonatal seizures have clinical features that can be seen, and only 27% of those were correctly identified by neonatal staff. In addition, over 70% of what are thought to be seizures are not associated with epileptiform discharges on EEG, highlighting the importance of neurophysiological monitoring [33]. aEEG is a simplified bedside neurophysiology tool widely used in neonatal units today, which can demonstrate background abnormalities and disturbance of sleep wake cycles. aEEG can also detect one-third of single seizures and two-thirds of repetitive seizures, but those that are short lasting (< 30 s) or distant from the electrodes may be missed [34]. Abnormalities of background EEG pattern and the loss of sleep wake cycling are commonly early after hypoxia-ischemia, and can be used to assess clinical recovery and predict outcome [32].

1.2.4.2. Neuroimaging

Different imaging modalities are available to detect neonatal brain injury, including cranial ultrasonography, computed tomography (CT) and magnetic resonance imaging. MRI is the gold standard imaging method to diagnose and assess the severity of HIE.

The two main patterns of injury in term neonates are peripheral or watershed pattern, and central or basal ganglia – thalamus (BGT) pattern. Mild to moderate hypoxic ischemic injury in a full-term neonate causes lesions in the watershed areas between the anterior and middle cerebral arteries and between the middle and posterior cerebral arteries and the border zone, the parasagittal cortex and subcortical white matter, while sparing the brainstem, cerebellum and the deep gray matter structures [35, 36]. Severe hypotension involves the metabolically active tissues in the brain, which are most susceptible to injury including the ventral and lateral aspects of the thalami, posterior aspect of the putamina, hippocampi, brainstem, perirolandic regions, and corticospinal tracts [35, 36].

1.2.4.2.1 Ultrasound (US)

Cranial ultrasonography is a non-invasive and relatively low cost method, which can be performed bedside without sedation, can be repeated as often as necessary being an advantage of the technique in unstable and/or very preterm infants. This imaging method is particularly suitable for screening and follow-up examinations by providing a wealth of anatomical and functional information [37, 38]. Duplex Doppler examination provides additional information on cerebral perfusion. Brain US is generally performed using the anterior fontanelle as an acoustic window. The posterior fontanelle and mastoid fontanelles can be used as additional acoustic windows to study the posterior fossa and the brainstem. The high sensitivity and reliability of cranial ultrasonography for detection of germinal matrix hemorrhage, intraventricular hemorrhage and periventricular leukomalacia in preterm infants is well-known [39, 40]. Diffuse white matter injury in preterm infants is less well detected by ultrasound [41]. The technique shows low sensitivity for the detection of abnormalities close to the convexity or involving the posterior fossa and it does not give detailed information about myelination. Although US is thought to have limited role in the evaluation in hypoxic-ischemic brain injury, a recent study consider brain US an increasingly effective imaging tool for determining the pattern, timing, and extent of injury in HIE as well as differentiating these findings from a host of diagnoses that can result in a similarly appearing clinical picture [42]. In our practice, US has a limited role in the diagnosis and follow-up of HIE, as MRI was found to be much more sensitive and specific.

1.2.4.2.2. Computed Tomography

CT is not sensitive in depicting edema and infarction in neonatal hypoxic-ischemic brain injury because of the high water content in the newborn brain, resulting in poor contrast resolution. CT should therefore not be used to visualize hypoxic ischemic brain injury in infants [36]. On the other hand, CT affords excellent detection of hemorrhage, however the use of ionizing radiation is a disadvantage of this imaging modality [43]. Since cranial ultrasonography also depicts most hemorrhages, the role of CT in young infants is very limited.

1.2.4.2.3. Magnetic Resonance Imaging and Spectroscopy

Performing magnetic resonance imaging in combination with proton magnetic resonance spectroscopy is a widely accepted imaging method for quantifying the extent of hypoxic ischemic brain injury, and predicting outcome [44-55]. MR imaging has the advantage of superbly displaying soft tissue contrast differentiation, moreover determining the exact extent and site of brain injury better than cranial ultrasonography [43]. In addition, the myelination process can be assessed by MRI. However, performing brain MRI is logistically more challenging in infants than brain US. Successful MR imaging starts well before the MR data acquisition. Communication between the staff in the neonatal intensive care unit and the radiology department is critical to ensure that the neonate does not wait in the MR imaging suite. The use of MR-compatible incubators with built-in coils can save considerable time in transport and improve patient safety [35]. Strategies for preventing movement of the infant during examination include swaddling, and use of a vacuum cushion. If needed, oral chloral hydrate or intravenous morphine sedation also may be used. Cardiac monitoring is performed with a pulse oximeter and electrocardiographic system that are MR compatible. The standard MR sequences in adults must be adapted for use in neonates; the neonatal brain has longer T1 and T2 relaxation times because of its higher water content and lower protein and lipid content. To optimize both the signal-to-noise ratio (SNR) and the contrast between white matter and gray matter in neonates, the repetition time (TR) in T1- and T2-weighted imaging sequences must be increased (to 9.000 - 10.000 ms). For T1-weighted sequences, the standard TR of 400-500 ms should be doubled [35]. Because of the high water content of the brain, fluid-attenuated inversion recovery (FLAIR) imaging is not useful within the first year after birth [54, 56, 57]. In case of an asphyxiated neonate the routine brain MRI protocol consists of the following sequences: conventional T1-, and T2-weighted pulse sequences and advanced techniques as diffusion-weighted imaging (DWI), hemosiderin sensitive techniques such as T2* gradient echo or susceptibility weighted imaging (SWI) and proton MR spectroscopy. MR sequences are usually applied in order of their priority, in case the status of the patient deteriorates or patient motion becomes intrusive before all the planned

sequences have been completed. In neonates with encephalopathy, diffusion-weighted imaging sequences are potentially the most informative and therefore applied first, followed by T1-, and T2-weighted sequences, gradient echo T2* and susceptibility weighted sequences and MR-spectroscopy. If signal intensity within the venous sinuses on images obtained with the initial sequences is suggestive of sinovenous thrombosis, MR venography may be performed with phase-contrast imaging or time-of-flight technique.

T1- and T2-weighted images are not effective in the early detection of cerebral edema and white matter lesions as they show prolonged relaxation times only 1- 2 days after the injury [55, 57, 58] and may appear normal during the first days after a hypoxic ischemic event despite severe brain damage [59, 60]. Hence the role of conventional sequences is supported by the fact that in many patients, the precise timing of the injury is not known [61]. Due to myelination changes associated with maturation process of the brain, T1- and T2- relaxation times change over time in the maturing brain, leading to changing contrast on T1- and T2-weighted images. During the first six months, the myelination process is best visualized in T1-weighted images, therefore T1-weighted images are advocated to be used for the assessment of the basal ganglia and the thalami and the myelination process in the neonatal period [48, 54, 62]. After six months T2-weighted images better reflect this process. Early detection of cortical involvement in HIE is possible with T2-weighting, which provides good contrast between cortical gray and subcortical white matter [35, 63, 64].

Diffusion-weighted imaging makes use of the hydrogen molecule's physical property of diffusion. Unless restricted, diffusion occurs in all directions. DWI is sensitive in the detection of restricted diffusion showing, e.g. cytotoxic oedema due to delayed energy failure, and is probably most sensitive two to five days after the hypoxic ischemic injury [59, 65, 66]. The abnormalities show a specific evolution [45, 59, 63]. Over time there are new areas appearing with restricted diffusion, besides simultaneous pseudonormalization at the anatomic regions that had showed diffusion restriction earlier [45, 51, 54, 59, 63, 67]. The evolution of the pattern is different in case of normothermia and hypothermia [51], but early MRI robustly predicts the extent of injury even if hypothermia treatment was adopted [68]. Neonatal stroke, which is important to consider as a possible differential diagnosis is also nicely visualized on DWI [69, 70].

Diffusion tensor imaging (DTI) may improve the ability to increase the detection of abnormal tissue by providing another parameter: the anisotropy or directional diffusivity within a tissue. Anisotropy increases with age as increasing myelination decreases radial diffusivity perpendicular to white matter (WM) tracts [58]. During the first week from delivery, fractional anisotropy (FA) values in the WM are significantly decreased not only in infants with severe abnormality, but also in those with moderate abnormality [71]. Of interest, given the phenomenon of pseudonormalization with ADC values, is that FA values in severe WM lesions are also significantly reduced during the second and the third weeks. In addition, anisotropy is significantly decreased in the first week throughout the BGT and become progressively more abnormal within the region of the ventrolateral nuclei. These findings suggest that a combination of ADC and FA values derived from DTI combined with visual analysis of conventional imaging offer a good approach for identifying and timing all abnormal tissue in perinatal brain injury [58].

Gradient-echo T2*- and susceptibility-weighted sequences are ideal for demonstrating hemorrhage and distinguishing it from ischemic foci (which also may have hyperintense signal on T1-weighted sequences) and for depicting cerebral sinovenous, cortical venous, and medullary venous thrombosis [35]. An SWI-based scoring system categorizing patients depending on the prominence of veins also may predict neurologic outcomes after hypoxic ischemic injuries [72].

MR angiography may detect anomalies that predispose to injury. Angiograms in infants with neonatal stroke will be asymmetrical once an infarct is established, but may show increased vessel outgrowth into infarcted regions. MR venography may detect abnormalities in sinus flow consistent with thrombosis. Thrombosis within the sagittal sinus results in hemorrhagic infarction of cortex and superficial WM [58].

Perfusion-weighted imaging assesses cerebral blood flow. These studies can be performed using contrast agents (dynamic susceptibility weighted contrast enhanced perfusion MR imaging) or without contrast agents (arterial spin labelling perfusion MR imaging). Arterial spin labelling (ASL) demonstrates improved resolution for T2-weighted scans and the improved signal to noise provides additional advantages for performing DTI, angiography

and functional studies. ASL is used for the assessment of cerebral blood flow in hypoxia-ischemia and evaluation of brain perfusion in congenital heart disease [73].

MR spectroscopy provides information about the concentration of numerous neurochemicals. Hypoxia-ischemia triggers anaerobic metabolism with production of lactate. MRS performed with an intermediate echo time of 135 – 144 ms within a region of interest positioned in the basal ganglia and thalami is useful for detecting significant amount of lactate (LAC), which appears as an inverted doublet at 1.3 ppm in spectra obtained immediately after acute hypoxic-ischemic insults [35]. The elevation of lactate starts at the time of the hypoxic-ischemic event, peaking at 3 to 5 days, whereas N-acetylaspartate (NAA) starts to decline around the third day [36, 59, 62, 63, 74]. Low apparent diffusion coefficient and high LAC/NAA ratios in the basal ganglia and thalamus are associated with an adverse outcome, also during and after therapeutic hypothermia [75].

1.2.5. Treatment of hypoxic ischemic encephalopathy, therapeutic hypothermia

In term or near-term infants (≥ 36 gestational weeks) with clinical signs of moderate to severe HIE, the current standard is therapeutic hypothermia for 72 hours started within 6 hours of life (within the acute and latent phase) decreasing mortality and morbidity [76, 77], and improving neurologic outcome in survivors [78].

Therapeutic hypothermia aims to lower the temperature of the vulnerable deep brain structures, the basal ganglia, to 32 °C to 34 °C. Two methods are being evaluated in newborn infants with HIE: whole body cooling and selective head cooling with mild systemic hypothermia. The rationale for selective head cooling is that the newborn infant's brain produces 70% of total body heat and that systemic hypothermia may be physiologically harmful to a sick neonate. Therefore the adverse effects of systemic cooling may be minimized by selectively cooling the brain more than the body [79]. However, a theoretical modelling of cooling investigating temperature distribution within the neonatal head found that the only situation that resulted significant reduction in deep brain temperature was when the core body temperature was lowered to 34 °C, implying that it is necessary to reduce systemic temperature to achieve deep brain cooling [80]. Whole body cooling relies on core

body and deep brain temperatures being similar. There are a number of postulated mechanisms by which hypothermia may be neuroprotective. Hypothermia may modify cells programmed for apoptosis, leading to their survival [81]. Cooling may also protect neurons by reducing cerebral metabolic rate, attenuating the release of excitatory amino acids (glutamate, dopamine), improving the ischemia-impaired uptake of glutamate and lowering the production of toxic nitric oxide (NO) and free radicals [82]. Mild hypothermia appears to be well tolerated in a variety of experimental animal models, as well as in adult human studies [21, 83-87]. A meta-analysis of several major randomized trials including the National Institute of Child Health and Human Development (NICHD) study [77] and the Total Body Hypothermia (TOBY) trial [78] has demonstrated a reduction in death and neurological impairment at 18 months following hypothermia [88]. The results of the Infant Cooling Evaluation Collaboration (ICE) trial, a multicenter, international, randomized controlled trial shown the reduction of the risk of death and major sensorineural disability at two years of age and concluded that whole-body hypothermia is a safe and effective neuroprotective method with minimal adverse effects [89, 90]. There were no reported serious adverse effects in four pilot studies in human newborns [91-94]. However hypothermia treatment has some consequences that the clinicians need to be aware of during treatment, e.g. cardiopulmonary, renal, hematological, and metabolic effects [95, 96]. Adverse effects, such as sinus bradycardia, increased blood pressure and increased oxygen requirement are all transient and reversible with re-warming [93]. Hematological effects - as prolongation of coagulation by slowing enzymatic activity of the coagulation cascade - are also temporary, but neonates with HIE are at high risk for coagulopathy and clinical bleeding in the setting of hypothermia [97]. The fact that coagulopathy is universal in HIE babies undergoing therapeutic hypothermia carries a potentially higher risk for intracranial hemorrhage (ICH) in HIE newborns [97].

1.2.6. Neonatal hypoxic ischemic encephalopathy and intracranial hemorrhage

Intracranial hemorrhage in term newborns is increasingly recognized, although its true incidence and prevalence is unknown [98, 99]. ICH is classified compartmentally as epidural (blood between the skull and outside the dura), subdural (blood between the dura and the

arachnoid membrane), subarachnoid (blood between the arachnoid and the pia membrane), intraventricular (blood is lateral, third and fourth ventricles), or intraparenchymal (blood within brain parenchyma), which may be supratentorial or infratentorial in location [99]. Subdural, subarachnoid, intraparenchymal and intraventricular hemorrhages are the most common types of ICH present in term infants [98-100]. The spectrum of germinal matrix hemorrhage – intraventricular hemorrhage (GMH-IVH) affects mainly premature infants [101]. Newborns rarely develop epidural hemorrhage (EDH), as the middle meningeal artery, which is not yet encased within the bone, is able to move freely following displacement of the skull [99]. Prolonged, precipitous, vaginal breech, instrumental, forceps, or ventouse delivery, primiparity, high multiparity, and extreme fetal weight are potential predisposing factors for symptomatic ICH in full term infants [99, 102, 103]. Only a fraction of neonates with ICH present with clinical features such as apnea, bradycardia and seizures.

The major causes of IVH are birth trauma and asphyxia [99].

Besides the fact that asphyxia may lead to ICH, hypothermic treatment of moderate to severe asphyxiated neonates with HIE also carries a potential risk for ICH. A Cochrane Collaboration review on the safety of therapeutic hypothermia has shown thrombocytopenia and hypotension to be the major side effects of this therapeutic approach [104]. As cooling may result in decreased platelet counts, it may lead to prolongation of coagulation carrying a potentially higher risk for ICH in HIE newborns [97]. Besides, asphyxia very often leads to impaired cerebral autoregulation [105] and asphyxia and hypothermia might also cause fluctuation of cerebral blood flow [106], being possible risk factors for intraventricular hemorrhage (IVH) [107].

1.2.7. Neonatal hypoxic ischemic encephalopathy, intracranial hemorrhage and outcome

Infants who survive HIE are at higher risk of developmental deficits as sensorineural hearing loss, visual loss, feeding difficulties, gross and fine motor deficits, sensory modulation disorders, maladaptive behavior as well as cognitive disorders [88].

The long term effects of HIE and the prognostic role of imaging can only truly be understood if affected infants are followed-up and evaluated into their childhood. Several former and

recent studies indicate that MRI is a useful tool in determination of prognosis. Involvement of the posterior limb of the internal capsule (PLIC) in HIE was found to be associated with abnormal motor outcome [44, 54]. Early death and the most severe motor impairment as cerebral palsy were seen in association with basal ganglia injuries [54]. In a meta-analysis including thirty-two studies and 860 infants with neonatal encephalopathy deep gray matter Lac/NAA was found to be the most accurate quantitative MR biomarker for prediction of neurodevelopmental outcome [53]. Yet, the different types of ICHs visible on MRI in asphyxiated neonates, were not considered in the previous studies, although they may be of additional impact on long term outcome of neonatal HIE, as they may carry a potential risk of intracranial complication when hypothermic treatment is adopted [97]. The many previous studies emphasizing the prognostic effect of signal abnormalities on conventional sequences, diffusion restriction pattern, and brain MRS either analyzed a relatively small sample size or MRS was performed after the first week of life or was not involved in the evaluation, meaning that those HIE positive infants having only spectroscopic abnormality were not involved in the study population [44, 46, 108-110].

2. Objectives

2.1. Development of a structured reporting template as part of an asphyxia database.

Our efforts were aimed to develop an evidence-based, standardized structured reporting method for brain MRI examinations in neonatal hypoxic ischemic encephalopathy suitable both for clinical and research use. We planned the SR template to be part of a complete database and to be searchable and exportable into various statistical software and file formats, and by being web-based, was planned to be able to facilitate collaboration between research groups regardless location.

2.2. Prognostication with early magnetic resonance imaging in hypothermia treated asphyxiated neonates with hypoxic ischemic encephalopathy and/or intracranial hemorrhage.

Knowing the hemostasis altering effects of therapeutic hypothermia, our retrospective observational study of cooled infants with the clinical diagnosis of HIE treated with whole-body hypothermia aimed to investigate whether the coexistence of the five major types of ICH on early MRI with the imaging signs of HIE (abnormal MRS and/or typical patterns of diffusion restriction) have an impact on the long-term neurodevelopmental outcome.

3. Methods

3.1. Development of a structured reporting template as part of an asphyxia database. Feasibility study of the novel structured reporting system.

3.1.1. Study population

Over a 2 - year period (2013 - 2015) 182 infants presented with clinically suspected asphyxia in our university hospital, a tertiary referral center with neonatal intensive care unit. Mildly asphyxiated patients who did not require whole body hypothermia according to the TOBY criteria were excluded from our study, the remaining 128 patients went through therapeutic hypothermia according to TOBY protocol [104, 111]. Further exclusion criteria as the presence of congenital malformations, metabolic disorders, exitus in the early perinatal period and the absence of at least one brain MRI examination disqualified further 22 subjects from inclusion in the study. The brain MRI of the enrolled 106 preterm and term infants were systematically retrospectively evaluated. The institutional review board (Semmelweis University Regional and Institutional Committee of Scientific and Research Ethics, SE TUKEB 62/2016) and the Hungarian Medical Research Council (ETT TUKEB 5705-1/2016/EKU) approved this study. Written informed consent was not required for this study as it was a retrospective trial without any research-oriented intervention.

3.1.2. MR imaging

Imaging was performed with a Philips Achieva 3T scanner (Philips Medical Systems, Best, The Netherlands) using an 8-channel SENSE head-coil with T1-weighted 3D spoiled gradient echo [TR = 10.68 - 10.88 ms, TE = 4.884 - 5.258 ms, slice thickness = 0.7 - 1 mm, gap = 0.7 - 1 mm], axial and coronal T2-weighted turbo spin echo [TR = 4000 ms (axial), 1489 - 2766 ms (coronal), TE = 100 ms, slice thickness = 3 mm, gap = 4 mm], axial T2*-weighted gradient echo [TR = 554.2 - 561.5 ms, TE = 16.11 ms, slice thickness = 3 mm, gap = 4 mm] and diffusion-weighted sequences [b-value = 1000 s/mm^2], and single-voxel proton MR spectroscopy with PRESS (Point RESolved Spectroscopy) acquisition [TE = 35 and/or

144 and/or 288 ms] obtained from the left thalamus. Total imaging time of the standard protocol did not exceed 30 minutes, however in select cases (neonatal stroke or pending venous sinus thrombosis) arterial time-of-flight MR angiography (TOF-MRA) [TR = 17.47 ms, TE = 3.45 ms, slice thickness = 1 mm, gap = 0.5 mm] and/or phase contrast venous MRA (PC-MRA) [TR = 20 ms, TE = 7.77 ms, sagittal and oblique single slice] was also performed.

3.1.3. Image analysis

Key MR imaging findings were assessed by re-evaluating the MRI examinations of 106 neonates with the clinical diagnosis of moderate to severe birth asphyxia. The initial free-text reports were written by two radiologists with at least 10 years of experience in neuro- and pediatric radiology. The retrospective re-evaluation was performed by a pediatric radiologist with 9 years of experience in radiology. Our reporting standards and the resulting findings were aligned with published evidence, as detailed below.

3.1.4. Implementation of a novel structured reporting template for HIE

To identify the relevant papers, a systematic review of the pertinent literature was performed in PubMed, Web of Science, and Scopus databases using search terms “infant”, “newborn”, “asphyxia”, “hypoxic ischemic encephalopathy”, “neonatal encephalopathy”, and “MRI”. Twenty-one review and original articles were considered relevant, after surveying 107 selected abstracts from the 896 search results. Based on the relevant literature the following imaging findings served as the main core of the SR template:

1. Diffusion characteristics and evolution of diffusion changes over time. Diffusion-weighted imaging has high sensitivity for early detection of hypoxic ischemic injury by showing diffusion restriction already after the first few hours following the insult [59, 65, 66]. The abnormalities peak at 3 - 5 days and show a specific evolution [45, 59, 63]. Over time there are new areas appearing with restricted diffusion, besides simultaneous pseudonormalization at the anatomic regions that had showed diffusion restriction earlier [45, 51, 54, 59, 63, 67]. The evolution of the pattern is different in case of normothermia or

hypothermia [51], but early MRI robustly predicts the extent of injury [68]. Neonatal stroke is also nicely visualized on DWI [69, 70].

2. Patterns of injury detected on standard anatomic sequences. T1- and T2-weighted images are not effective in the early detection of cerebral edema and white matter lesions as they show prolonged relaxation times only 1 - 2 days after the injury [55, 57, 58] and may appear normal during the first days after a hypoxic-ischemic event despite severe brain damage [59, 60]. Hence the role of conventional sequences is supported by the fact that in many patients, the precise timing of the injury is not known [61]. T1-weighted images are advocated to be used for the assessment of the basal ganglia and the thalami [48, 54, 62], while cortical involvement is best seen with T2-weighting [35, 63, 64].

3. Typical MR-spectroscopy changes in perinatal asphyxia. Single-voxel proton MR-spectroscopy (PRESS) performed in the basal ganglia and/or thalamus reveals reduced relative concentrations of N-acetyl-aspartate (NAA) and choline and the presence of a lactate peak. The elevation of lactate starts at the time of the hypoxic-ischemic event, peaking at 3 to 5 days, whereas NAA starts to decline around the third day [36, 59, 62, 63, 74].

4. Additional findings seen on T2* gradient echo or SWI sequences which might be related or unrelated to HIE, but have a significant therapeutic consequence as the sequelae of germinal matrix/intraventricular hemorrhage in preterm infants, incidental extra-axial or intraparenchymal hemorrhage [112] or sinovenous thrombosis [35, 62, 72]. Both T2*-weighted gradient echo and SWI imaging results are included in the reporting template to accommodate for differences in imaging protocols, e.g. during the reported period of 2013 - 2015 our protocol included a T2*-weighted gradient echo series, but upon a system update in 2016 we changed our protocol to include SWI instead.

The above-listed primary attributes designated the most important imaging findings to be included in a radiology report in case of HIE. The reporting template was developed in the iSORT (intelligent structured online reporting tool) software framework created by Bioscreen Ltd., Debrecen, Hungary is commercially available (www.bioscreen.hu) and can be used for developing any kind of structured reporting module.

3.1.5. Evaluation of the novel structured reporting template for HIE

In order to test the utility of the reporting template, the initial development and improvement was followed by an evaluation of the SR template with re-reporting of retrospective imaging data. The aim of this re-reporting based data input and basic data analysis on all the 106 patients was to find out whether the proposed system can be used in every-day clinical practice. Imaging findings were recorded in the reporting template during reading. We estimated the time-demand of report-filling and explored whether substantial anatomic regions or statements are missing which should be definitely added in the report. A basic descriptive statistical analysis was also performed to evaluate the temporal evolution pattern of diffusion changes observed during the review of our patient population. Furthermore we aimed to find out whether the clinical diagnosis of asphyxia was supported by MR imaging or not.

3.2. Prognostication with early magnetic resonance imaging in hypothermia treated asphyxiated neonates with hypoxic ischemic encephalopathy and/or intracranial hemorrhage.

3.2.1. Study Population

Patients were selected from 210 consecutive newborn infants (gestational age ≥ 36 weeks) between March 2007 and March 2016, admitted to the First Department of Pediatrics, Semmelweis University, Budapest, Hungary, a university-affiliated tertiary care neonatal intensive care unit functioning as a regional cooling center for neonatal HIE. Subjects were included in this study if they were clinically diagnosed as moderate or severe HIE, underwent therapeutic whole body hypothermia and had at least one brain MRI within the first 7 days of life as part of the diagnostic protocol (**Figure 2**). As the aim of our study was to investigate ICH present during or early after hypothermia treatment and detect diffusion and spectral changes of HIE known to have a temporal evolution we only considered brain MRI performed during the first week after birth.

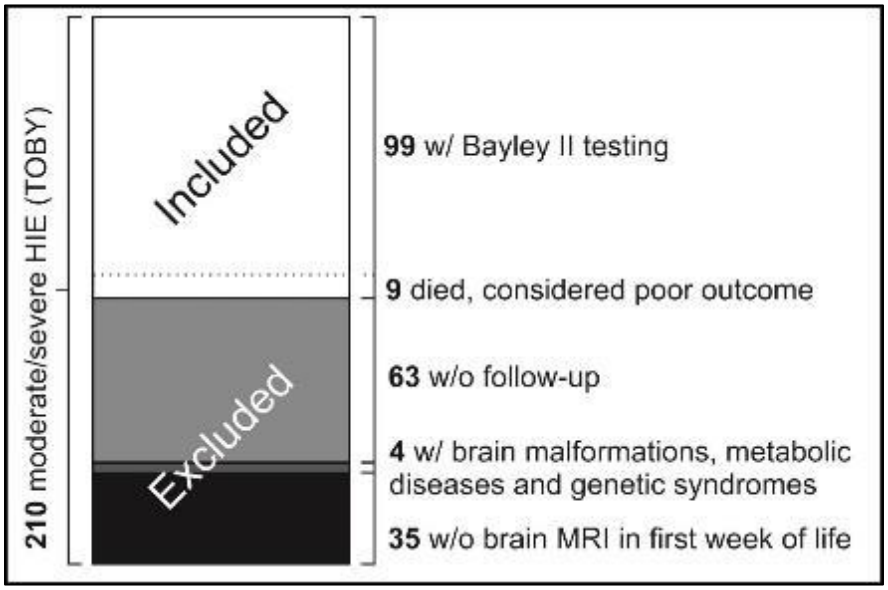

Figure 2 Patient enrollment
Based on the inclusion and exclusion criteria 108 neonates were selected in the study from the initial 210 patients. w/: with; w/o: without.

Inclusion was based on the following diagnostic criteria of the international TOBY trial (**Table 1**) [78, 104], corresponding to moderate or severe asphyxia: (1) at least of one of the following: continuous need for resuscitation/ventilation at 10 min after birth, OR Apgar score ≤ 5 at five min after birth OR arterial cord pH < 7,0 or base deficit ≥ 16 mmol/L within 60 min after birth AND (2) altered levels of consciousness (lethargy, stupor, coma) AND hypotonia OR abnormal reflexes or seizures AND (3) abnormal brain background activity registered on amplitude-integrated electroencephalography.

Exclusion criteria included: metabolic and/or genetic syndromes, structural brain malformations, lack of neurodevelopmental follow up data. Exception from the neurodevelopmental criterion was made in case of early death (< 28 postnatal days) OR death > 28 days associated with HIE in 9 patients who died before neurodevelopmental testing hence they were considered as poor outcome. Altogether, 108 patients met the criteria and were included in the analysis. There were no significant differences in the main clinical parameters between the included and excluded groups, see **Table 6**, and the Results section for details.

The primary outcome of the study was to find the possible association between ICH and/or MRI/MRS signs of HIE and neurodevelopmental outcome based on the Bayley Scales of Infant Development II. scale.

The Institutional Ethics Committee (Semmelweis University Regional and Institutional Committee of Scientific and Research Ethics, SE TUKEB 62/2016) and the Medical Research Council Ethics Committee of Hungary (ETT TUKEB 5705-1/2016/EKU) approved this retrospective study.

Table 1 Inclusion and exclusion criteria of therapeutic hypothermia in the TOBY trial

Inclusion and Exclusion Criteria of Therapeutic Hypothermia (TOBY trial)		
INCLUSION CRITERIA: The infant will be assessed sequentially by criteria A, B and C listed below. Infants that meet criteria A will be assessed for whether they meet the neurological abnormality entry criteria (B) by trained personnel. Infants that meet criteria A & B will be assessed by aEEG (read by trained personnel).		
A. *Infants ≥ 36 completed weeks gestation admitted to the NICU with at least one of the following:*	***B.*** *Moderate to severe encephalopathy, consisting of altered state of consciousness (lethargy, stupor or coma) AND at least one of the following:*	***C.*** *At least 30 minutes duration of aEEG recording that shows abnormal background aEEG activity or seizures. There must be one of the following:*
• Apgar score of ≤ 5 at 10 minutes after birth	• hypotonia	• normal background with some seizure activity
• Continued need for resuscitation, including endotracheal or mask ventilation, at 10 minutes after birth	• abnormal reflexes including oculomotor or pupillary abnormalities	• moderately abnormal activity
• Acidosis within 60 minutes of birth (defined as any occurrence of umbilical cord, arterial or capillary pH < 7.00)	• absent or weak suck	• suppressed activity
• Base Deficit ≥ 16 mmol/L in umbilical cord or any blood sample (arterial, venous or capillary) within 60 minutes of birth	• clinical seizures	• continuous seizure activity
EXCLUSION CRITERIA: • Infants expected to be > 6 hours of age at the time of randomization • Major congenital abnormalities, such as diaphragmatic hernia requiring ventilation, or congenital abnormalities suggestive of chromosomal anomaly or other syndromes that include brain dysgenesis.		

3.2.2. Study Interventions and Exposures

3.2.2.1. Whole-body hypothermia

Whole-body hypothermia treatment was initiated as soon as possible, using a water-filled mattress (Tecotherm©; TecCom, Halle, Germany). The target rectal temperature was between 33 and 34 °C, maintained for 72 hours. In the rewarming phase, temperature increase velocity was 0.5 °C/h. All infants were ventilated throughout the cooling and rewarming phase. Knowing that severe hyperoxaemia and severe hypocapnia are associated with adverse outcome in infants with post-asphyxial HIE [113-115] closer monitoring and individualized oxygen supplementation and ventilation was maintained. Initial parameters of mechanical ventilation were set according to the local protocol: synchronized intermittent mandatory ventilation with volume guarantee (target tidal volume 5 ml/kg, respiratory rate and end expiratory pressure set as needed). Taking into consideration of the fact that asphyxiated infants may need lower ventilator settings to maintain normocarbia, our protocol was designed to maintain a pCO2 of 40 to 60 mmHg consistently. Therefore, during the first hours of life, oxygen supplementation and ventilation were rigorously controlled with blood gases routinely taken every 30 to 60 mins, until a steady state was reached, then every 6 hours afterwards during the whole extent of hypothermia treatment. This protocol ensured timely adjustment of ventilation parameters to evade sustained excursion from optimal blood gas values.

Continuous morphine (Morphine hydrochloride 10 mg/mL; TEVA Magyarország Zrt., Gödöllő, Hungary) sedation (10 µg/kg BW/h) was started following the loading dose (0.1 mg/kg BW) administered when the cooling was initiated. Phenobarbitone (Gardenal 40 mg; Aventis, Maisons-Alfort, France, 20 mg/kg BW) was given as the first line of anticonvulsant therapy if clinical or electrophysiological seizures were detected. In case of non-controlled seizures, the phenobarbitone loading dose was repeated, or midazolam (Midazolam Torrex 5 mg/ml; Chiesi Pharmaceuticals GmbH, Vienna, Austria) was given in single or repeated doses (0.1 mg/kg BW) or in continuous infusion (0.1 mg/kg BW/h). In some cases, newborns received lidocaine, phenytoin, diazepam or chloral hydrate alternatively, according to the attending clinician’s decision.

3.2.2.2. MR imaging

All MRIs were acquired in the first 7 days of life on a Philips Achieva or Ingenia 3T scanner (Philips Medical Systems, Best, The Netherlands), with 8-channel SENSE head-coils, at the former MR Research Center of Semmelweis University. Brain MRI included the following sequences: T1-weighted 3D spoiled gradient echo [TR = 10.68 - 10.88 ms, TE = 4.884 - 5.258 ms, slice thickness = 0.7 - 1 mm, gap = 0.7 - 1 mm], axial and coronal T2-weighted turbo spin echo [TR = 4000 ms (axial), 1489 - 2766 ms (coronal), TE = 100 ms, slice thickness = 3 mm, gap = 4 mm], axial T2*-weighted gradient echo [TR = 554.2 - 561.5 ms, TE = 16.11 ms, slice thickness = 3 mm, gap = 4 mm] OR axial SWI (susceptibility weighted imaging) [TR = 31 ms, TE = 7.2 ms, slice thickness = 2 mm, gap = 1 mm (interleaved slices)] and diffusion-weighted images [b-value = 1000 s/mm^2] with ADC maps, and single-voxel proton MR spectroscopy with PRESS (Point Resolved Spectroscopy) acquisition [TE = 35 and/or 144 and/or 288 ms] obtained from the left thalamus – basal ganglia. Average imaging time was 30 minutes. A neonatologist was present throughout the procedure. For the time of the examination, the infants were removed from the incubator and received continuous morphine sedation. Heart rate and oxygen saturation were monitored using a Medrad® Veris® MR monitoring system. In case of intubated infants, skilled personnel provided manual ventilation with an AMBU bag throughout the MRI examination.

3.2.2.3. Neurodevelopmental follow-up

Neurodevelopmental outcome was measured by Bayley Scales of Infant Development II tool-kit (BSID-II), performed between 18 - 26 months of age by trained personnel, blinded to the MRI results. Although BSID-II was updated to a 3rd edition during the follow-up period of our study, it was not translated and standardized until 2018, therefore BSID-II test was performed in all our patients. BSID-II comprises two scales including the Mental Developmental Index (MDI) and Psychomotor Developmental Index (PDI). The MDI provides an assessment of memory, problem solving, sensory perception, hand-eye coordination, imitation and early language. The PDI measures gross and fine motor skills [116, 117]. The normal range of PDI and MDI is between 85 and 114, a score lower than 85

suggests mildly delayed development, and a score below 70 represents significantly delayed development. A score greater than or equal to 115 stands for accelerated performance. For the Chi-square test we defined poor outcome as either early death OR mildly to significantly delayed performance (MDI or PDI < 85). All other outcomes were considered as good outcome. A neurodevelopmental outcome score was non-applicable (N/A) when obtaining a reliable measurement was not achievable. Logistic regression analysis was based on individual scores (see below).

3.2.2.4. Data analyses

Data recording and extraction were made using our novel in-house built asphyxia registry database, iSORT (Intelligent structured online reporting tool, Bioscreen Ltd. Debrecen, Hungary) [118]. Trained pediatric radiologist blinded to the clinical history and neurodevelopmental results retrospectively evaluated the imaging signs of HIE and the presence and type of hemorrhage. HIE related abnormality was reported, when a lactate peak and relatively low values of normal metabolites (represented by Lac/NAA height ratios measured on MRS with TE = 144ms) were present on MR-spectroscopy [75, 119] AND/OR HIE related diffusion restriction or signal abnormalities on T1- and T2 weighted images were present [65, 120, 121]. Predominantly basal ganglia-thalamus pattern was reported when central gray matter nuclei and perirolandic cortex involvement was seen bilaterally with or without associated hippocampal and brain stem involvement and the absence of a normal high-signal intensity of the posterior limb of the internal capsule [65]. Watershed predominant pattern injury was diagnosed when the vascular watershed zones (anterior-middle cerebral artery and posterior-middle cerebral artery) were involved uni- or bilaterally affecting the white matter or in severe cases the overlying cortex as well [65]. In total brain injury widespread involvement of the subcortical white matter and cortex was seen with relative sparing of the immediate periventricular white matter and central gray matter [120]. The predominant (basal ganglia/watershed/total brain injury) patterns of HIE were primarily identified on the DWI and ADC maps on early MRI. As abnormalities observed with diffusion imaging depend on the delay between birth and MRI showing pseudonormalization

around the 6th and 7th day after the insult, conventional T1- and T2 weighted sequences were also evaluated. MRI was considered normal in the absence of all the above listed findings. Neonatal intracranial hemorrhage was assessed on T2*GRE, SWI and T1-weighted images. The following five subtypes of ICH were distinguished: subdural hemorrhage (SDH), subarachnoid hemorrhage (SAH), germinal matrix hemorrhage (GMH), intraventricular hemorrhage (IVH) and intraparenchymal hemorrhage (P) [100]. The location, size and the presence/absence of mass-effect were assessed.

Descriptive statistical analysis was carried out; continuous measurements were presented as mean ± SD (min - max) while categorical measurements were presented in numbers and percentages. Parameters of the included and excluded cohorts were compared with Mann-Whitney U test, as some of the data was ordinal (e.g. Apgar, pH, etc.). Patients were categorized into four groups based on the presence or absence of ICH and HIE on MRI. BSID-II scores were registered for every patient, detailed above. Chi-square test was performed to assess whether the observed distributions of PDI and MDI and the MRI signs of HIE and ICH are independent regarding the outcome (null hypothesis) or if there is proof for a relationship between late neurodevelopmental outcome and initial MRI findings (alternative hypothesis). We performed multivariate logistic regression analysis (in Matlab 9.2, The MathWorks Inc. Natick, MA) on survivors to detect possible relationships between poor outcome (BSID-II score < 85) and/or ICH and/or HIE signs on MRI including other covariates as clinical predictors of interest: 5 minute Apgar score, baseline pH and age at MRI. One could argue for the inclusion of base excess and/or temperature, however the latter two should not affect the association as they are mostly collinear with other already included parameters, hence they were omitted. The results are provided in terms of odds ratios, and confidence intervals.

4. Results

4.1. Development of a structured reporting template as part of an asphyxia database. Feasibility study of the novel structured reporting system.

4.1.1. Imaging findings in HIE

Our imaging findings regarding the MRI examinations of 106 (19 preterm and 87 term) neonates were concordant with the pathognomonic signs found in the literature.

1. Diffusion-weighted images: Early signs of HIE as diffusion restriction were seen in 42% (n = 8/19) of the premature and in 32% (n = 28/87) of the term infants. Pseudonormalization, showing the temporal evolution of diffusion changes was obvious with follow-up imaging (**Figure 3**).

2. T1- and T2-weighted images: The late signs of HIE visible on the conventional sequences appeared less frequently in the examined patient population, presumably due to effective therapeutic hypothermia and the timing of the MRI examination (**Figure 4**).

3. MR-spectroscopy: Reduced relative concentrations NAA and choline with the presence of a lactate peak were found in all patients with restricted diffusion (35%) (**Figure 5**). In 4 term infants the MRS abnormality was the only sign of HIE.

4. T2*-weighted images: Hemorrhage affected a remarkable share, about 35% of our patient population. In preterm infants subependymal-intraventricular hemorrhage occurred most frequently (n = 9/19). Term infants were mainly affected with intraparenchymal hemorrhage in 15% (n = 13/87) and with subdural hemorrhage in 13% (n = 11/87), with the latter evolving due to traumatic delivery in most of the cases. Extra-axial hemorrhages as subgaleal (n = 2), subarachnoid (n = 1) and epidural hemorrhage (n = 1) and sinovenous thrombosis were uncommon, seen in only some cases.

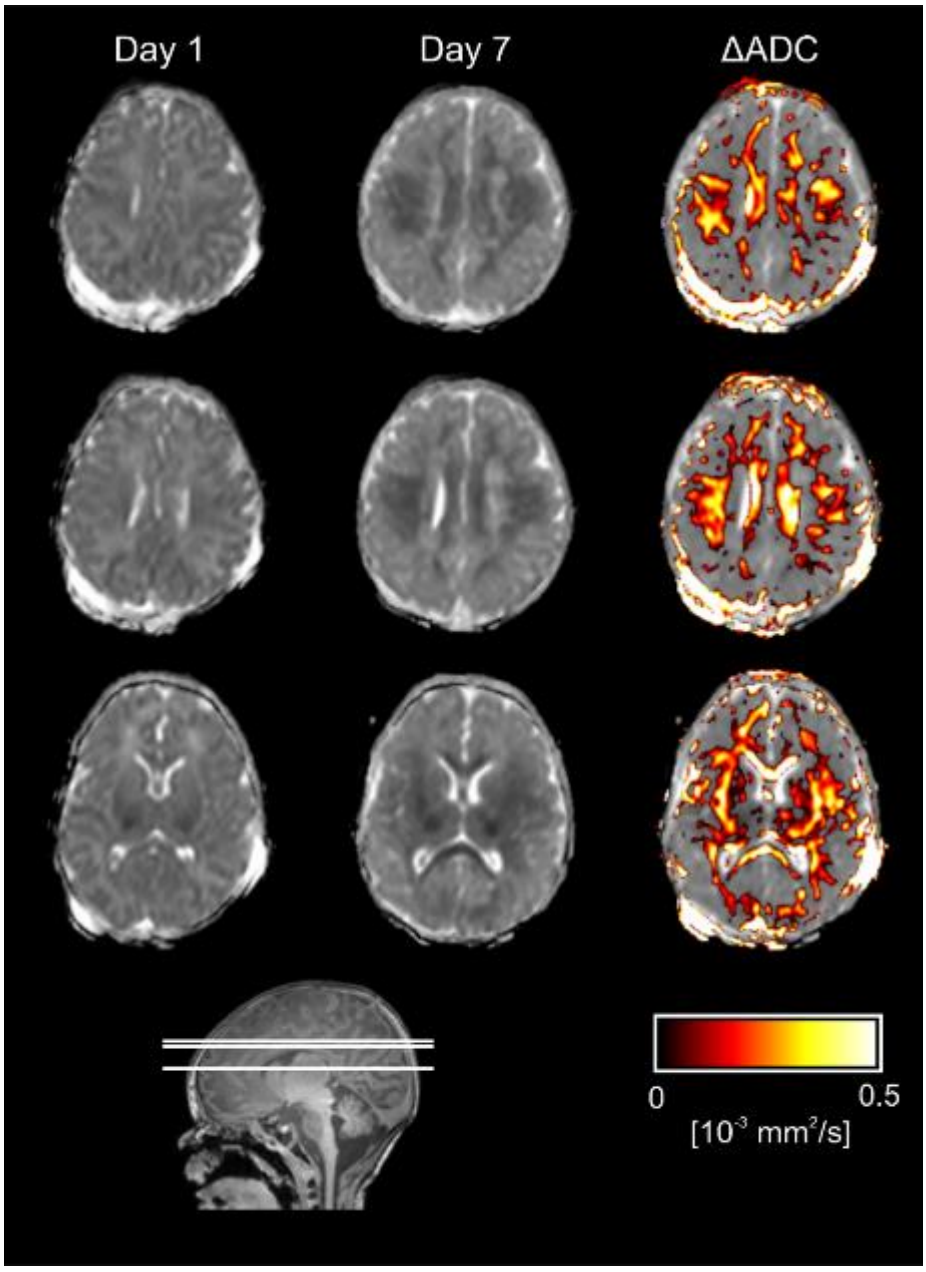

Figure 3 Evolution of the diffusion changes over time
Two sets of ADC-maps at different time points (day 1 and day 7) and the corresponding overlay images (ΔADC) show the timely pattern of diffusion changes. The first column of images were obtained at the age of 1 day, the second 7 days after birth. The involvement of the thalami and the putamina seen on the 1st day shows expansion to the corpus callosum and the corona radiata on the 7th day.

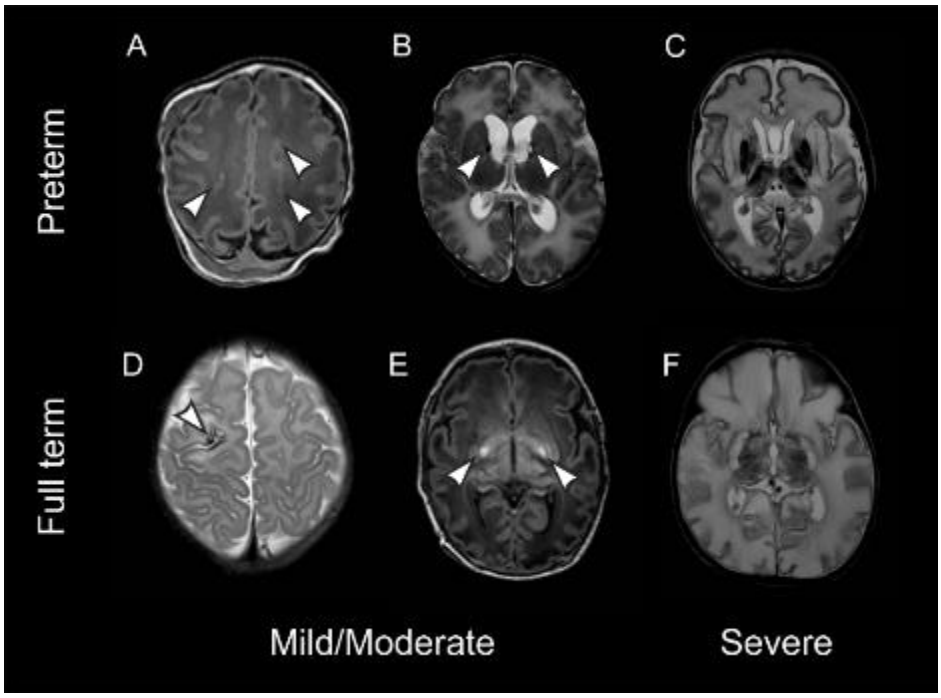

Figure 4 Brief spectrum of MR imaging findings in mild to moderate and severe asphyxia

The upper row (A-C) represents the changes seen in preterm infants. The patterns characteristic for term infants are shown in the lower row (D-F). Axial T1W-image (A) shows multiple bilateral high signal intensity foci in the periventricular white matter (arrows) representing acute periventricular leukomalacia in an infant born on the 34th week of gestation. T2W-image (B) shows bilateral germinal matrix hemorrhage (arrows) in infant born on the 36th week of gestation. The examination was performed on the 28th day of life. Axial T2W-image (C) shows abnormal signal intensity and diminished volume of the white matter, the thalami and the basal ganglia as a result of diffuse neuronal and axonal damage in a preterm infant born on the 34th week of gestation. T2W-image (D) shows cortical laminar necrosis and subcortical damage in the right precentral gyrus and the neighboring superior and middle frontal gyri (arrow) in a three-week-old term infant. These findings are suggestive of the peripheral pattern of HIE. T1W-image (E) of an 8-day-old term infant shows abnormal high signal intensity in the globi pallidi (arrows), and slight signal change in the medial aspect of the putamina in keeping with basal ganglia pattern of HIE. T2W-image (F) of a 2-week-old severely asphyxiated term infant shows the diffuse, extensive gray- and white matter damage involving of the thalami and the basal ganglia.

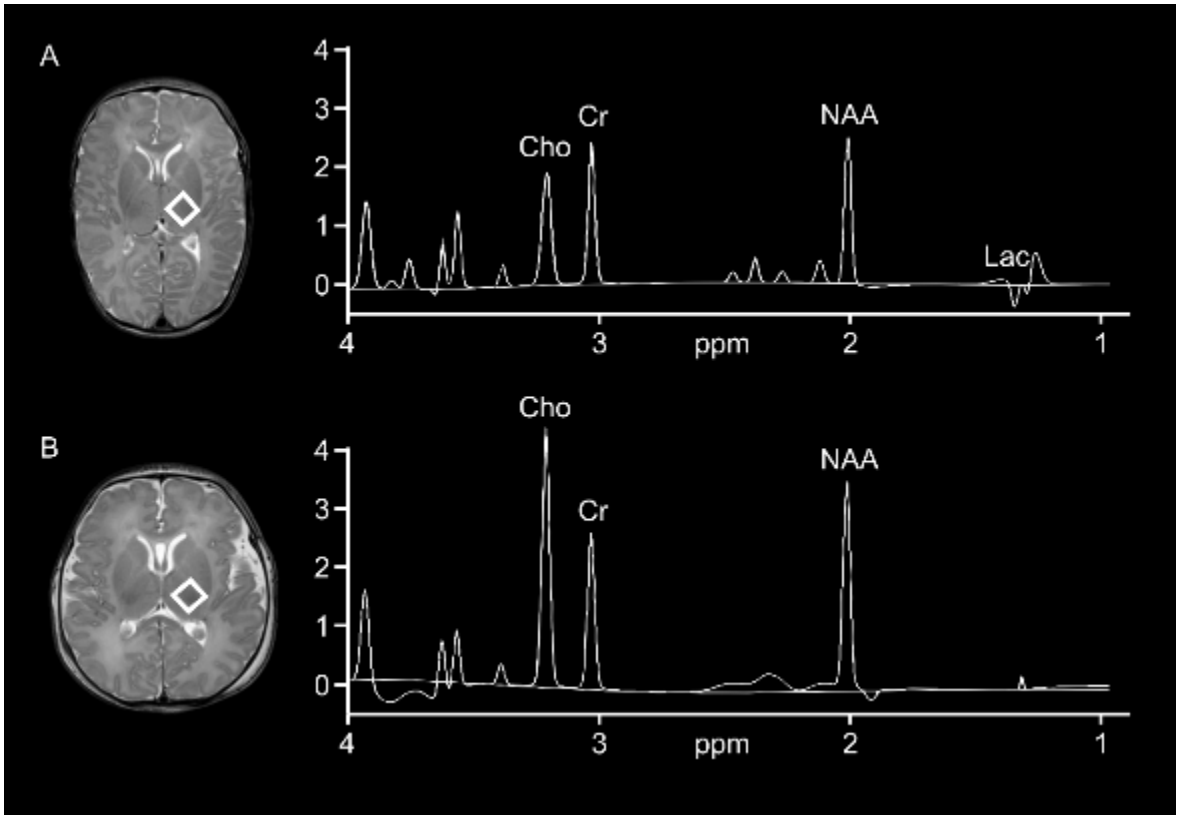

Figure 5 Abnormal spectrum in comparison with normal spectrum
(A) Proton SV-MR spectroscopy acquired from the left thalamus (TE = 144 ms) on the 2nd day of life of a term infant shows prominent lactate peak, a characteristic inverse doublet, resonating at 1.3 ppm, and decreased NAA and choline (Ch) compared with creatine (Cr), suggestive of severe HIE. (B) Normal metabolite levels for age are shown for comparison.

4.1.2. Implementation of a novel structured reporting template for HIE

Following multiple appointments with neonatologists, a standard lexicon and the clinical viewpoints were determined with the above-detailed four core radiological principles providing the backbone of the reporting template. The SR template was devised to follow a systematic outline with headings and subheadings in a tree structure. Separate sections of clinical details, technique, imaging findings and final impression were distinguished, see **Table 2** for details.

Table 2 Main sections of the iSORT for HIE MRI reporting template

iSORT for HIE framework			
Section I.	**Section II.**		**Section III.**
Patient information	**T1/T2WI**	**Ventricular system**	**Final impression**
		Subarachnoid space	
		Signal changes	
	T2*WI	**Hemorrhage**	
Clinical data, Indication		**Thrombosis**	**HIE grading**
	DWI+ADC	**Restricted diffusion**	
		Facilitated diffusion	
		Stroke	
MRI Technique	**MRS**	**Peak of normal metabolites**	**File upload**
		Presence of lactate peak	
	MRA	**Arteries**	
		Veins	

The first section is composed of patient data and the technical aspects of the MRI examination. The possible etiologies of HIE, the scanner types, the sequences and acquisition parameters are listed herein with the most frequent answers marked as default options. The length of the scanning and the patient's age at the time of the examination are calculated automatically from the specified data. **The second part** records signal intensity changes in nested anatomic landmarks. Making subdivisions according to the conventional sequence types, DWI, the MRS pattern and MRA (the latter performed only in select cases) contributes to the lucidity of the system. The **third section** includes the radiologist's opinion and enables file upload. The peculiarity of the system is that predefined terms such as anatomic sites, observation descriptors and distinct values appear in divisions and subdivisions at different levels, starting from a broader range, tapering to a more specific option (**Table 3, 4**).

Table 3 Division of the anatomic regions of the cerebrum in the iSORT for HIE template

Cortex				Deep gray matter			White matter			CC
L	Frontal	Precentral gyrus		L	Thalamus	VL	L	Internal capsule	ALIC	Rostrum
		Superior	frontal gyrus			Rest			PLIC	
		Middle						External capsule		
		Inferior			Putamen	PL		Corona radiata		
	Temporal	Superior	temporal gyrus			Rest		Centrum semiovale		
		Middle								
		Inferior								
		Medial	occipito-temporal gyrus		Globus pallidus			Optic radiation		Genu
		Lateral			Caudate nucleus			Corticospinal tract		
		Gyrus parahippocampalis			Germinal matrix (caudothalamic groove)			Frontal	subcortical	
	Parietal	Postcentral gyrus							periventricular	
		Superior	parietal lobule					Temporal	subcortical	
		Inferior							periventricular	
		Supramarginal gyrus						Parietal	subcortical	
		Angular gyrus							periventricular	Corpus
	Occipital	Occipital pole			Claustrum			Occipital	subcortical	
		Lingual gyrus								
		Occipitotemporal gyrus								
		Calcarine (visual) cortex							periventricular	
		Cuneus								
R	Frontal	Precentral gyrus		R	Thalamus	VL	R	Internal capsule	ALIC	
		Superior	frontal gyrus			Rest			PLIC	Splenium
		Middle						External capsule		
		Inferior			Putamen	PL		Corona radiata		
	Temporal	Superior	temporal gyrus			Rest		Centrum semiovale		
		Middle			Globus pallidus			Optic radiation		
		Inferior			Caudate nucleus			Corticospinal tract		
		Medial	occipito-temporal gyrus							
		Lateral								
		Gyrus parahippocampalis			Germinal matrix (caudothalamic groove)			Frontal	subcortical	
	Parietal	Postcentral gyrus							periventricular	
		Superior	parietal lobule					Temporal	subcortical	
		Inferior							periventricular	
		Supramarginal gyrus						Parietal	subcortical	
		Angular gyrus							periventricular	
	Occipital	Occipital pole			Claustrum			Occipital	subcortical	
		Lingual gyrus								
		Occipitotemporal gyrus							periventricular	
		Calcarine (visual) cortex								
		Cuneus								
O	Cingulate gyrus									

Table 4 Division of the anatomic regions of the liquor filled spaces in the iSORT for HIE template

<table>
<tr><td colspan="8">Liquor filled spaces</td></tr>
<tr><td>Septum pellucidum abnormality</td><td colspan="4">Ventricular system</td><td colspan="2">Subarachnoid space</td><td></td></tr>
<tr><td>SPC</td><td colspan="3">paired</td><td>unpaired</td><td colspan="2">paired</td><td>unpaired</td></tr>
<tr><td>cavum Vergae</td><td rowspan="11">Lateral ventricles</td><td rowspan="6">L</td><td>Frontal horn</td><td rowspan="6">III.rd ventricle</td><td rowspan="6">L</td><td>Frontal</td><td>Interhemispheric fissure</td></tr>
<tr><td rowspan="11">cavum velum interpositum</td><td>Temporal horn</td><td>Parietal</td><td>Suprasellar cistern</td></tr>
<tr><td>Occipital horn</td><td>Temporal</td><td>Ambient cistern</td></tr>
<tr><td>Trigone</td><td>Occipital</td><td>Quadrigeminal cistern</td></tr>
<tr><td>Cella media</td><td>Posterior fossa</td><td>Prepontine cistern</td></tr>
<tr><td rowspan="5">R</td><td rowspan="5">IV.th ventricle</td><td rowspan="5">R</td><td>Frontal</td><td>Interpeduncular cistern</td></tr>
<tr><td>Temporal horn</td><td>Parietal</td><td>Cerebellopontine cistern</td></tr>
<tr><td>Occipital horn</td><td>Temporal</td><td>Premedullary cistern</td></tr>
<tr><td>Trigone</td><td>Occipital</td><td>Meckel cave</td></tr>
<tr><td>Cella media</td><td>Posterior fossa</td><td>Cisterna Magna</td></tr>
<tr><td>Foramen Monroe</td><td colspan="2">L</td><td rowspan="2">Cerebral aqueduct</td></tr>
<tr><td colspan="2">R</td></tr>
<tr><td>Foramen Luschka</td><td colspan="2">L</td><td rowspan="2">Foramen Magendie</td></tr>
<tr><td colspan="2">R</td></tr>
</table>

The reporting radiologist has the freedom of choice whether to go into details or not. The reporting form is composed of single- and multiple-choice questions with point-and-click options of the allotted answers. Free text fields are also available to write comments and notes in cases when the predefined answers do not suite the reporting radiologist. The data points are saved to an on-site database where they can be queried and imported into statistical ready format for further analysis. An example of the working version of the template is shown in Figure 6. Note, that the iSORT framework provides flexibility to extend the template if it becomes necessary based on new clinical evidence or novel research goals.

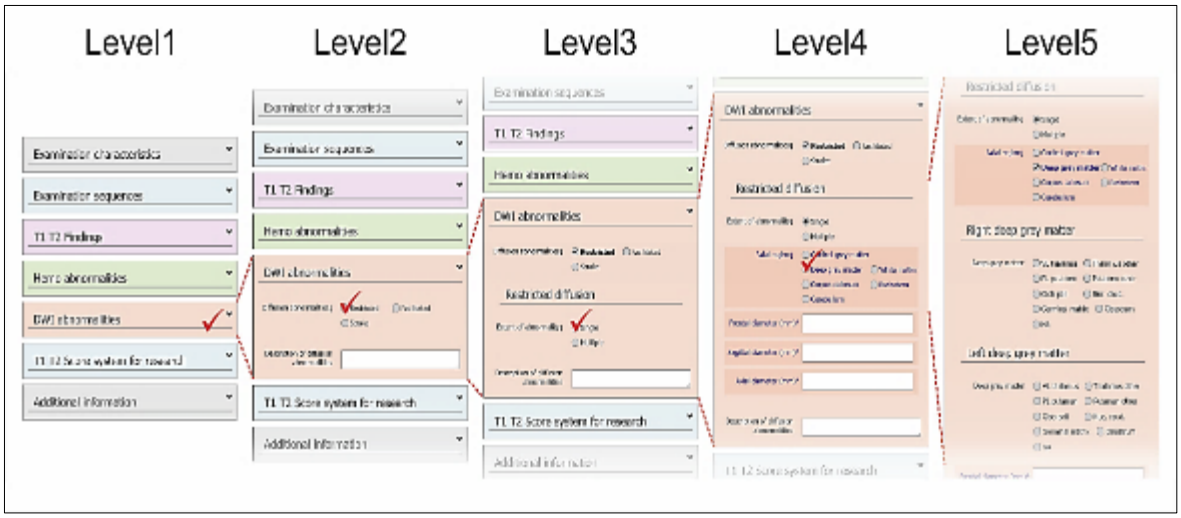

Figure 6 Data input example for the iSORT for HIE template
The template consists of nested levels of terms starting from broad categories tapering towards more detailed, narrow descriptions. Detailed input of observations are guided by the responsive nature of the template, i.e. mouse clicks (represented by red checkmarks) at a given level of description, result in the extension of the terms representing a sublevel. Multiple levels can be nested under each observation or anatomical region, and selections are non-exclusive, i.e. cortical gray matter, white matter, etc. can simultaneously be selected in Level4, leading to structure specific subcategories in Level5 from which only deep gray matter is detailed in the figure.

4.1.3. Evaluation of the novel structured reporting template for HIE

The HIE reporting template was easy to use, and it helped in efficient recording of the imaging findings in a reasonable time frame as the learning curve was relatively fast. Completing one report after 2 hours of training took approximately 1 - 5 minutes depending on the complexity of the imaging findings.

We relied on the flexibility of the iSORT framework by performing iterative adjustments to the template during the feasibility study, by changing and adding descriptors and including an option to measure the detected signal abnormalities. When giving full particulars which were beyond possibility a not available (N/A) option was also added.

Data access and basic statistical analysis was also facilitated by the iSORT framework, it was easy to query clinical information from the database. Example of information obtained with

minimal effort included gestational weight (mean ± SD = 3149 ± 582 g; range = 1490 – 4300 g), gestational age (mean ± SD = 38.3 ± 2.2 weeks; range = 30.0 - 43.0 weeks), brain MRI examination time (mean = 5.8 ± 2.9 days; range = 1 - 14 days) of the 106 evaluated neonates. It also became evident that 78% of the MRI examinations was performed after the completion of therapeutic hypothermia, while the remaining 22% was performed during or prior to therapy. Evaluating imaging patterns revealed that diffusion changes show a characteristic temporal evolution (**Table 5**). Moreover, it stood out that 18% (n = 19/106) of the infants who were clinically considered asphyxiated had isolated axial-extraaxial hemorrhage without the imaging signs of HIE.

Table 5 Temporal evolution of diffusion changes in infants who presented with restricted diffusion on MRI examination

The table shows the diffusion changes over time in infants who presented with restricted diffusion on MRI examination. 36 infants of the total of 106 showed restricted diffusion at one or more anatomic areas. Age at the time of MRI-examination is indicated in the upper horizontal row. The affected anatomic areas are shown in the left vertical column. 'n' represents the number of patents. The percentages show the occurrence of diffusion restriction in the different anatomic areas at different ages.

Partitioning the patients regarding the age at the MRI examination and the affected anatomic area showed the evolution of changes over time and space. The incidence of the diffusion restriction in the thalami showed a steady decline, while the involvement of the optic radiations increased until the 7-8th day.

Region \ Age	1-2 days	3-4 days	5-6 days	7-8 days	9-10 days
	n = 9	n = 12	n = 7	n = 4	n = 4
Thalamus	77,78%	33,33%	28,57%	25,00%	25,00%
Putamen	11,11%	0,00%	0,00%	25,00%	0,00%
Globus Pallidus	0,00%	0,00%	0,00%	25,00%	0,00%
Caudate Nucleus	0,00%	0,00%	14,29%	0,00%	0,00%
PLIC	33,33%	8,33%	0,00%	25,00%	0,00%
Optic Radiation	44,44%	66,67%	42,86%	100,00%	50,00%
Corticospinal Tract	44,44%	0,00%	0,00%	0,00%	25,00%
Corpus Callosum	33,33%	50,00%	71,43%	75,00%	50,00%

4.2. Prognostication with early magnetic resonance imaging in hypothermia treated asphyxiated neonates with hypoxic ischemic encephalopathy and/or intracranial hemorrhage.

Clinical characteristics of 108 neonates with moderate-to-severe HIE meeting the eligibility criteria and 102 patients excluded from the study are presented in **Table 6**. Clinical parameters of the included and excluded group of patients showed no significant difference.

Table 6 Perinatal characteristics of HIE newborns enrolled and excluded from the study
GA: gestational age, BE: base excess, n: number of patients

Variable	Included (n = 108)	Excluded (n = 102)	p val.
Age at MRI (h) mean ± SD (range)	65.12 ± 46.34 (4.42 - 165.67)	-	-
GA (wks) mean ± SD (range)	38.5 ± 1.51 (36 - 43)	39.05 ± 1,56 (36 - 43)	0.1293
Birth weight (g) mean ± SD (range)	3099.52 ± 447.89 (1490 - 4300)	3196.78 ± 497.94	0.7357
1-min Apgar score median (range)	2 (0 - 8)	2 (0 - 8)	0.4560
5-min Apgar score median (range)	4 (0 - 9)	5 (0 - 9)	0.2226
10-min Apgar score median (range)	6 (0 - 9)	6 (0 - 9)	0.0698
pH mean ± SD (range)	7.04 ± 0.18 (6.3 - 7.38)	7.01 ± 0.21 (6.34 - 7.6)	0.2217
BE (mEq/l) mean ± SD (range)	-16.57 ± 5.94 (-28 - 1)	-16.04 ± 6.55 (-29 - 1.7)	0.4985

The average age at which brain MRI scans were obtained was 65.12 ± 46.34 hours. All brain MRIs were performed after passive cooling started during transport or after the initiation of therapeutic hypothermia. Of these 108 patients 9 patients died in the perinatal period (6.67%). None of our patients died between 28 days and the neurodevelopmental follow-up examination. Twelve children had significantly delayed development (MDI and/or PDI < 70). Seven of these patients were diagnosed with cerebral palsy. Twenty-seven children received an MDI and/or PDI score compatible with mildly delayed development (70-84).

The 108 subjects were divided into four groups based on the presence (+) or absence (-) of the MRI signs of ICH (**Figure 7**) and HIE (**Figure 8 & 9**): Group1: Infants presenting neither the signs of HIE nor ICH (**Table 7**). Group2: Patients without the imaging signs of HIE showing ICH (**Table 8**). Group3: Both HIE and ICH is visible (**Table 9**). Group4: Only HIE signs are present (**Table 10**). Neurodevelopmental outcome results were registered for each patient.

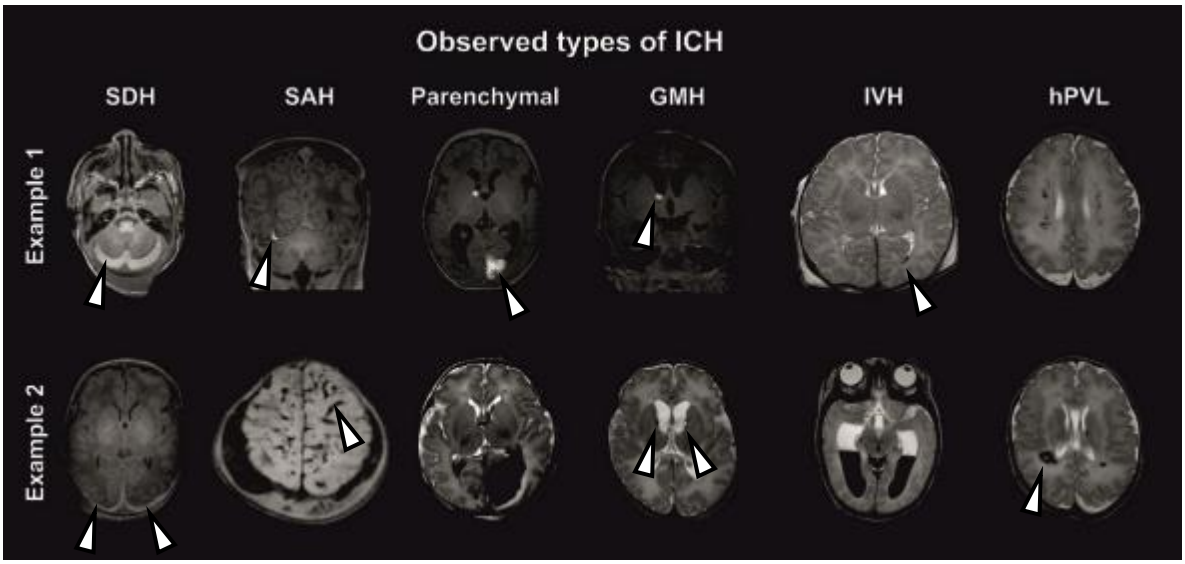

Figure 7 Observed types of ICH
MR images show two sets of examples for intracranial hemorrhages of different types, locations and sizes observed in asphyxiated infants.
Example 1 (left to right): High signal intensity SDH located in the posterior fossa along the cerebellar hemispheres (axial T1WI); Right temporal SAH (coronal T1WI); Intraparenchymal hemorrhage in the left occipital lobe without significant mass effect and small GMH in the right caudothalamic groove (axial T1WI); Small GMH in the right caudothalamic groove (coronal T1WI); Small IVH in the left occipital horn (axial T2WI); Low T2 signal intensity petechial foci bilaterally affecting the periventricular WM in keeping with hemorrhagic PVL (axial T2WI). Example 2 (left to right): SDH over the occipital lobes (axial T1WI); Extensive bilateral convexal SAH, with bilateral subgaleal hematoma (axial SWI); Left occipital intraparenchymal hemorrhage with mass effect, compressing the trigone of the posterior horn of the lateral ventricle on the ipsilateral side (axial T2WI); Bilateral GMH visible in the caudothalamic groove (axial T2WI); Hemorrhage in the dilated occipital horns of the lateral ventricles bilaterally (axial T2WI); Multiple low signal intensity foci in the periventricular white matter suggestive of hPVL (axial T2WI).
SDH: subdural hemorrhage, SAH: subarachnoid hemorrhage, GMH: germinal matrix hemorrhage, IVH: intraventricular hemorrhage, hPVL: hemorrhagic periventricular leukomalacia.

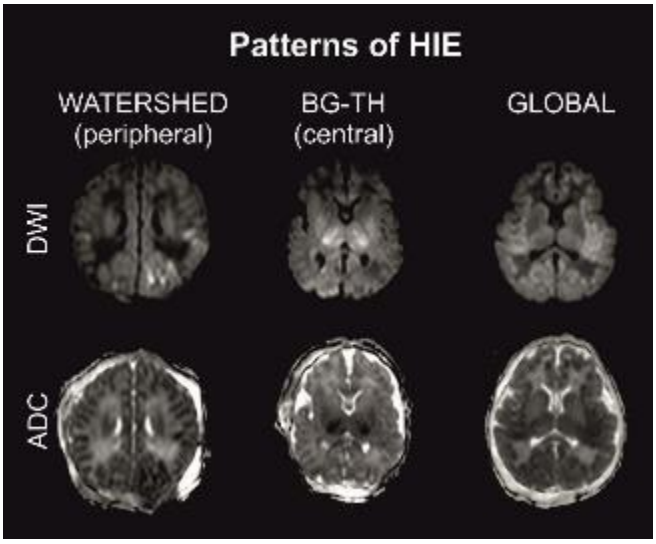

Figure 8 Patterns of HIE
Watershed (peripheral) type of injury, diffusion restriction bilaterally; Basal ganglia – thalamus (central) pattern, restricted diffusion in bilateral thalami and putamina; Global diffusion restriction on DWI and ADC.

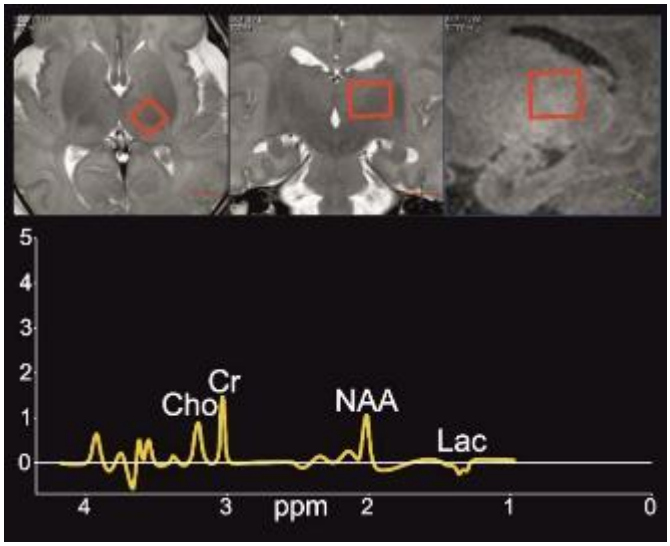

Figure 9 MRS pattern in HIE
Point-Resolved Spectroscopy (PRESS) acquired from the left thalamus (TE = 144 ms) on the 2nd day of life of a term infant shows prominent lactate peak, a characteristic inverse doublet, resonating at 1.3 ppm and decreased N-acetyl-aspartate (NAA), creatine (Cr) and choline (Cho).

Group1: HIE-/ICH- cases:

Fifteen infants showed no MRI or MRS signs of HIE (although they received cooling based on clinical criteria of moderate to severe HIE) and no ICH. The majority of these patients (80%, n = 12) showed normal neurodevelopmental outcome.

Table 7 MRI findings and neurodevelopmental outcome in cooled infants with no signs of HIE and ICH on early MRI

Normal MDI & PDI ≥ 85, abnormal MDI & PDI < 85. (SI: signal intensity, WM: white matter, MDI: Mental Developmental Index, PDI: Psychomotor Developmental Index, N: normal, AN: abnormal).

Group1: HIE-/ICH-			
No. of pts.	*Comments, MRI findings*	*MDI*	*PDI*
1.1	negative	N	N
1.2	negative	N	N
1.3	negative	N	N
1.4	negative	N	N
1.5	negative	N	N
1.6	negative	N	N
1.7	negative	N	N
1.8	negative	N	N
1.9	negative	N	N
1.10	negative	N	N
1.11	negative	N	N
1.12	negative	N	N
1.13	negative	AN	AN
1.14	negative	AN	AN
1.15	negative	N	AN

Group2: HIE-/ICH+ cases:

Altogether 15 hypothermia treated patients had isolated ICH without the MRI signs of HIE. Eight patients had only one type of extra-axial or intraparenchymal hemorrhage. The other seven patients had intracranial hemorrhages of multiple types and localizations. The most common ICH types were SDH (n = 9) and SAH (n = 9), which were small without any mass-effect and caused most probably by traumatic delivery. The extra-axial hemorrhages predominantly occurred in the posterior cranial fossa, along the tentorium cerebelli. IVH was present in three patients, intraparenchymal hemorrhage in two infants and GMH in one neonate. All fifteen patients with hemorrhage but without the MRI signs of HIE achieved a normal PDI score (≥ 85) on neurodevelopmental testing. The MDI scores were abnormal in two patients; one of whom had IVH and SAH with multiple foci of GMH besides space occupying cerebral and cerebellar intraparenchymal hemorrhages leading to hydrocephalus.

Table 8 MRI findings and neurodevelopmental outcome in cooled infants with ICH and the imaging signs of HIE

Normal MDI & PDI ≥ 85, abnormal MDI & PDI < 85. *N/A: non applicable, no reliable measurement was available. (SDH: subdural hemorrhage, SAH: subarachnoid hemorrhage, IVH: intraventricular hemorrhage, GMH: germinal matrix hemorrhage, P: intraparenchymal hemorrhage, L: left side, R: right side, B: bilateral, N: no mass effect, Y: hemorrhage with mass effect, WM: white matter, BG-TH: basal ganglia thalamus pattern, PVL: periventricular leukomalacia, SSS: superior sagittal sinus, MDI: Mental Developmental Index, PDI: Psychomotor Developmental Index, N: normal, AN: abnormal).

Group2: HIE-/ICH+							
No. of pts.	*Type of ICH*	*Localization of ICH*	*ICH max. size (mm)*	*ICH mass effect*	*Comments*	*MDI*	*PDI*
2.1	SDH	B. occipital, B. infratentorial	≤3	N		N	N
2.2	SDH, SAH	SDH: B. occipital, B. infratentorial, SAH: B. fronto-temporo-parietal	≤7, ≤1	N, N		N	N
2.3	SDH, SAH	SDH: B. occipital, B. parafalcial, B. infratentorial, SAH: B. occipital	≤4, ≤1	N, N		N	N
2.4	IVH	L. occipital	≤7	N		N	N
2.5	SAH, IVH	SAH: B. occipital, IVH: L. occipital	≤2, ≤6	N, N		N	N
2.6	SDH, SAH	SDH: R. parieto-occipital, B. infratentorial SAH: B. occipital, B. infratent.	≤2, ≤2	N, N		N	N
2.7	GMH1,GMH2, SAH, IVH, P1, P2, Plexus	GMH1: R. caudothalamic, GMH2: B. mpx. perivent., SAH: L. infratent., IVH: B. occip., P1: L. occip., P2: R. cerebellar, Plexus: R. frontal	≤6, ≤1, ≤1, ≤2, 15x19x27, 39x33x37, ≤5	N, N, N, N, Y, Y, N	Hydro-cephalus	AN	N
2.8	SDH, SAH	SDH: B. frontal, SAH: L. fronto-temporal, B. occipital, B. infratent.	≤4, ≤1	N, N		N	N
2.9	SDH	R. infratentorial	≤3	N		N	N
2.10	SDH	R. infratentorial	≤2	N		N	N
2.11	P	L. occipital	10x5	N		AN	N
2.12	SDH, SAH	SDH: B. parafalcial, B. infratentorial, SAH: B. occipital, B. infratentorial	≤4, ≤1	N, N		N	N
2.13	SDH	L. parafalcial, R. infratentorial	≤2	N		N	N
2.14	SAH	L. frontal	≤1	N		N	N
2.15	SAH	R. temporo-occipital	≤1	N		N	N

Group3: HIE+/ICH+ cases:

Twenty-four patients showed MRI signs of HIE as well as ICH. There were 10 neonates (41%) who only had abnormal MRS (without restricted diffusion and T1-, T2- signal abnormality). Four patients (17%) were affected by global severe HIE, four neonates (17%) showed watershed pattern, and another four (17%) presented with basal ganglia-thalamus pattern of injury. In two patients (8%) the signs of hemorrhagic PVL were seen. All but one patient (#3.3) had small ICHs, mainly petechial intraparenchymal hemorrhages in the periventricular white matter (n = 10) or non-complicated SAH (n = 8), IVH (n = 9) and SDH (n = 7) supposed to be traumatic in origin. Low MDI and/or PDI scores in keeping with an adverse outcome were present in 50% (n = 12) of this patient group.

Table 9 MRI findings and neurodevelopmental outcome in cooled infants with ICH without the imaging signs of HIE

Normal MDI & PDI ≥ 85, abnormal MDI & PDI < 85. (SDH: subdural hemorrhage, SAH: subarachnoid hemorrhage, IVH: intraventricular hemorrhage, GMH: germinal matrix hemorrhage, P: intraparenchymal hemorrhage, L: left side, R: right side, B: bilateral, N: no mass effect, Y: hemorrhage with mass effect, PCA: posterior cerebral artery, MDI: Mental Developmental Index, PDI: Psychomotor Developmental Index, N: normal, AN: abnormal).

Group3: HIE+/ICH+									
No. of pts.	*Type of ICH*	*Localization of ICH*	*ICH max. size (mm)*	*ICH mass effect*	*Pattern of HIE*	*HIE on MRS*	*Comments*	*MDI*	*PDI*
3.1	SAH, IVH, P	SAH: B. fronto-temporo-parietal, IVH: B. occipital horn, P: B. mpx. fronto-temporo-parietal	≤1; ≤7; ≤1	N, N, N	Global	N	Diffuse brain swelling, EXITUS	AN	AN
3.2	P	Periventricular by R. occipital horn	≤1	N	Hemorrh. PVL	Y		N	AN
3.3	P	P1: R. occipital, P2: L. occipital	21x21x30; 38x26x26	Y, Y	Watershed (peripheral)	Y		N	N
3.4	P	R. frontal	≤5	N	-	Y		N	N
3.5	IVH, GMH, P	IVH: B. occipital, GMH: L. caudothalamic, P: L. cerebellar	≤2; ≤1; ≤4	N, N. N	-	Y		N	N
3.6	IVH	B. occipital	≤3	N	-	Y		AN	AN
3.7	IVH	B. occipital	≤2	N	BG-TH (Central)	Y		N	AN
3.8	SDH, SAH	SDH: B. occipital, B. infratentorial, SAH: B. occipital, B. infratentorial	≤3; ≤1	N,N	-	Y	Suspected thrombosis of SSS & transverse sinuses	N	N
3.9	IVH	L. occipital	≤4	N	Watershed (peripheral)	Y		N	N
3.10	SAH	B. occipital, B. infratentorial	≤1	N	-	Y		N	N

No. of pts.	*Type of ICH*	*Localization of ICH*	*ICH max. size (mm)*	*ICH mass effect*	*Pattern of HIE*	*HIE on MRS*	*Comments*	*MDI*	*PDI*
3.11	P	B. peritrigonal	≤1	N	-	Y		N	N
3.12	IVH	B. occipital	≤4	N	-	Y		AN	AN
3.13	SDH, IVH	SDH: B. supra-, infratentorial, IVH: R. occipital	≤3; ≤2	N, N	-	Y		N	N
3.14	SDH, SAH	SDH: B. infratentorial, SAH: B. parietal	≤4; ≤1	N, N	BG-TH (Central)	Y		N	N
3.15	SDH, SAH	SDH: B. infratentorial, SAH: B. occipital	≤2; ≤1	N, N	-	Y		N	N
3.16	SAH, IVH	SAH: B. infra-, supratentorial, IVH: B. occipital	≤1; ≤1	N, N	Global	Y		AN	AN
3.17	SDH, SAH	SDH: B. infra-, supratentorial, SAH: L. parieto-occipital	≤2; ≤1	N, N	-	Y		N/A*	N
3.18	P	R. putamen	14x5	N	BG-TH (Central)	Y		AN	AN
3.19	SDH, IVH	SDH: B. infra-, supratentorial, IVH: B. occipital	≤2; ≤6	N, N	BG-TH (Central)	Y		AN	AN
3.20	P	Mpx. B. fronto-parieto-occipital periventricular WM	≤5	N	Watershed (peripheral)	Y	SSS & transverse sinus thrombosis	AN	N
3.21	P	Mpx. B. hemispheres	≤2	N	Global	Y	EXITUS	AN	AN
3.22	P	Mpx. B. hemispheres, periventricular WM	≤1	N	Hemorrh. PVL	Y		AN	N
3.23	SDH, SAH	SDH: B. supra-, infratentorial, SAH: B. supra-, infratentorial	≤3; ≤1	N, N	Watershed (peripheral)	Y		N	N
3.24	P	Mpx. B. cerebellar	≤5	N	Global	Y		AN	AN

Group4: HIE+/ICH- cases:

Altogether 54 patients composed the group of HIE signs on MRI without intracranial hemorrhage. Isolated ^{1}H-MR-spectroscopy abnormality (without restricted diffusion and T1-, T2- signal abnormality) was present in 19 patients (35%). Eight patients (15%) were affected by global severe HIE, seven neonates (13%) showed watershed pattern, and eighteen infants (33%) presented with basal ganglia-thalamus pattern of injury. In two patients (4%) the prominent deep medullary veins were suggestive for HIE. Low MDI and/or PDI scores in keeping with an adverse outcome were present in 61% (n = 33) of this patient group.

Examples for the observed types of ICH, the main patterns and the typical spectral abnormalities in HIE are presented on **Figure 7, 8 and 9**.

Table 10 MRI findings and neurodevelopmental outcome in cooled infants showing the imaging signs of HIE without ICH

Normal MDI & PDI ≥ 85, abnormal MDI & PDI < 85. (BG-TH: basal ganglia thalamus pattern, PVL: periventricular leukomalacia, B: bilateral, N: normal spectrum, Y: spectrum representing HIE, MDI: Mental Developmental Index, PDI: Psychomotor Developmental Index, N: normal, AN: abnormal).

Group4: HIE+/ICH-					
No. of pts.	*Type of HIE*	*HIE on MRS*	*Comments*	*MDI*	*PDI*
4.1	-	Y		N	N
4.2	-	Y		N	N
4.3	B. prominent deep medullary veins	N		AN	AN
4.4	B. prominent deep medullary veins	Y		N	N
4.5	-	Y		N	N
4.6	BG-TH (Central)	Y		N	AN
4.7	BG-TH (Central)	Y		N	N
4.8	BG-TH (Central)	Y		AN	AN
4.9	BG-TH (Central)	Y		N	N
4.10	BG-TH (Central)	N		N	N
4.11	-	Y		N	N
4.12	BG-TH (Central)	Y		AN	AN
4.13	BG-TH (Central)	N		AN	N
4.14	Global	Y	EXITUS	AN	AN
4.15	Global	Y		N	AN
4.16	BG-TH (Central)	N		N	N
4.17	Global	Y		AN	AN
4.18	BG-TH (Central)	Y		AN	AN
4.19	BG-TH (Central)	N		N	N
4.20	Watershed (Peripheral)	N		N	N
4.21	Watershed (Peripheral)	Y		AN	N
4.22	Global	Y	EXITUS	AN	AN
4.23	-	Y		N	N
4.24	Watershed (Peripheral)	Y		AN	N
4.25	Global	Y		N	AN
4.26	BG-TH (Central)	Y		AN	N
4.27	-	Y	EXITUS	AN	AN

4.28	BG-TH (Central)	Y		N	N
No. of pts.	Type of HIE	HIE on MRS	Comments	MDI	PDI
4.29	BG-TH (Central)	Y	EXITUS	AN	AN
4.30	Global	N		AN	AN
4.31	-	Y		N	N
4.32	-	Y		AN	N
4.33	-	Y		N	N
4.34	Watershed (Peripheral)	Y		AN	AN
4.35	-	Y		N	N
4.36	BG-TH (Central)	Y	EXITUS	AN	AN
4.37	-	Y		N	N
4.38	-	Y		AN	N
4.39	-	Y		AN	AN
4.40	Watershed (Peripheral)	Y	embolization	N	N
4.41	-	Y		AN	AN
4.42	-	Y		AN	AN
4.43	-	Y		N	N
4.44	-	Y		AN	N
4.45	-	Y		AN	AN
4.46	-	Y		AN	AN
4.47	BG-TH (Central)	Y		AN	AN
4.48	Global	N	PVL	AN	AN
4.49	BG-TH (Central)	Y	EXITUS	AN	AN
4.50	BG-TH (Central)	Y		N	N
4.51	Watershed (Peripheral)	N		AN	AN
4.52	BG-TH (Central)	Y		N	N
4.53	Watershed (Peripheral)	N		AN	N
4.54	Global	Y	EXITUS	AN	AN

Chi-square test and logistic regression analysis:

Data on neurodevelopmental outcome and MRI results of the four groups were summarized in two by four contingency tables (**Table 11**). Approximately 36% (n = 39) of the examined patient population had axial or extra-axial bleeds, mainly intraparenchymal or subdural hemorrhages. HIE was present in 62% (n = 24) of such patients (all with intracranial hemorrhage), while in the other 38% (n = 15) of the infants with ICH the imaging signs of HIE were completely absent. MRI evidence of HIE was absent in 28% (n = 30) of the neonates who were treated with hypothermia. Chi-square test demonstrated significant relationship between ICH and HIE and the outcome measured by PDI ($\chi^2 = 13.025$, df = 3, p = 0.0046) and MDI ($\chi^2 = 14.2673$, df = 3, p = 0.0026).

After proving the dependence between the patient groups and neurodevelopmental outcome, further analysis using logistic regression was performed in patients whose PDI (n = 99) and MDI (n = 98) scores were available (9 infants died early on, one had N/A MDI score). Distribution of neurodevelopmental scores in the four patient groups are presented on bean plots (**Figure 10**).

Table 11 Two by four contingency table summarizing results of MRI and MDI, PDI
Normal MDI ≥ 85, abnormal MDI < 85. †MDI was N/A in 1 patient. Lowest expected value = 6.111; $\chi 2 = 14.2673$; df = 3; p = 0.0026. Normal PDI ≥ 85, abnormal PDI < 85. Lowest expected value = 5.278; $\chi 2 = 13.025$; df = 3; p = 0.0046. (HIE: hypoxic ischemic encephalopathy, ICH: intracranial hemorrhage, MDI: Mental Developmental Index, PDI: Psychomotor Developmental Index).

		HIE-/ICH-	HIE-/ICH+	HIE+/ICH-	HIE+/ICH+	Total
		No. of pts.	No. of pts.	No. of pts.	No. of pts.	
MDI	normal	13	13	24	13	**63**
	abnormal	2	2	30	10	**44**
	total	**15**	**15**	**54**	**23**†	**107**
PDI	normal	12	15	29	14	**70**
	abnormal	3	0	25	10	**38**
	total	**15**	**15**	**54**	**24**	**108**

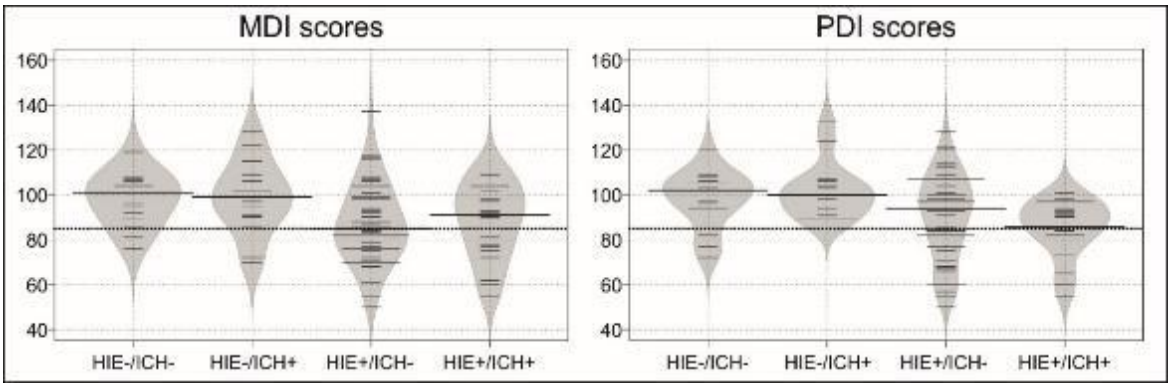

Figure 10 Distribution of neurodevelopmental outcome scores
Bean plots showing the distribution of neurodevelopmental outcome scores (MDI and PDI) in the 4 patient groups. Wide black lines represent the medians, the dotted line at 85 represents the threshold between good and poor outcome.

Multivariate logistic regression was used to evaluate the effect of HIE and/or ICH on neurodevelopmental outcome, measured by MDI and PDI scores, adjusting for other clinically relevant parameters including age at MRI, 5 minute Apgar score and pH. **Table 12** demonstrates the adjusted and unadjusted odds ratios for each variable. Regarding MDI, the unadjusted logistic regression analysis ($\chi^2 = 11.1$, df = 94, p = 0.011) showed that the presence of MRI signs of HIE had significant negative effect on the outcome (OR = 6.2292; 95% CI [1.2642; 30.6934]; p = 0.0246), meaning neonates who exhibited imaging signs of HIE had six times higher odds of an abnormal MDI score, than those without imaging signs of HIE or ICH. In the same model, neither ICH, nor the simultaneous presence of ICH and HIE had significant modulatory effect (p > 0.9999 and p = 0.7121, respectively). Regarding PDI, the logistic regression analysis ($\chi^2 = 14.4$, df = 95, p = 0.002) showed that none of the conditions (signs of HIE, ICH, or both) proved to have significant modulatory effect on psychomotor development (p = 0.2014, p > 0.9999, and p > 0.9999, respectively). After adjusting for confounds, HIE remained an independent risk factor for delayed neurodevelopment with respect to MDI (logistic regression model: $\chi^2 = 16.000$, df = 88, p = 0.014, effect of HIE: OR = 6.2496; 95% CI = [1.2018; 32.4983], p = 0.0294), while ICH remained to have no significant effect. Similarly, regarding PDI the adjusted logistic regression model ($\chi^2 = 16.9$, df = 88, p = 0.010) revealed no modulatory effect of the presence of HIE, ICH, or both (p = 0.1997, p > 0.9999, and p > 0.9999, respectively). Neither the 5 minute Apgar score, nor the

pH, nor the time of MRI exam proved to be significant covariates for MDI (p = 0.1158, p = 0.3415, and p = 0.4105, respectively) or PDI (p = 0.1675, p = 0.8622, and p = 0.5268, respectively).

Table 12 Logistic regression predicting the likelihood of adverse outcome
OR: odds ratio, aOR: adjusted odds ratio, CI confidence interval. Logistic regression model predicting likelihood of adverse outcome on the Bayley Scales of Infant Development II Test, based on the presence of MRI signs of HIE and ICH on early MRI, the time of the MRI examination, the 5 minute Apgar score, and the initial pH.

	MDI unadjusted (model fit: $\chi^2 = 11.1$, df = 94, p = 0.011)			**MDI adjusted** (model fit: $\chi^2 = 16.000$, df = 88, p= 0.014)		
	OR	**(95% CI)**	**p**	**aOR**	**(95% CI)**	**p**
ICH	NA	NA	0.9999	1.2408	(0.1445 - 10.6554)	0.8441
HIE	**6.2292**	**(1.2642 - 30.6934)**	**0.0246***	**6.2496**	**(1.2018 - 32.4983)**	**0.0294***
Time of MRI (h)				0.9954	(0.9847 - 1.0063)	0.4105
5 min Apgar				0.8259	(0.6507 - 1.0482)	0.1158
pH				0.3014	(0.0255 - 3.5682)	0.3415
ICH×HIE	0.6421	(0.0611 - 6.7517)	0.7121	0.5939	(0.0540 - 6.5381)	0.6703
	PDI unadjusted (model fit: $\chi^2 = 14.4$, df = 95, p = 0.002)			**PDI adjusted** (model fit: $\chi^2 = 16.9$, df = 88, p = 0.010)		
	OR	**(95% CI)**	**p**	**aOR**	**(95% CI)**	**p**
ICH	NA	NA	0.9999	NA	NA	0.9999
HIE	2.4828	(0.6152 - 10.0198)	0.2014	2.5692	(0.6074 - 10.8666)	0.1997
Time of MRI (h)				0.9963	(0.9851 - 1.0077)	0.5268
5 min Apgar				0.8443	(0.6639 - 1.0737)	0.1675
pH				0.8019	(0.0663 - 9.7067)	0.8622
ICH×HIE	NA	NA	0.9999	NA	NA	0.9999

5. Discussion

5.1. The SR template

5.1.2. Implementation of a novel structured reporting template for HIE

Imaging represents an important, yet limited part of available clinical information for a given patient or condition. Nevertheless in order to successfully integrate imaging results to the medical “big data” either for diagnostic or research purposes it is inevitable to create user friendly databases. Such systems can be considered effective only if they save time and eliminate repeated (multiple) data input, by being capable for everyday use in radiology reporting while providing enough detail for research purposes, as well.

Here we introduced a novel SR template for HIE dedicated to report brain MRI examinations of asphyxiated neonates. Besides the personal expertise and experience of the collaborating radiologists and non-radiologists, published evidence served as foundation of the template. The main advantage of the proposed template is that its questions direct the attention of the radiologist towards the “not to miss” findings of HIE. However, this guidance can also be considered a disadvantage by some, claiming that it limits the radiologist’s latitude of idiosyncratic reporting. To ease the constraints enforced by the structure of the template, comment fields provide opportunity for notes, and remarks in cases when the predefined structure do not fully suite the reporting radiologist needs.

The main limitation of our currently proposed SR template is that it is customized for a particular modality and a specific patient population, i.e. MRI in asphyxiated infants. Yet, the basic constitution is adaptable to report brain MRI of other indications and age groups, and the template can be extended to include other modalities, as well.

5.1.3. Evaluation of the novel structured reporting template for HIE

There was a high proportion (18%) of isolated intracranial hemorrhage cases without the MRI signs of HIE. This remarkable finding emphasizes the importance of early MRI examinations in therapeutic decision making. Indeed, early imaging may help to avoid

unnecessary hypothermia treatment with all its possible adverse effects. Yet, the protocols allow a very narrow time window (maximum of 6 hours from birth) for the initiation of cooling that seriously limits the opportunity of performing MRI in these critically ill and instable newborns [122, 123].

Our feasibility study showed a very specific temporal evolution of diffusion patterns that further emphasizes the importance of the timing of MRI examinations. Moreover, based on the temporal evolution of diffusion changes the timing of the hypoxic event may also be better estimated.

Regarding research applications, the results of the evaluation proved that our SR template provides a quick, precise and effective means of data input for research purposes, too. Using the iSORT for HIE module more detailed statistical analysis will be accessible in future projects involving a wide range of non-imaging parameters, as well.

5.1.4. The SR template in clinical and research workflow

The proposed reporting system leads to faster data recording and more detailed, and standardized information compared to conventional free-text report with a steep learning curve. By integrating our SR template with the comprehensive clinical database (e.g. hospital information system, HIS) the radiologist may have access to clinical data and at the same time quantified imaging results become immediately available for clinical use. Furthermore, the system may prove particularly beneficial in clinical research, too by enabling bulk data input, arrangement, search and export leading to high quality curated data.

Reducing interpretation ambiguity may have an immediate direct positive impact on patient care in a routine clinical setting, while also providing high quality data for research purposes. Nevertheless, no template is perfect, and only time can pinpoint its weaknesses through usage and systematic re-evaluation, which we plan to pursue alongside its extension for further pediatric conditions in the near future.

5.2. Effect of HIE and/or ICH signs on MRI on neurodevelopmental outcome

Our study attempted to determine the predictive value of intracranial hemorrhage in association with HIE related MR imaging signs in comparison with neurodevelopmental results in cooled asphyxiated infants. Intracranial hemorrhage took a remarkable share affecting approximately one-third of infants treated with hypothermia. Intracranial hemorrhagic complications which were present before or evolve during treatment showed no significant influence on outcome despite the known negative hematological (platelet dysfunction, thrombocytopenia) effects of cooling. Having more than six time higher odds for abnormal neurodevelopmental outcome the presence of HIE related MR-spectroscopy abnormalities and diffusion restriction proved to have important prognostic value. Therefore, the implementation of early MRI in the diagnostic algorithm needs to be considered [124].
We assessed the rate of ICH in a cohort of patients with clinical signs of HIE, and also considered the effect of ICH on the long term outcome in this patient population. Several studies demonstrate the benefits and compare the accuracy of MRI in identifying HIE and predicting the long term neurodevelopmental outcome [35, 63, 68, 125, 126], nevertheless, to our knowledge this was the first study considering the possible relevance of ICH accompanying HIE. Three major randomized controlled trials as the NICHD study [77], the TOBY trial [78] and the ICE trial [89, 90] have demonstrated a reduction in death and neurological impairment after hypothermia treatment. The above trials also included brain MRI, but compared to our study these were relatively late examinations performed after the first week of life in average, assessing the patterns of injury classified by Rutherford mainly on conventional T1- and T2-weighted sequences, and partially on diffusion weighted imaging. The average age on completion of MRI in our study was around the third day of life. The pattern of the injury defined as predominantly basal ganglia or thalamic lesions, watershed predominant injury or global brain insult were classified on diffusion weighted images in most of the cases. MR-spectroscopy was also considered, revealing 29 patients with spectra compatible with HIE and without other imaging signs of hypoxic ischemic injury.

Published incidence of asymptomatic ICH after vaginal delivery of full-term neonates is approximately 25%,[127] yet symptomatic ICH is much less common, accounting for 4 per 10,000 live births [99]. The rate of ICH in our patient population of cooled asphyxiated infants was higher (36%) than found in literature. The majority of ICHs in our study were small extra-axial or petechial intraparenchymal hemorrhages localized in the posterior fossa, but there also were multifocal hemorrhages with various patterns of bleeding. The origin of the observed hemorrhages may be related to delivery [128] or to the cooling itself [106, 107], and while the cooling-induced thrombocytopenia [89] may potentially lead to a progression of these bleedings, we have no evidence of progression in our data, partly due to a lack of follow-up imaging. Nevertheless, progression seems to be unlikely given the fact that these ICHs proved to have no significant modulatory effect on the long term mental (MDI) and psychomotor (PDI) developmental outcome.

Early MRI evidence of HIE proved to be a significant predictor of an adverse outcome eventuating more than six times higher odds for abnormal mental development in an asphyxiated child compared to a neonate without the imaging proof of HIE with or without the presence of ICH. Vice versa, in almost all of the cases clinically categorized as HIE (n=30) but lacking MRI evidence of HIE the neurodevelopmental outcome was within normal limits. This is in line with the converging evidence showing the negative outcome associated with the presence of HIE signs on MRI imaging performed after the first week of life [77, 78, 89, 90], and also consistent with the literature regarding early MRI [75].

There are some aspects of the study that can be considered as limitations, the first is the retrospective nature of the data presented. A prospective trial could allow for better controlled patient selection, and could also lead to more consistent data acquisition, nevertheless clinical data obtained in a general setting is equally important [119]. While our data derived from 210 consecutive patients gives a cross sectional overview of the patient population we observed in a 9-year period, it has its own inconsistencies regarding imaging and follow-up, eventually leading to a relatively high rate of exclusion. This may be considered a limitation of our study, nevertheless the lack of significant differences in the basic clinical parameters (e.g. Apgar scores, pH, etc.) between the included and excluded patient cohorts suggests that

our sampling is representative of the population categorized as HIE patients based on clinical grounds, i.e. the TOBY criteria [78].

It is important to note, that we excluded those patients whose first MRI was performed after the first week of life, given the main body of HIE-related literature [75, 121, 125] this can be considered as a shortcoming, however our goal was to investigate the early and transient signs of HIE on MRI alongside with the presence of ICH. The fact that our findings on the outcome-modifying effects of HIE signs present on MRI are in line with the literature obtained on later acquired imaging data [77, 78, 89, 90] justifies the appropriateness of our selection criteria.

The relatively wide age range at follow-up developmental testing can also be considered as a potential limitation, however the BSID-II is standardized to be used between 1-42 months of age, and the patient's age is properly taken into consideration for the final scores [117, 129]. Furthermore, one may also consider the use of BSID-II instead of BSID-III a limitation, please note however that the BSID-III was not translated and standardized to Hungarian until 2018; till then the BSID-II was the standard developmental test battery available in Hungarian.

The lack of an objective scaling system to image the severity of HIE may also be considered as limitation. Although, there are several scoring systems available, most of the scales depend on late MRI and conventional images, some of them on the early diffusion pattern alone, yet there is no score including MR spectroscopy in the grading, which could be used in our evaluation [65, 72, 110, 130, 131]. The reason for the lack of published MRS grading is that there is very narrow time window for the initiation of the hypothermia (maximum of 6 hours from birth) [132, 133], which limits the opportunity of performing an early MRI and there are still many centers where MR-spectroscopy is not included in the imaging protocol [122, 123]. The recent recommendation of the American College of Obstetricians and Gynecologists outlines the importance of early MRI (first 24-96 hours of life) for likely timing of the hypoxic ischemic insult and further follow-up imaging (7 - 21 days of life) to define the full nature of the abnormalities [67], but does not define or suggest a protocol for brain MRI in an asphyxiated infant.

One can consider the fact that MR examinations in our study were performed after passive cooling during transport or under or after hypothermic treatment as a limitation of our study, however we do not consider this a clinically relevant limitation as there is published evidence that the predictive value of MRI for subsequent neurological impairment is not affected by previous hypothermia [134]. In fact, MRI is accurate for evaluating the presence and extent of hypoxic brain injury under and after hypothermia [135].

Finally, there are numerous additional demographic factors and different kind of therapeutic and treatment options for HIE and associated conditions beyond the neonatal period as physical therapy, behavioral and emotional therapy, sensory integration therapy, occupational therapy etc. which were not considered in the statistical evaluation due to lack of data.

To successfully overcome the above-mentioned limitations more studies on early MRI need to be performed involving more subjects and gathering more imaging and clinical data to gain better insight whether there is any interference between hypothermia treatment, and imaging that may render the MRI results of asphyxiated infants unremarkable.

6. Conclusions

6.1. The SR template

The first part of our research was dedicated to create an advanced methodology of reporting brain MRI examinations in hypoxic ischemic encephalopathy. The in-house built SR template was found suitable for reporting HIE cases, moreover it uncovered time and location dependent evolution of diffusion abnormalities (and pseudonormalization, as well), suggesting its usefulness in clinical research applications. The feasibility study of the template also revealed a high number of intracranial hemorrhage affecting this patient population, which was an interesting finding, not published yet.

6.2. Effect of HIE and/or ICH signs on MRI on neurodevelopmental outcome

The second part of our study attempted to determine the predictive value of intracranial hemorrhage in association with HIE related MR imaging signs in comparison with neurodevelopmental results in cooled asphyxiated infants. Intracranial hemorrhage took a remarkable share affecting approximately one-third of infants treated with hypothermia. Intracranial hemorrhagic complications which were present before or evolve during treatment showed no significant influence on outcome despite the known negative hematological (platelet dysfunction, thrombocytopenia) effects of cooling. Having more than six time higher odds for abnormal neurodevelopmental outcome the presence of HIE related MR-spectroscopy abnormalities and diffusion restriction proved to have important prognostic value. Therefore, the implementation of early MRI in the diagnostic algorithm needs to be considered.

7. Summary

The aim of our study was to find out the prognostic role of early brain MRI, performed within the first week of life in term born asphyxiated neonates.

In order to implement a comprehensive study, which evaluates not only the imaging results but the relevant clinical and laboratory findings as well, a detailed, web-based, easily exportable database was designed in collaboration with neonatologists of the 1st Department of Pediatrics of Semmelweis University and medical entrepreneurs of the Bioscreen Ltd.

The created iSORT (intelligent structured online reporting tool) asphyxia database includes a brain MRI reporting module, based on both empirical and literature data, composed of single- and multiple choice questions built in a tree-structure. Answering the elemental questions regarding hypoxic ischemic encephalopathy (HIE) are obligatory. Besides the MRI reporting module, the asphyxia database includes searchable and exportable laboratory findings and clinical reports regarding each patient.

Following the iSORT database creation and data input, a feasibility study of the system revealed an interesting finding about neonates affected with HIE: intracranial hemorrhage (ICH) was relatively common in this patient group.

Knowing that whole-body hypothermia, the gold standard treatment in moderate to severe HIE, may cause thrombocytopenia, our research purposes were extended to examine not only the neurodevelopmental effect of the presence or absence of MRI signs of HIE but also the possible prognostic impact of ICH. ICHs, which were mainly small in size, without mass effect or obstructed cerebrospinal fluid flow were present in more than one-third of the included 108 infants. Our results showed that early MRI evidence of HIE proved to be a significant predictor of an adverse outcome eventuating more than six times higher odds for abnormal mental development in an asphyxiated child compared to a neonate without the imaging proof of HIE with or without the presence of ICH. Vice versa, in almost all of the cases clinically categorized as HIE but lacking MRI evidence of HIE the neurodevelopmental outcome was within normal limits. Interestingly, ICHs although being present in about one third of all cases had no significant effect on neurodevelopmental outcome, despite the known hemostasis altering effects of hypothermia.

8. Összefoglalás

Kutatásunk elsődleges célkitűzéseként az érett, ashyxiás újszülötteknél végzett korai, első élethéten készült koponya MR vizsgálatok prognosztikai szerepét terveztük vizsgálni.

Egy átfogó kutatás megvalósítása érdekében, a képalkotó vizsgálatok mellett az elérhető legtöbb releváns klinikai adat felhasználását megcélozva, első lépésként a Semmelweis Egyetem I. számú Gyermekgyógyászati Klinika neonatológus orvosaival, valamint a Bioscreen Kft. orvos-informatikus szakembereivel együttműködésben egy részletes, egyszerű adatexportálást biztostó, web-alapú adatbázis létrehozását terveztük. A munkacsoport által felépített iSORT (intelligent structured online reporting tool) asphyxia adatbázis koponya MR leletezési modulja a szabad szöveges leletezéssel szemben mind irodalmi adatokon, mind tapasztalaton alapuló, tematikusan, fa-struktúrában felépített, egyszerű és többszörös választási lehetőségeket kínál. A hypoxiás ischaemiás encephalopathia (HIE) szempontjából fontos adatok kötelező jelleggel kitöltendők. Az MR leletezési modul mellett az asphyxia adatbázisban elemezhető formában rendelkezésre állnak a laboratóriumi vizsgáltok leletei, illetve a klinikai adatok.

Az iSORT adatbázis megvalósulását és az adatbevitelt követően a rendszer tesztelése kapcsán többek között arra az érdekes megfigyelésre jutottunk, hogy a hypoxiás ischaemiás encephalopathiában szenvedő újszülöttek esetén relatíve nagy arányban fordult elő társuló intracranialis vérzés (ICH). Mivel ismert a közepesen súlyos, valamint súlyos HIE esetében „gold-standardként” alkalmazott teljes test hypothermia thrombocytopeniát okozó hatása, ezért kutatási tervünket a HIE MR jeleinek megléte/hiánya mellett az ICH esetleges fejlődésneurológiai kimenetelre gyakorolt hatásának vizsgálatára is kiterjesztettük. A beválasztott 108 újszülött több, mint egyharmadánál volt kimutatható többnyire kis kiterjedésű, térszűkítést, illetve liquor keringési zavart nem okozó ICH. Eredményeink alapján a hypothermiával kezelt asphyxiás újszülöttek esetén a korai MR vizsgálaton HIE-re típusos mintázatok megjelenésekor hatszor nagyobb az esély a rossz kimenetelre, szemben azokkal az újszülöttekkel, akik bár a klinikai skálák alapján HIE szerint kezeltek, de encephalopathia tekintetében MR negatívak. Ezzel szemben az ICH megléte vagy hiánya nincs szignifikáns hatással a fejlődésneurológiai kimenetelre.

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