Prognostic Role of Early MRI in Neonatal Hypoxic Ischemic Encephalopathy

PhD thesis summary

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1. INTRODUCTION

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. Our intent was to create a clear and consistent brain magnetic resonance imaging (MRI) 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”.

1.2.1. Neonatal 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. About 10% to 60% of the affected infants die, and at least 25% of survivors have long term neurodevelopmental sequelae as sensorineural hearing loss, visual loss, feeding difficulties, gross and fine motor deficits, sensory modulation disorders, maladaptive behavior as well as cognitive disorders.

1.2.2. Therapeutic hypothermia in neonatal HIE

In term or near-term infants with clinical signs of moderate to severe HIE, the current standard is therapeutic hypothermia for 72 hours started within 6 hours of life decreasing mortality and morbidity, and improving neurologic outcome in survivors. By lowering the temperature of the vulnerable deep brain structures to 32 - 34 °C, hypothermia may modify cells programmed for apoptosis, leading to their survival and may also protect neurons by reducing cerebral metabolic rate, attenuating the release of excitatory amino acids, improving the ischemia-impaired uptake of glutamate and lowering the production of toxic nitric oxide and free radicals. Adverse effects of hypothermia appear to be transient and reversible with re-warming. 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.

1.2.3. Intracranial hemorrhage and asphyxia

Intracranial hemorrhage (ICH) in term newborns is increasingly recognized, although its true incidence and prevalence is unknown. Subdural, subarachnoid, intraparenchymal and intraventricular hemorrhages (IVH) are the most common types of ICHs present in term infants. The major causes of IVH are birth trauma and asphyxia. Asphyxia very often leads to impaired cerebral autoregulation and asphyxia and hypothermia might also cause fluctuation of cerebral blood flow, being possible risk factors for IVH. As cooling in HIE may

result in thrombocytopenia, it may lead to prolongation of coagulation carrying a potentially higher risk for ICH.

1.2.4. Prognostic role of MRI in neonatal HIE

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. Early death and the most severe motor impairment as cerebral palsy were seen in association with basal ganglia injuries. Involvement of the posterior limb of the internal capsule in HIE was found to be associated with abnormal motor function.

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.

Some of the previous studies emphasizing the prognostic effect of signal abnormalities on conventional sequences, diffusion weighted images, and brain MRS analyzed a relatively small sample size. In some other studies with larger patient population MRS was performed after the first week of life or spectroscopic data was not involved in the evaluation, meaning that those HIE positive infants having only spectroscopic abnormality were not analyzed.

2. AIMS

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

The aim of our study was to develop an evidence-based, standardized structured reporting (SR) method for brain MRI examinations in neonatal HIE 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 MRI in hypothermia treated asphyxiated neonates with HIE and/or ICH

Knowing the hemostasis altering effects of therapeutic hypothermia, our retrospective observational study of cooled infants with the clinical diagnosis of HIE 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 SR template as part of an asphyxia database. Feasibility study of the novel SR system

3.1.1. Study population

Altogether 106 near-term or term asphyxiated infants were enrolled. Exclusion criterion were congenital malformations, metabolic disorders, exitus in the early perinatal period and the absence of at least one brain MRI examination. Mildly asphyxiated infants, who did not require whole body hypothermia were also excluded.

3.1.2. MR imaging and image analysis

Imaging was performed with a Philips Achieva 3T scanner using an 8-channel SENSE head-coil with T1-weighted 3D spoiled gradient echo, axial and coronal T2-weighted turbo spin echo, axial T2*-weighted gradient, and diffusion-weighted sequences, and single-voxel proton MR spectroscopy with Point RESolved Spectroscopy acquisition [TE = 35 and/or 144 and/or 288 ms] obtained from the left thalamus. Heart rate and oxygen saturation were monitored by neonatologists. In case of intubated infants, skilled personnel provided manual ventilation with an AMBU bag throughout the MRI examination. Key MR imaging findings were assessed by re-evaluating the MRI examinations of 106 neonates.

3.1.3. Implementation of a novel SR template for HIE

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.
2. Patterns of injury detected on standard anatomic sequences.
3. Typical MR-spectroscopy changes in perinatal asphyxia.
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.

The reporting template was developed in the iSORT (intelligent structured online reporting tool) software framework created by Bioscreen Ltd., Hungary.

3.1.4. Evaluation of the novel SR template for HIE

In order to test the utility of the reporting template 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 in particular.

3.2. Prognostication with early MRI in hypothermia treated asphyxiated neonates with HIE and/or ICH

3.2.1. Study Population

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 the aim of our study was to investigate ICH present during or early after hypothermia treatment and to detect diffusion and spectral changes of HIE (both of which have well know temporal evolution) we only considered brain MRI performed during the first week after birth. Altogether, 108 patients met the criteria and were included in the analysis.

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. The target rectal temperature was between 33 and 34 °C, maintained for 72 hours. All infants were ventilated throughout the cooling and rewarming phase.

Continuous morphine sedation was administered when the cooling was initiated. Phenobarbitone was given as the first line of anticonvulsant therapy if clinical or electrophysiological seizures were detected. 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 with 8-channel SENSE head-coils, at the former MR Research Center of Semmelweis University. Brain MRI protocol included the same sequences as in the SR study (3.1.2.).

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. 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. 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). Logistic regression analysis was based on individual scores.

3.2.2.4. Data analyses

Data recording and extraction were made using our novel in-house built asphyxia registry database developed in the iSORT framework.

The imaging signs of HIE and the presence and type of hemorrhage were evaluated on MRI. 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 AND/OR HIE related diffusion restriction or signal abnormalities on T1- and T2 weighted images were present. The following five subtypes of ICH were distinguished on MRI: subdural hemorrhage, subarachnoid hemorrhage, germinal matrix hemorrhage, intraventricular hemorrhage and intraparenchymal hemorrhage. The location, size and the presence/absence of mass-effect were assessed. 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.

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 or if there is proof for a relationship between late neurodevelopmental outcome and initial MRI findings.

We performed multivariate logistic regression 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 5 min Apgar score, baseline pH and age at MRI.

4. RESULTS

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

4.1.1. Imaging findings in HIE

MR imaging findings of 19 preterm and 87 term neonates were the following:

1. Diffusion-weighted images: Early signs of HIE were seen in 42% (n = 8/19) of the premature and in 32% (n = 28/87) of the term infants.

2. T1- and T2-weighted images: The late signs of HIE appeared less frequently, presumably due to effective therapeutic hypothermia and the timing of the MRI examination.

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%). In 4 term infants the MRS abnormality was the only sign of HIE.

4. T2*-weighted images: Hemorrhage affected about 35% of our patient population. In preterm infants subependymal-intraventricular hemorrhage occurred most frequently (n = 9/19). In term neonates intraparenchymal hemorrhage was present in 15% (n = 13/87) and subdural hemorrhage in 13% (n = 11/87), with the latter evolving probably due to traumatic delivery in most of the cases. Other types of extra-axial hemorrhages and sinovenous thrombosis were uncommon.

4.1.2. Implementation of a novel SR template for HIE

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.

4.1.3. Evaluation of the novel SR template for HIE

The HIE reporting template was easy to use, completing one report after 2 hours of training took approximately 1 - 5 minutes depending on the complexity of the imaging findings.

We performed iterative adjustments to the template during the feasibility study, by changing and adding descriptors and including an option to measure the detected signal abnormalities

Evaluating imaging patterns revealed that diffusion changes show a characteristic temporal evolution. 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.

4.2. Prognostication with early MRI in hypothermia treated asphyxiated neonates with HIE and/or ICH

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 early perinatal period (6.67%). 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.

The 108 subjects were divided into four groups based on the presence or absence of the MRI signs of ICH and HIE: Group1: Infants presenting neither the signs of HIE nor ICH. Group2: Patients without the imaging signs of HIE showing ICH. Group3: Both HIE and ICH is visible. Group4: Only HIE signs are present. Neurodevelopmental outcome results were registered for each patient.

4.2.1. Chi-square test and logistic regression analysis

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 (χ^2 = 13.025, df = 3, p = 0.0046) and MDI (χ^2 = 14.2673, df = 3, p = 0.0026).

4.2.2. Multivariate logistic regression analysis

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. Statistical analysis 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).

Regarding MDI, the unadjusted logistic regression analysis (χ^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 (χ^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, neither the 5 minute Apgar score, nor the pH, nor the time of MRI exam proved to be significant covariates for MDI or PDI.

5. CONCLUSIONS

5.1. 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 structured reporting template enabled fast recording of detailed and standardized information. It was found suitable for reporting HIE cases, moreover it uncovered time and location dependent evolution of diffusion abnormalities and pseudonormalization, suggesting its usefulness in clinical research applications. The characteristic temporal evolution of diffusion patterns of HIE further emphasizes the importance of the timing of MRI examinations. The feasibility study of the template also revealed high number of intracranial hemorrhages affecting this patient population, which was an interesting finding, not published yet.

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

The second part of our study attempted to assess the rate of ICH in a cohort of patients and 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.

The presence of ICH on early MRI has no significant effect on late neurodevelopmental outcome.

Intracranial hemorrhage took a remarkable share affecting approximately one-third (36%) of infants treated with hypothermia. The rate of ICH was higher than previously described 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 traumatic delivery, to asphyxia or to the cooling itself, and while the cooling-induced thrombocytopenia 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.

The presence of HIE signs on early MRI and MRS have more than six time higher odds for abnormal neurodevelopmental 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.

As 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.

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