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Brain MRI after therapeutic hypothermia in asphyxiated newborns: predictive value at one year of imaging features

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Abstract

Purpose: to compare early brain MRI using a composite imaging score and outcome at one year in asphyxiated newborns treated by hypothermia.

Methods

This retrospective study included for two years consecutive asphyxiated term newborns treated by hypothermia for hypoxic-ischemic encephalopathy, and who had brain MRI before day 8. Therapeutic hypothermia was initiated within the first 6 hours of life and continued for 72 hours. Imaging protocol included T1 and T2 sequences, diffusion-weighted imaging (DWI), evaluated with a specific composite score, and spectroscopy. Clinical evaluation was performed at one year of age, outcome was classified as favorable/unfavorable. The primary endpoint was the correlation between our MRI score and outcome with the definition of a threshold. The secondary endpoints were to find the most relevant criteria within the score and to evaluate objective signal measurements to support subjective criteria.

Results

Among the 33 included patients, 9 died during the first days of life, 20 had a favorable outcome, 4 an unfavorable one. MRI score was correlated to a poor clinical outcome ($p < 0.001$). Most of the criteria within the score and spectroscopy results were relevant ($p < 0.05$). Cerebral edema was objectively assessed by the signal intensity ratio of white matter compared to cerebrospinal fluid (CSF) on T2-weighted images ($p < 0.001$).

Conclusion

MRI score was predictive of neurodevelopmental outcome at one year. The most relevant criteria within the score were DWI abnormalities in basal ganglia and thalami and loss of white-cortical grey matter differentiation. Signal intensity ratio between white matter and CSF higher than 0.75 supports the presence of edema.

Keywords:

Brain MRI

Spectroscopy

Asphyxia

Hypoxic-ischemic encephalopathy

Therapeutic hypothermia

Newborns

Abbreviations:

MRI: magnetic resonance imaging

DWI: diffusion-weighted imaging

HIE: hypoxic-ischemic encephalopathy

WA: weeks of amenorrhea

PLIC: posterior limb of the internal capsule

BGT: basal ganglia and thalamus

CSF: cerebrospinal fluid

ADC: apparent diffusion coefficient

NAA: N-acetyl-aspartate

Cr: creatine

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1. Introduction

Neonatal encephalopathy is a relevant cause of death or delayed psychomotor development. The main cause is anoxo-ischemia [1,2], described as a defect in materno-fetal exchange leading to hypoxia associated with metabolic acidosis in the newborn. The sole clinical treatment in use is moderate hypothermia, which must be initiated within the first 6 h for newborns suffering of hypoxic-ischemic encephalopathy (HIE) in order to benefit from its neuroprotective role. Many previous studies demonstrated that therapeutic hypothermia allows decreasing death, short and long-term handicap with poor secondary effects [3–7].

Brain magnetic resonance imaging (MRI) in such cases helps to predict neurodevelopmental outcome in early or middle childhood [8–12]. It helps pediatricians to give information to the parents. These different studies described the lesions seen on MRI and several scores have been proposed [10,13–16]. The aim of this study was to analyze brain lesions seen on MRI and search for correlation with neurodevelopmental outcome at one year in such newborns. For this, we used a composite MRI score [10,15] including imaging features. MR spectroscopy and relative signal intensity ratios were also calculated on T1 and T2 images and compared to the clinical outcome.

2. Material and methods

2.1. Study design

Our study is a retrospective single-center observational study conducted in the University Hospital.

2.2. Ethics and data protection

This study was approved by our institutional review board (N° CE-GP-2021-08). An information letter was sent to all parents of patients who satisfied the inclusion criteria. They could indicate their refusal either by e-mail or by mailing back. Non-opposition was considered acquired after a month. The patients kept a right of withdrawal at any time of the study. This work shall comply with the framework for the protection of personal health data and the protection of privacy provided for in Article 65-2 of the amended Data Protection Act and the General Regulation on the Protection of Personal Data.

2.3. Population

Patients were identified from an internal clinical database. We included consecutive term newborns who were treated by therapeutic hypothermia, in the neonatal intensive care unit, for a moderate or severe HIE, and who then had a brain MRI, between January 1st, 2017 and December 31st, 2019.

The inclusion criteria were: term newborns (≥ 36 weeks of amenorrhea), weight at birth ≥ 1800 g, background of neonatal asphyxia, moderate or severe HIE according to the Sarnat score (II or III) [17], and at least one of the following criteria of the “Société Française de néonatalogie” [18] : Apgar score < 3 at five minutes or ≤ 5 at ten minutes of life, persistent resuscitation at ten minutes of life, acidosis: pH < 7 at sixty minutes, base deficit ≥ 16 mmol/L or bicarbonates < 9 mmol/L or venous lactates > 9 mmol/L at sixty minutes. Therapeutic hypothermia was initiated during the first six hours of life and continued for seventy-two hours. Brain MRI was performed within the first eight days of life, after the end of therapeutic hypothermia. Clinical evaluation was performed at one year of age for each alive child.

The exclusion criteria were: preterm newborns (< 36 weeks of amenorrhea), weight at birth < 1800 g, congenital malformation, genetic abnormalities or other pathology, no hypothermia, no available brain MRI.

2.4. Imaging protocol

Before hypothermia, brain ultrasonography was performed to check the absence of intracranial hemorrhage that would contraindicate hypothermia because of the risk of increasing the bleeding. Other abnormalities were also recorded, and resistive arterial indexes were measured. Global hypothermia was conducted thanks to a heating table (Criticoool ®). The target rectal temperature was 33.5 – 34.5 °C.

Brain MRI was performed before the 8th day of life and included at least the following sequences: axial and coronal T2, axial T2*, axial T1 (inversion recovery or spin-echo) or T1 bravo (3D T1 inversion recovery gradient echo), axial diffusion with ADC cartography, multivoxel spectroscopy (chemical shift imaging) with long echo time. MRI examinations were acquired on 1.5 or 3T MR systems of different brands: (1) 1.5-T Magnetom Avanto, Siemens Healthineers, Erlangen, Germany, (2) Achieva 1.5-T, Philips Medical Systems, Best, the Netherlands, (3) 3-T Discovery MR750wt, General Electric Healthcare, Milwaukee, WI, USA, (4) 1.5-T Aera, Siemens Healthineers, Erlangen, Germany. Table 1 summarizes the protocols and acquisition parameters for each system.

2.5. Imaging analysis

In a first step, an imaging score (ranged from 0 to 22) derived from Rutherford [10], given in table 2, was assessed by two independent radiologists (CB, JFC) blinded to clinical data.

Then, in addition to the MRI score, brain signal intensity in different regions of interest (ROI) was measured, in order to calculate the following ratios and appreciate the validity of the subjective results observed on the first step:

- T2 white matter/CSF: right and left white matter in front of the frontal horns of the lateral ventricles / cerebrospinal fluid (CSF),
- T1 progression: progression of signal to noise ratio (SNR) between the brainstem and basal ganglia and thalami (BGT), defined as follows:

T1 progression = (SNR BGT – SNR brainstem) / SNR brainstem, with

SNR = mean signal / $\sqrt{\text{std noise}}$,

Std = standard deviation.

We measured the signal in the brainstem in the anterior side of the cerebellar peduncles because it was the location where the signal intensity on T1 was the most constant.

- T1 BGT/CSF: measured in the place with the highest signal in the BGT,
- T2 BGT/CSF: measured with a ROI as large as possible within the thalamus,
- Apparent diffusion coefficient (ADC) was measured in specific regions of the brain: corpus callosum, right and left frontal and parietal white matter, right and left thalami.

The two radiologists' results differences were measured and compared. On one hand, if differences were less than 10%, the results average was used. On the other hand, if differences were greater than 10%, a new reading in pairs was carried out in order to find a consensus. If consensus was not possible to be found, a third measurement was performed. Then the average of the three measurements was considered.

Finally, MR spectroscopy was evaluated with the following ratios, considering the most relevant peak of lactate within the CSI grid: lactate/N-acetyl-aspartate (NAA) and NAA/creatine (Cr) within the same voxel.

2.6. Clinical evaluation during follow-up

The clinical outcome was defined as a clinical examination (OB), conducted thanks to Brunet-Lézine and Amiel-Tison scores, at one year of age for the living children. A favorable outcome was defined as a normal clinical evaluation. An unfavorable outcome was defined as death within the first days of life or delay in psychomotor development or motor/sensorial handicap.

2.7. Endpoints

The primary endpoint was the correlation between the imaging score and the clinical examination at one year of age, and the definition of a threshold. The secondary endpoints were the relevance of the criteria of the imaging score and the correlation between subjective criteria and measured ratios.

2.8. Statistical analysis

Software R, version 3.5.2, was used to perform statistical analysis.

Patients were divided into two unmatched groups according to their clinical outcome at one year.

Data were described by their medians and interquartile ranges (IQR) for quantitative variables and by their frequency and percentages for qualitative variables.

The non-parametric Wilcoxon-Mann-Whitney test was used to compare the quantitative variables. Qualitative variables were compared with either the Chi2 test (with or without Yates correction) or the exact Fisher's test, depending on the expected sample sizes. Correlations were analyzed using Spearman Test. Significance was defined by a threshold of p-value < 0.05.

We established a threshold for the imaging score. We determined the diagnostic performance of MRI for the clinical outcome at one year (sensitivity, specificity, positive predictive value, negative predictive value, and their 95% confidence intervals). Based on the Bayes theorem and according to our results, a 39.4 % prevalence of poor clinical outcome at one year was used for the calculations. The performance was analyzed according to ROC curves related to it.

Univariate analysis was performed for the criteria of the score. Multivariate analysis could not be performed with a backward stepwise selection given the small number of events.

3. Results

3.1. Description of the population

Between January 1st, 2017 and December 31st, 2019, 87 newborns were diagnosed with neonatal encephalopathy, 54 patients were excluded (most of them were not treated by hypothermia (n=24) or premature (n=11)) and 33 were included. In our population, 56.7% were female, the median term of birth was 39 weeks of amenorrhea (WA). The median weight at birth was 3210 g and most of the newborns were eutrophic (78.8%). Most of the babies were born out of the University Hospital (66.7%) and most of the time by C-section (78.1%). Fetal heart rhythm abnormalities were frequent (83.9%), and the etiology of the asphyxia was not found in many cases (45.5%).

For the statistical analysis, the patients were split into two groups: favorable or unfavorable outcome. There was no statistical difference between the two groups regarding the perinatal conditions (supplementary material table A.1).

In the 33 included patients, 9 died within the first days of life, 20 were alive with a favorable outcome at one year of age, 4 were alive with an unfavorable outcome: one child developed a West syndrome, one child had a psychomotor developmental delay (motor, cognitive, language), one child had spastic tetraparesis, and one child had hearing loss. There was no patient lost to follow-up. The population is described within the flowchart, figure 1.

In this population, no significant abnormality was present at the first brain ultrasonography.

3.2. Primary endpoint

Brain MRI was performed between the 4th and the 7th day of life, with an average of 5.6 days. MRI score was correlated to the clinical outcome: the score was 11 for children with unfavorable outcome (8 – 14) against 2 for children with favorable outcome (1.75 – 3), $p < 0.001$ (figure 2). We obtained the following ROC curve (figure 3) with area under the curve (AUC) = 0.9219. We set a threshold of 5. All but one patient with a score greater than 5 had an unfavorable outcome. All but one patient with a score below 5 had a favorable outcome. The sensibility was 85.4 % and the specificity was 91.5 %. Figure 9a-c shows a normal MRI with a zero score.

3.3. Criteria of the imaging score

Most of the criteria within the score were relevant (table 3). Loss of white/grey matter differentiation (figure 4a-e), white matter edema (figure 4a), T1 or T2 abnormalities of BGT (figure 4a-c) and BGT water diffusion restriction (figure 5c, d) were the most significant.

3.4. Objective results regarding ratios

In our series, the measure of progression of T1 signal in BGT, or measuring the ratio of T1 signal in BGT compared to CSF signal, did not increase the accuracy of the evaluation of a relatively high signal ($p=0.924$ and $p=0.970$). Subjective BGT T2 signal abnormalities did not correlate with the calculation of the T2 signal ratio between BGT and CSF ($p=0.116$).

The presence of cerebral edema found during the first subjective evaluation appears to be objectively assessed by measuring the ratio between the white matter signal compared to CSF (table 4 and figure 4a).

On the right side of the brain, the area under the curve (AUC) was 0.8558 (figure 6). The threshold was 0.75. Sensibility was 69.7 % and specificity was 80.6 %.

On the left side of the brain, the AUC was 0.86 (figure 7). The threshold was 0.725. Sensibility was 86.0 % and specificity was 69.3 %.

As this is a confirmatory diagnostic test, we searched the threshold with the best specificity, so we propose to use the threshold of 0.75.

3.5. Spectroscopy

The results of the spectroscopy were significant: the mean lactate/NAA ratio was 1.33 (IQR = 0.82 - 2.06) for unfavorable outcome against 0.52 (0.27 - 0.69) for favorable outcome ($p = 0.008$). The NAA/Cr ratio was not significant ($p = 0.09$).

3.6. Univariate and multivariate analyses

The results of the univariate analysis are given in supplementary material (table A.2). The most relevant criteria were, in decreasing order: BGT diffusion abnormalities (OR = 42, IQR = 4.2 - 439.5), the loss of white-grey matter differentiation (OR = 30, IQR = 4.3 - 210.7), the increase of lactate/NAA ratio in spectroscopy (OR = 26, IQR = 1.4 - 511) (figure 5e and figure 9d), BGT T2 abnormalities (OR = 20, IQR = 53.1 - 132.3), the loss of T1 hypersignal of the posterior limb of the internal capsules (PLICs) (OR = 15, IQR = 1.40 - 161.1) (figure 8a-c and figure 4c), the presence of an edema (OR = 10, IQR = 4.3 - 210.7), the presence of a T1 hyperintensity in BGT (OR = 9, IQR = 1.7 - 47.7) and white matter diffusion abnormalities in more than 1 location (OR = 8, IQR = 1.4 - 45.8) (figure 4f, g and figure 5a, b). Multivariate analysis did not give any significant result, given the low number of subjects of the cohort.

Finally, resistive arterial index measured with initial brain Doppler sonography was not correlated with the outcome of babies.

4. Discussion

The prognosis of children with HIE has been significantly improved by therapeutic hypothermia. However, it remains a difficult situation due to the high risk of death, delayed psychomotor development, or disability. Pediatricians have several tools to predict the outcome of children and thus to adapt initial care: clinical scores, biology, electroencephalogram. Early brain MRI post-hypothermia constitutes another tool that has already proven its diagnostic and prognostic performance. Imaging score related to MRI may help its accuracy.

4.1. About the imaging score,

Into our cohort, the imaging score was statistically related to clinical outcome at 1 year of age. Our results agree with those of the literature. The performance of the MRI score has already been shown in the article by Meyer-Witte [15], derived from the Rutherford score [10]. Other scores have been used in the literature with comparable results [13,14,16]. We observe once again the value of a reproducible score, which is also relevant due to its simplicity, reliability, non-invasiveness, acceptable cost, and impact in treatment.

4.2. About the criteria on the MRI,

Most of the individual MRI criteria were related to outcome: BGT diffusion abnormalities, the loss of white-grey matter differentiation, BGT T2 abnormalities, the loss of T1 high signal of the PLIC, the presence of brain edema, the presence of a T1 high signal in BGT, white matter diffusion abnormalities in more than one location, T1 high signal within the cortex. Their combination increased their relevance. The increase of lactate/NAA ratio in spectroscopy was also related to outcome.

Some of these criteria (the loss of T1 high signal of the PLICs, T1 or T2 signal abnormalities in BGT or white matter and cortical involvement) were already used in the score of Rutherford [10]. These abnormalities were also described by Shankaran et al. [11] and were related to intellectual quotient (IQ) in middle childhood. Tharmapooopathy [19] used the Rutherford score compared to clinical outcome at 18 months of age and found a sensibility of 0.95 and a specificity of 0.94. Our score adds the results of DWI.

- We observed that the most relevant criterion was water restriction in BGT. The importance of diffusivity decrease in BGT was also shown by Rutherford in 2004 [20] and other authors such as Alderliesten et al. [8], Bednarek [21] or Meyer-Witte [15]. This is in relation to cytotoxic edema secondary to acute ischemia, but this feature could change with the delay between the end of hypothermia and MRI performance.

- The loss of white-cortical grey matter differentiation may be due to edema of subcortical white matter associated with a thickening of the cortex, blurring the white-grey matter junction on T2-WI [22].

- T2 signal abnormalities of basal ganglia can be a high or low signal. One hypothesis is that high signal is due to edema, whereas low signal indicates the permanent nature of the lesions [23].

- The PLICs are often injured. This is probably because of the increased metabolic rate of the corticospinal tract induced by early myelination [24]. It is therefore very sensitive to energy deficiency. Another cause can be glutamate excitotoxicity: Deng showed that in the developing brain [25] the myelinating oligodendrocytes were very sensitive to hypoxia and one of the causes was increased excitotoxicity due to glutamate. Indeed, dead or injured cells release glutamate and create excitotoxicity. Let's notice that in a rat model, NMDA receptor blockade was efficient against white matter injury in asphyxiated newborns [26]. Kukley showed that the release of neurotransmitters is not confined to the synapses of the grey matter. The release of glutamate is also present along the axons and it is captured by the receptors on the immature oligodendrocytes in the white matter [27].

Rutherford [28] showed 20 years ago that lesions of the PLICs were related to poor neurodevelopmental outcome at one year of age with very good predictive value (Se = 0.90, Sp = 1, PPV = 1, NPV = 0.87). In this original article, she described normal PLIC as physiological T1 hyperintensity in at least one external third of the limb or a smaller area of T2 hypointensity (figure 8a-c and figure 9a, b). Other studies, as recently Procianoy et al. [29], found that PLICs lesions were correlated to a poor motor, cognitive and language outcome. Although Barkovich described these abnormalities as delayed myelination, according to Rutherford they seem secondary to acquired changes in myelination, caused by edema or infarction within the motor cortical area.

- Presence of brain edema can be explained by secondary failure of the Na/K pumps [30] and later vasogenic edema [22].

- T1 hyperintensity of BGT may be explained by several causes: necrosis [23,31], capillary proliferation happening within hours after asphyxia, and shortening T1, and the presence of lipids after membrane breakdown. Rutherford also explains that BGT have a high metabolic rate, like the corticospinal tract, because of myelinating, and is therefore very sensitive to asphyxia. Moreover, this region presents a high proportion of excitatory neurotransmitters [31].

- White matter diffusion abnormalities happen in case of moderate but prolonged ischemia (cf. infra).

- T1 high signal of the cortex may be explained by laminar necrosis (figure 4c, d, e). Castillo correlated in 1996 brain MRI to pathology and showed that T1 high signal in laminar necrosis was due to the presence of lipid-rich macrophages after necrosis of deep layers of the cortex [22]. Edema of underlying white matter was often associated. The resorption of the necrotic material begins 7 days after ischemia [32].

- Punctate white matter abnormalities and extra-axial bleeding did not seem related to outcome in our series. Punctate lesions are rarely secondary to petechial parenchymal hemorrhages in this population [33]. Hayman rather suggests an ischemic etiology in asphyxiated newborns. They often lead to cerebral palsy, especially when they are located around the corticospinal tract. Some postmortem examinations show early gliosis in newborns with punctate high signal T1 lesions of white matter but normal susceptibility-weighted imaging (SWI) [34].

Intracranial hemorrhages are quite common after vaginal delivery and most of the time asymptomatic. They can also be a side effect of hypothermia in cooled newborns. In the same way, a recent review showed that intracranial hemorrhage was often observed in this population but was not related to long-

term outcome [35]. Castillo reported one case of white matter petechial hemorrhage after ischemia, seen on pathology study, perhaps due to breakdown of the blood-brain barrier and extravasation of blood, but this was not visible on MRI [22].

4.3. About the subjective criteria and ratio measurements,

- Proportion of water is higher within the newborn brain compared to the adult brain and therefore is responsible for the overall T2 high signal. Therefore, the subjective assessment of cerebral edema is difficult. In our series, the presence of this edema was supported by measuring the signal ratio between white matter and CSF. The threshold of 0.75 adds some confidence.
- Measuring ADC in many parts of the brain did not increase significance to the visual aspect seen on the diffusion sequence (trace image) in our series. The low correlation rate between ADC measurements and clinical outcome can be explained by two hypotheses: the low number of patients or the diffusion evolution over time. The ADC decreases after the ischemic event until day 3-4, then increases to normal values at day 7-14, and then increases to a plateau at several weeks. The diffusion signal also changes over time, but the top of the curve seems generally stable between day 3 and day 8, the period during which the MRI is performed [36].
- In our series, measuring progression of T1 signal in BGT, or measuring T1 signal ratio between BGT and water, was not able to support the presence of relative high signal. This is probably due to the heterogeneity of our parameters in relation to different MRI devices. Indeed, many types of T1 sequences have been used in our cohort: axial T1 inversion recovery, T1 bravo (3D inversion recovery T1 gradient echo), or axial T1 spin echo. Signals measured in these different sequences were not comparable. We propose to homogenize the T1 sequences in order to improve the reproducibility of the readings while maintaining good contrast on each sequence. Thus, we propose to preferentially use the 3D T1 ultrafast GRE sequence or its equivalent which presents the advantage of good contrast and comparable signal measures (all positive). In the literature, the most frequent sequences used were T1 SE [10,11,13,15,29,37,38] but Rutherford reported that the lesions were more evident on T1 IR [28]. According to Barkovich [39], the best T1-weighted images come from 3D gradient-echo volumetric sequence at 3T (such as SPGR, MPRAGE...). If not available, T1 IR also gives excellent contrast, using TR/TE = 600/20 ms and TI = 750 ms.
- Subjective basal ganglia T2 signal abnormalities did not correlate with measurement of the T2 signal ratio between basal ganglia and CSF. This is probably because T2 signal abnormalities could be both high and low signal, as observed in our cases.

4.4. About the spectroscopy,

For the spectroscopy, we used the CSI technique with a long echo time. Using multivoxel spectroscopy decreases the quality of the spectrum and increases artifacts, compared to monovoxel spectroscopy, but such acquisition allows a larger study of different structures with only one acquisition. Long echo time allows to evaluate lactate peak and decreases artifacts. On the contrary, a study with a short echo time permits the detection of glutamate peak, elevated in acute hypoxic circumstances. Hypothermia decreases the peak of glutamate because of the decrease of metabolic rate and thus decrease of excitatory neurotransmitters release in the synaptic cleft [40].

In our study, the lactate/NAA ratio was significantly related to the outcome, increased in unfavorable cases. While Cady was demonstrating that asphyxia in piglets was correlated with changes in proton and phosphorus spectroscopy [41], the correlation between low NAA or high lactate and clinical outcome in human newborns was first shown in the 90s' by Groenendaal [42]. Some authors proposed a threshold of 0,4 for the lactate/NAA ratio [8], or 0,3 [15]. The threshold of 0.3 was not significant in our series.

Whereas lactate has long been considered as a waste product from lactic acid fermentation under anaerobic metabolism, it may be an attractive energy source for neurons [43]. Actually, a newborn

brain is said to differ from an adult brain because of its limited glucose requirements. Thus, alternative substrates such as lactate would preferably be used. The lactate transfer pathway would preferentially be directly from the blood capillary to the neuron, with the existence of a second path, with transfer of lactate from the bloodstream to the astrocyte, then from the astrocyte to the neuron via the lactate-shuttle. In the above-mentioned study, only after hypoxic-ischemia, pups lactate injection reduced brain lesions visible in diffusion. Here, almost all patients had a relevant increase in lactate concentration on spectroscopy compared to NAA (all but 4 patients had a lactate/NAA ratio ≥ 0.3): could it be an adaptive capacity of neurons, using lactate as a substrate, produced by other cells of the body under anaerobic conditions, and ending up in the bloodstream?

4.5. Biases and strong points

Our cohort has only a small number of patients, but it is consistent with the incidence of the disease. Moreover, despite this reduced number, the presence of significant results is encouraging and leads to highlighting the statistical strength of the studied elements.

There is no imaging gold standard to compare our brain MRI. For the statistical analysis, we used the clinical examination at one year as a gold standard, as the clinical outcome is the important issue for children.

One bias in our study could be related to the presence of multidisciplinary consultation meetings (MCM), during hospitalization in intensive care unit, which may be the source of reverse causal bias. Indeed, each child who died was so after a decision in MCM to stop active therapy. However, the decision of MCM did depend on multiple criteria, including clinical, biological, and electrophysiological elements, in addition to imaging results.

Moreover, the lesions of newborns were studied on 4 different MRI machines, with different sequence parameters. This did not lead to difficulties for T2-WI or DWI, because the sequences were comparable, but the T1 sequences used were very heterogeneous (cf supra).

Time of realization of MRI was between day 4 and day 7, with a median age of 5,6 days. It cannot be shorter because the MRI must happen after rewarming, and if made too early may underestimate lesions. Results observed with DWI may be altered with a longer delay.

Another limitation of our study is a relatively short follow-up time. However, other previous studies have already shown that MRI results and neurological examination in early childhood (12-24 months) correlate with clinical outcome in middle childhood (6-8 years) [7,11,44].

One of the strengths of our study is related to the absence of patient follow-up loss. The risk of classification bias is limited because a majority (19 out of 24 survivors) of our patients were seen at one year of age by the same pediatrician. The other ones (5) were followed by pediatricians accustomed to HIE sequelae.

4.6. Physiopathology

An epidemiological study can only show an association, not a causality. However, functional anatomy and physiology allow us to support the association between MRI score and clinical outcome. Indeed, we know that lesions due to a sudden event preferentially concern the basal ganglia, while prolonged events affect the white matter and the cortex because of the adaptation of cerebral circulation from anterior to posterior [23,45]. Besides, failure of Na/K ATPases pumps secondary to energy deficiency is responsible for brain edema [30]. Finally, cytotoxic edema is early visible on the diffusion sequences [36].

5. Conclusion

In this retrospective study, we show the prognostic relevance of one MRI composite score derived from the Rutherford score. We also observed that the subjective cerebral edema presence assessment

can be supported by measuring the signal in white matter compared to CSF, which could make it possible to standardize practices.

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Tables and figures

Table 1: MRI parameters. Sag: sagittal, ax: axial, coro: coronal, SE: spin-echo, GE: gradient-echo, IR: inversion-recovery, TE: time of echo, TR: time of repetition, TI: time of inversion, FoV: field of view, CSI: chemical shift imaging.

Table 2: MRI score. CSF: cerebrospinal fluid, PLIC: posterior limb of internal capsule, BGT: basal ganglia and thalami.

Figure 1: flow chart of the population included in the study, Bordeaux, 2017-2019.

Figure 2: MRI score of patients with favorable (left) and unfavorable (right) outcome.

Figure 3: ROC curve of MRI score.

Table 3: criteria of the imaging score. CSF: cerebrospinal fluid, PLIC: posterior limb of the internal capsule, BGT: basal ganglia and thalami, NR: not reached.

Figure 4: child n°13. Unfavorable outcome.

Birth at 41 WA + 6 days by cesarean section for fetal bradycardia. Context of decrease of fetal active movements for 2 days. Analysis of the placenta revealed ischemic and thrombotic changes. Death at day 11.

MRI on day 7. Axial T2 (a), axial T1 spin-echo (b), axial T1 inversion-recovery (c, d, e), diffusion (f), ADC mapping (g). MRI score = 19. White matter/CSF ratio in the left part of the brain = 0.83.

Presence of cerebral edema, loss of white-cortical grey matter differentiation in several locations, T2 low signal and T1 high signal in the BGT, loss of PLICs T1 high signal, cortical T1 high signal, T1 punctate abnormalities of white matter, intra-parenchymatous hemorrhages, restriction of diffusion in the corpus callosum and in some areas of the cortex.

Figure 5: child n°6. Unfavorable outcome (death). Diffusion (a, c) and ADC mapping (b, d): water restriction in the corticospinal tract (a, b) and in BGT and optic radiations (c, d). Spectroscopy (e): lactate/NAA ratio = 1.92 in the left thalamus.

Table 4: Ratios of white matter/corticospinal fluid when edema is present or absent. IQR: inter-quartile range.

Figure 6: ROC curve of white matter/cerebrospinal fluid ratio on the right part of the brain.

Figure 7: ROC curve of white matter/cerebrospinal fluid on the left part of the brain.

Figure 8: child n°2. Favorable outcome. Axial T1 spin-echo (a), axial (b) and sagittal (c) reconstructions of T1 bravo. Physiological high signal of the PLICs is better seen on T1 bravo sequence. The corticospinal tract is visible on the sagittal sequence.

Figure 9: child n°12. Favorable outcome. Axial T2 (a), axial T1 inversion-recovery (b), diffusion (c), spectroscopy (d). Normal MRI. Score = 0. Lactate/NAA ratio increased at 0.53 in the white matter.

- Patients with neonatal encephalopathy
 - carried out in University Hospital Center of Bordeaux
 - from January 2017 to December 2019
- n = 87

- Non-inclusion and exclusion criteria
- Early death before the end of the hypothermia protocol

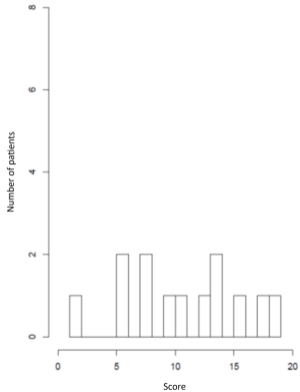
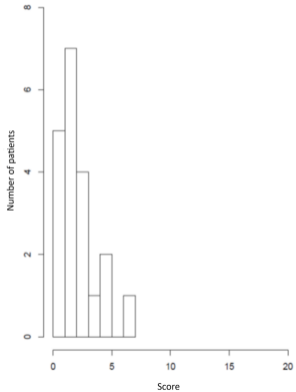
Patients included n = 33

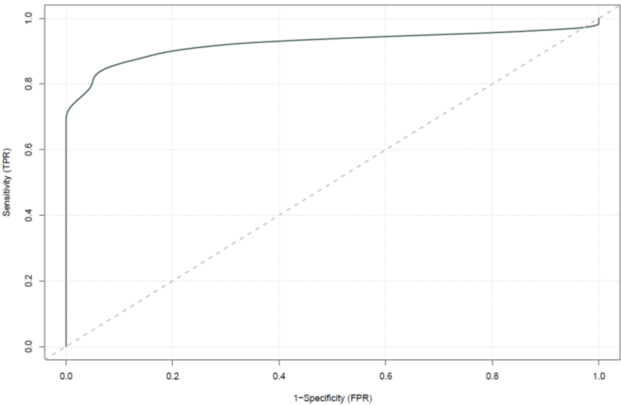
Patients dead n = 9

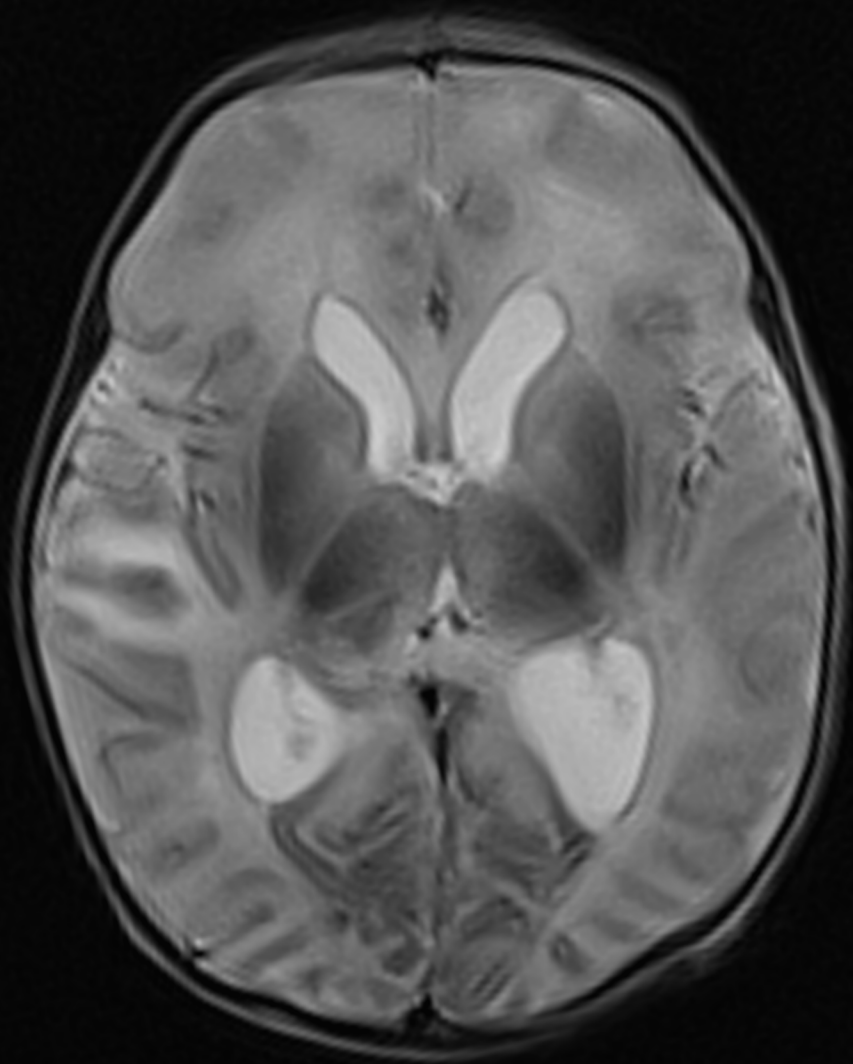
Patients alive n = 24

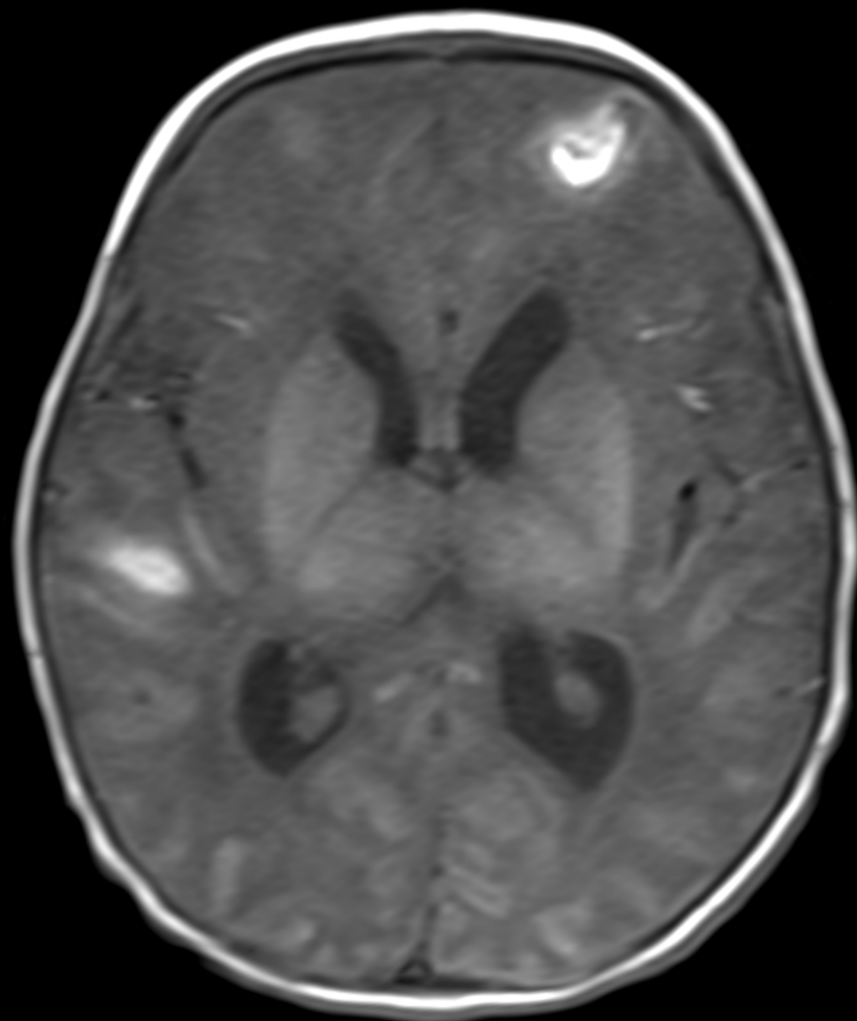
Unfavorable outcome
n = 4

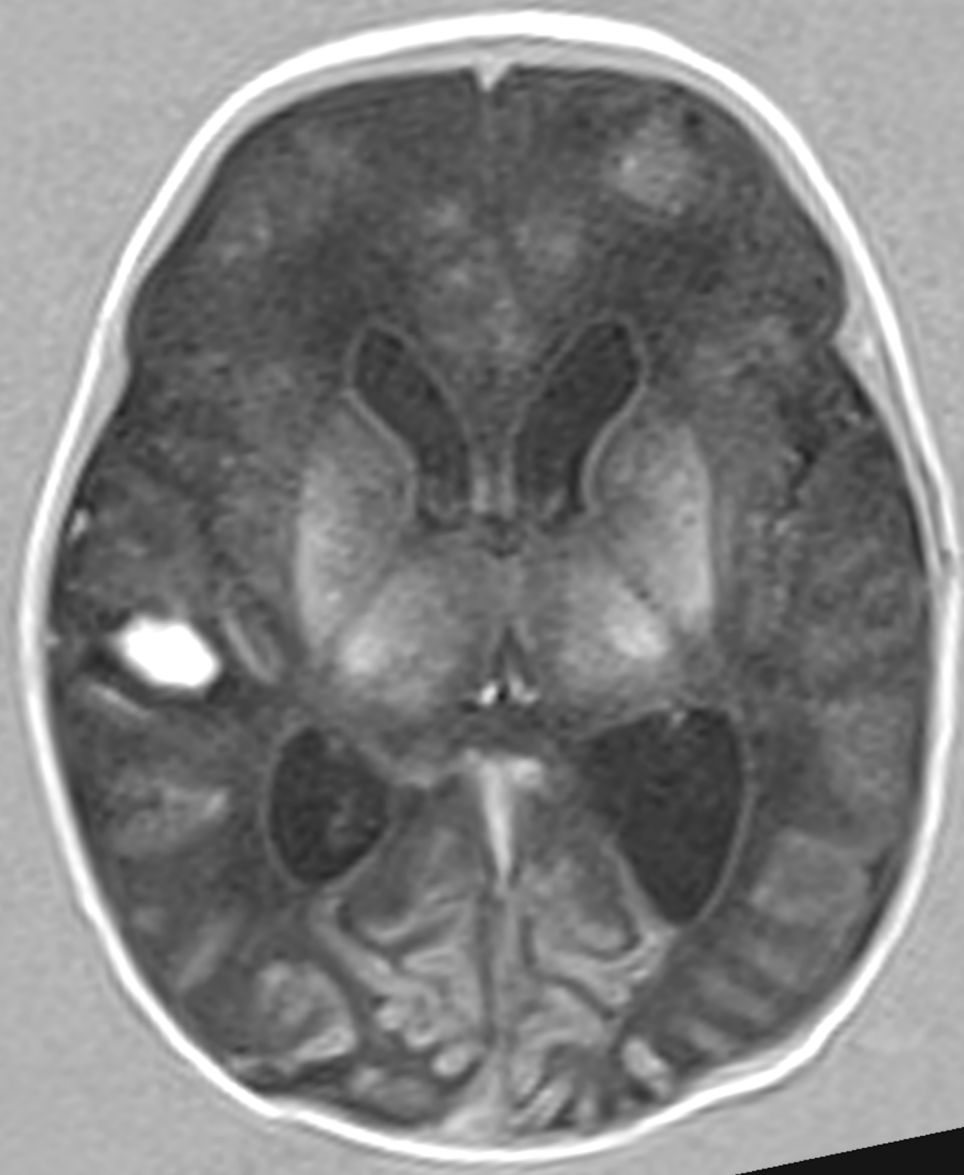
Favorable outcome
n = 20

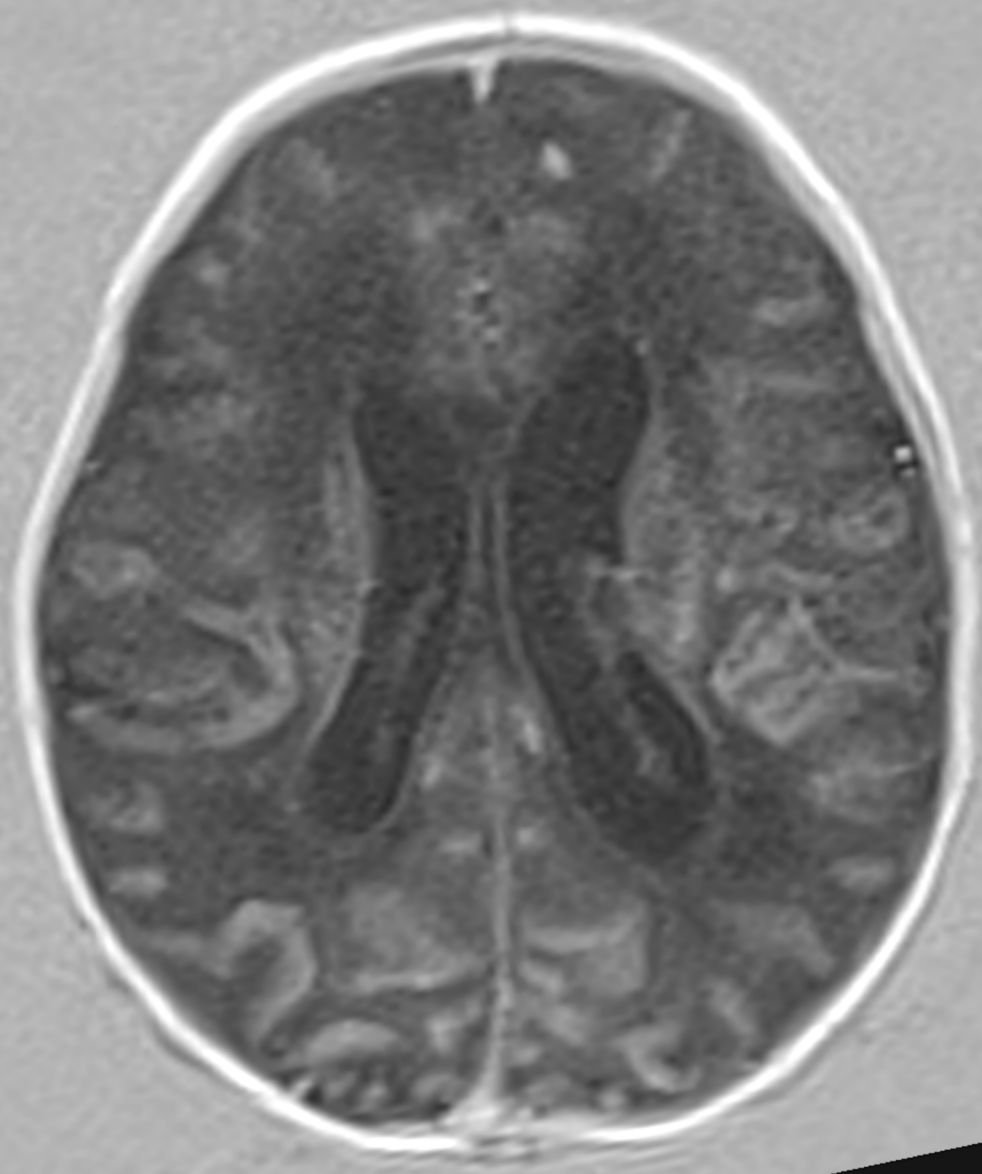


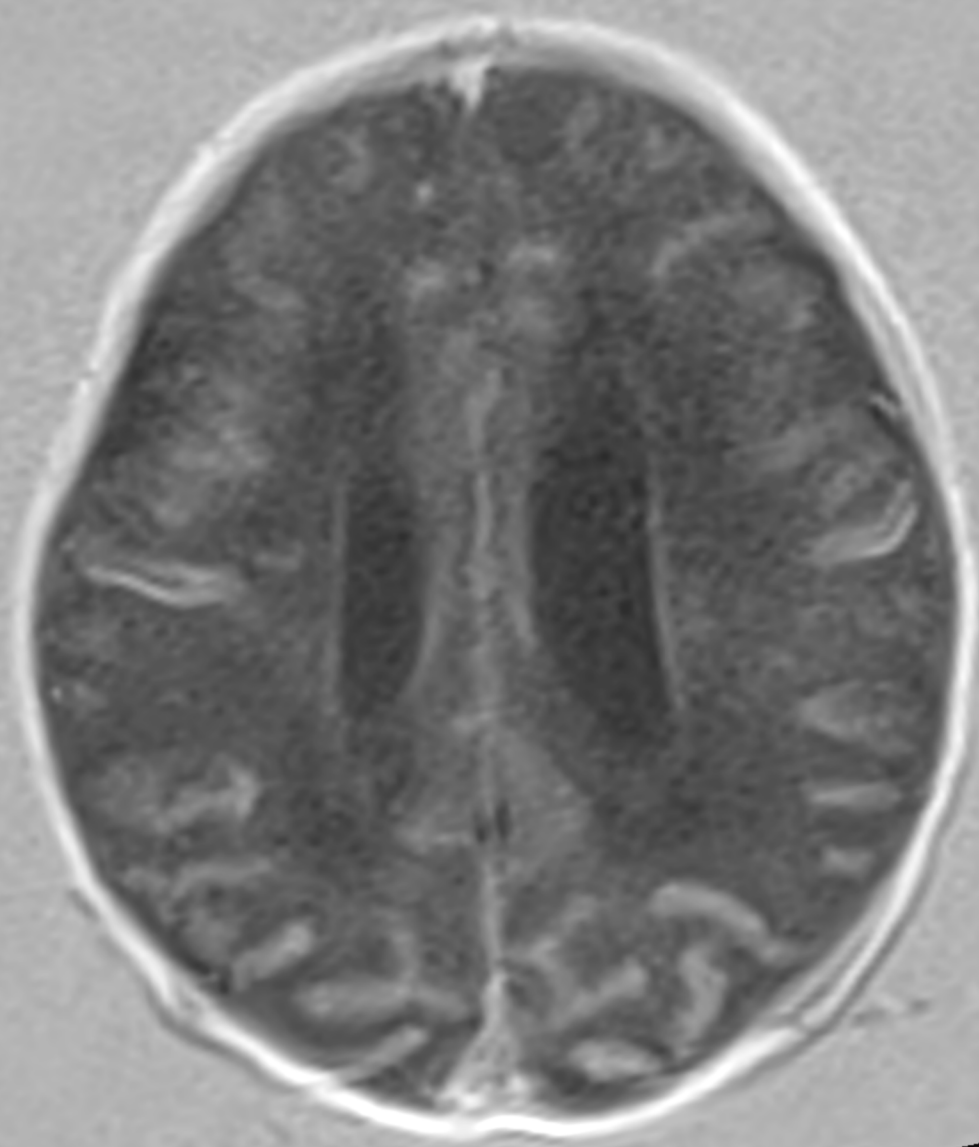


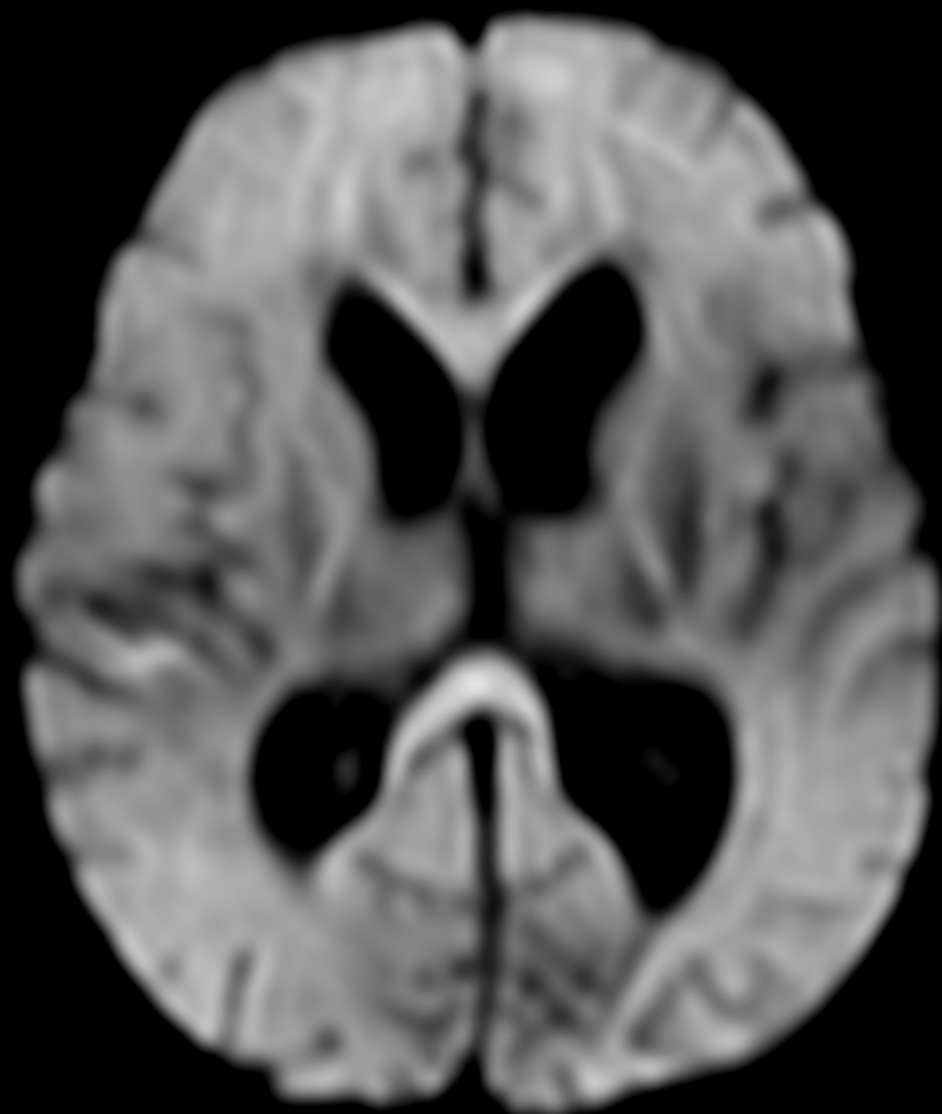


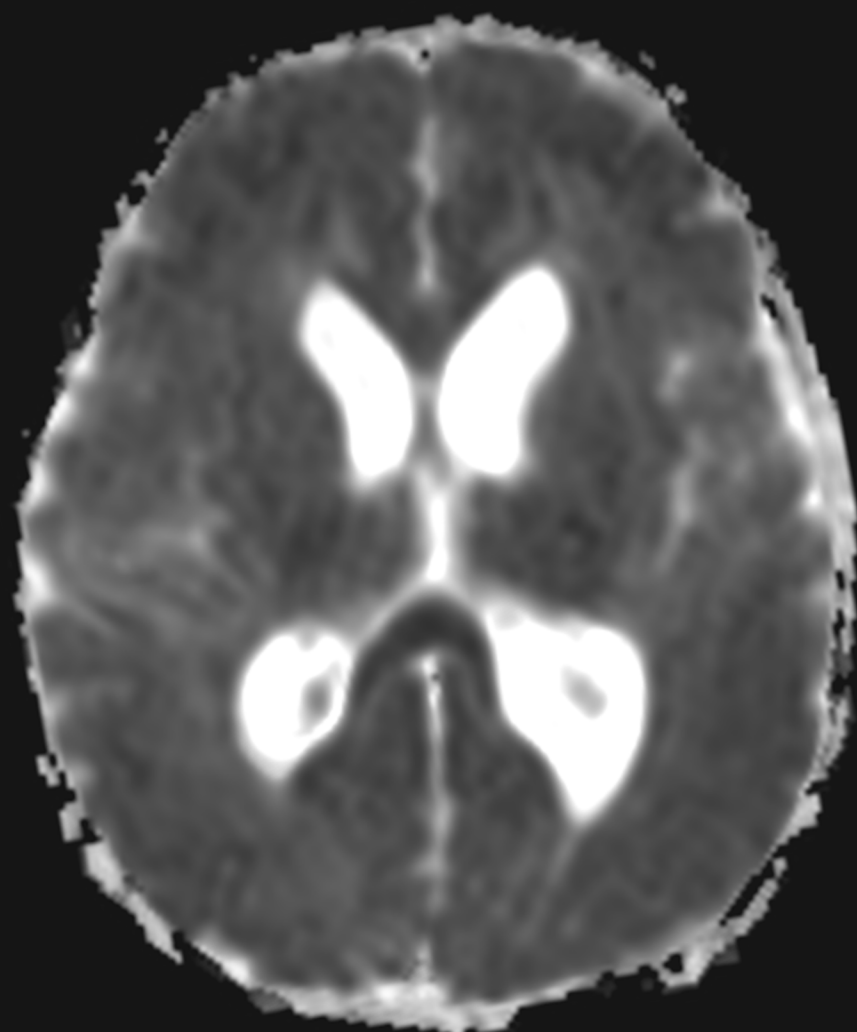


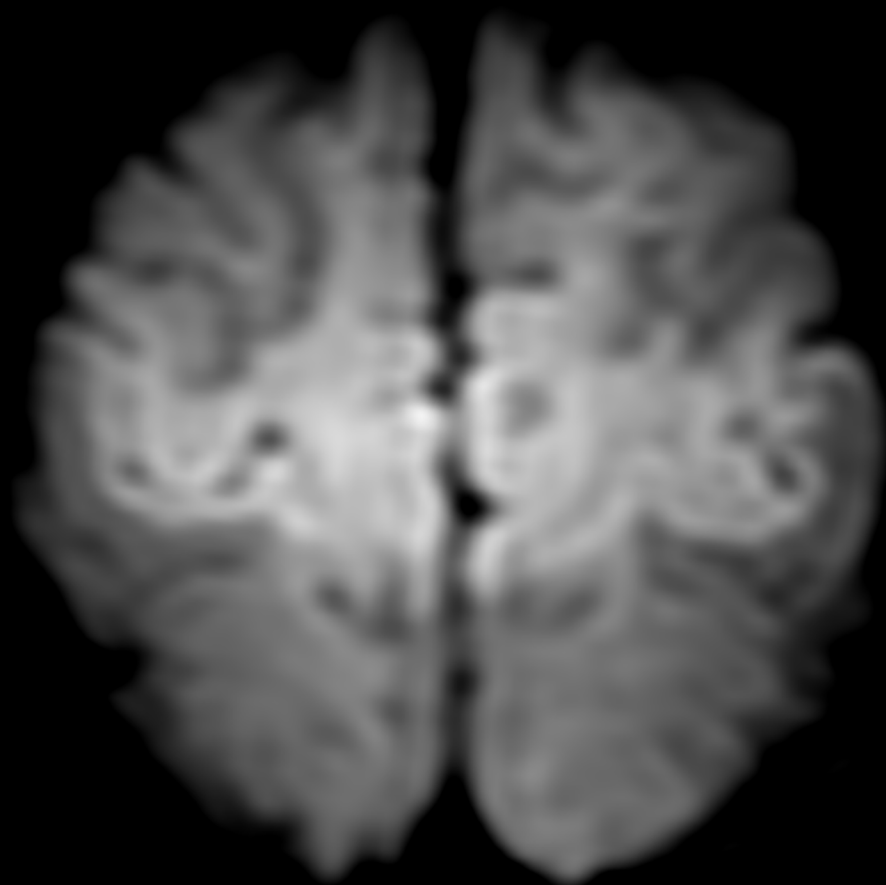


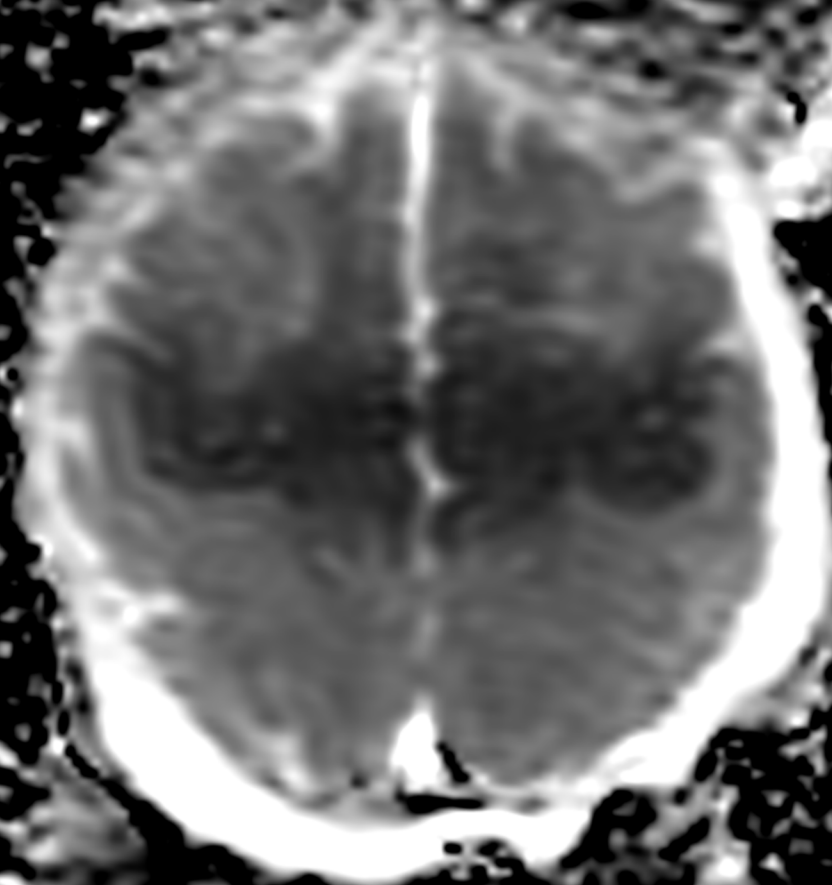


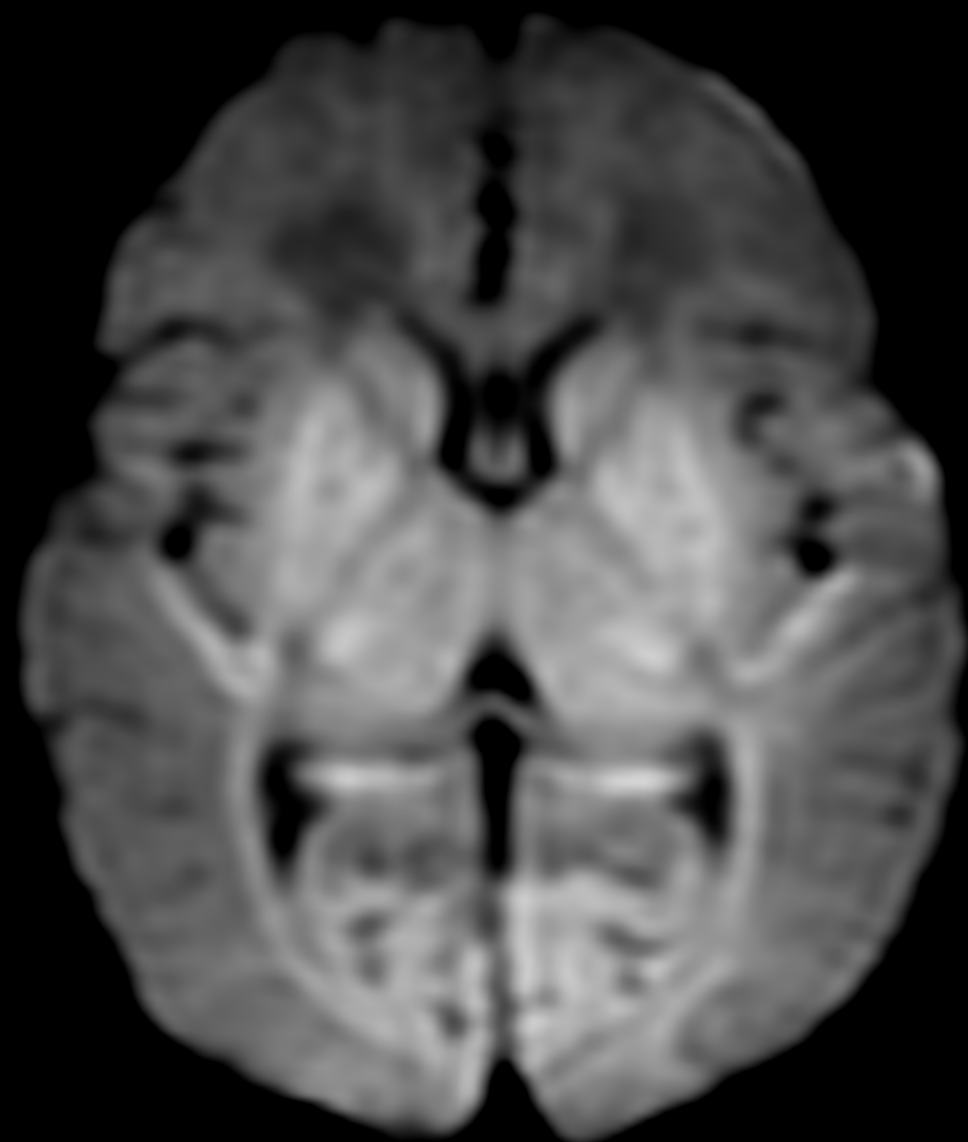


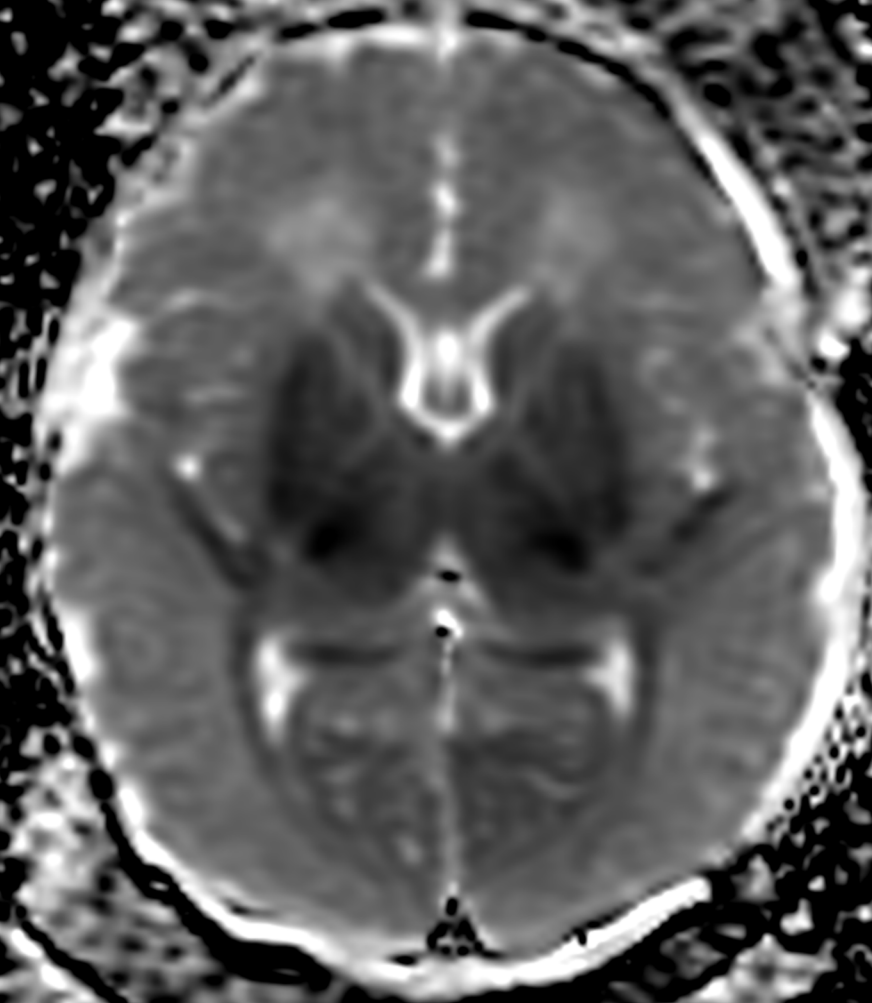




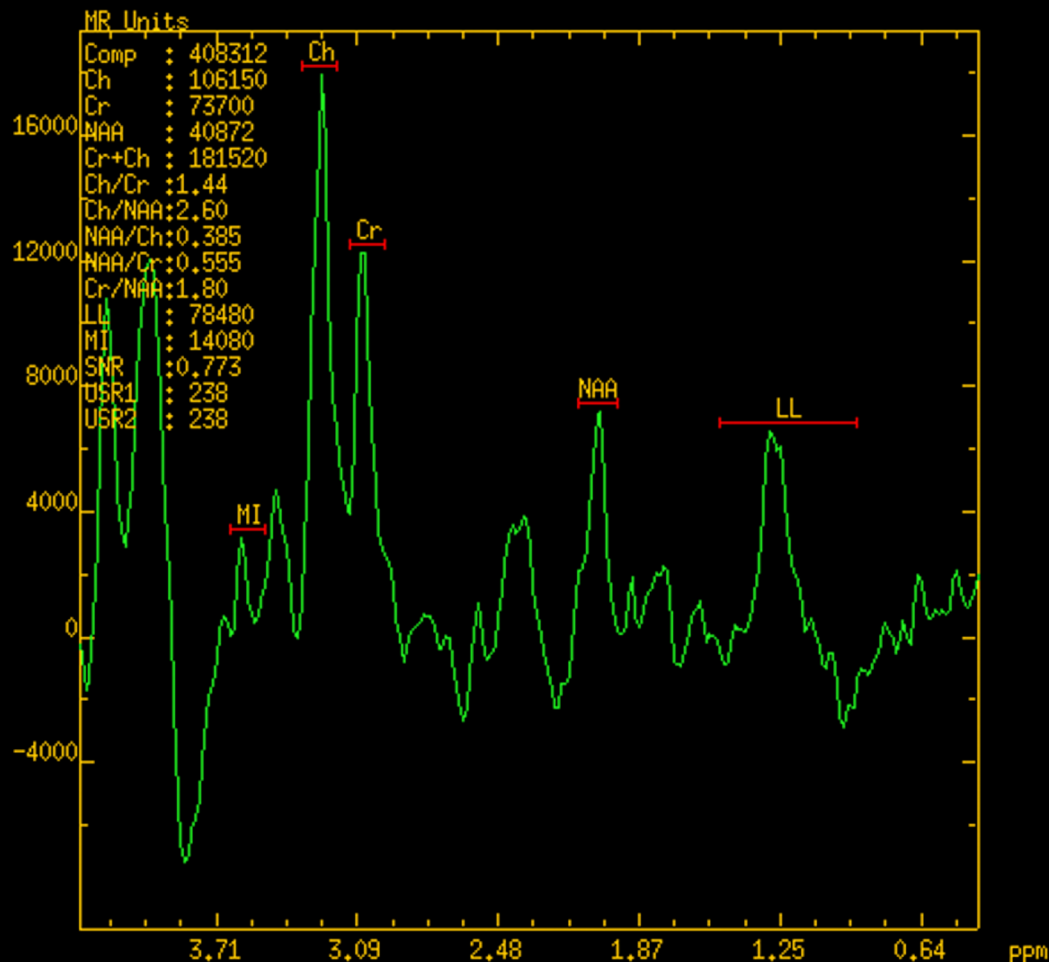


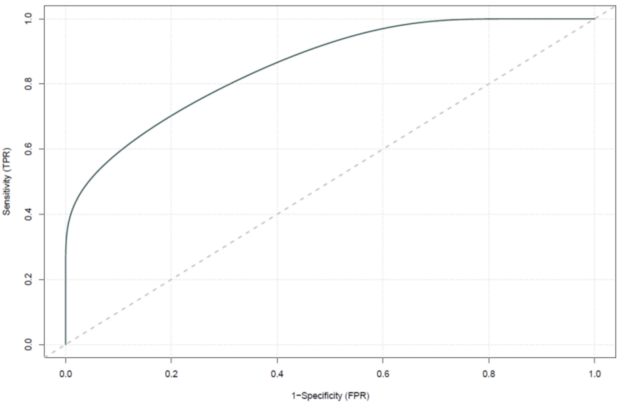




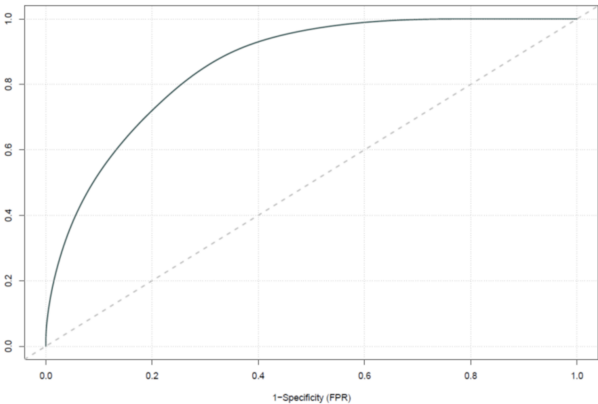


SPECTRUM

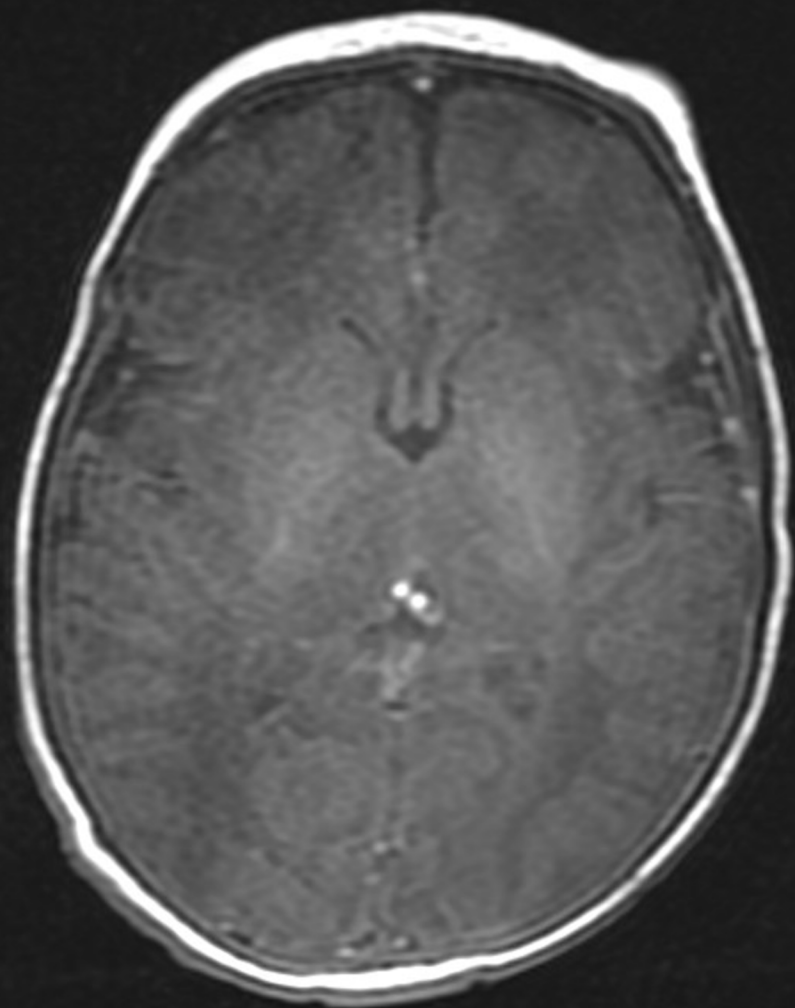


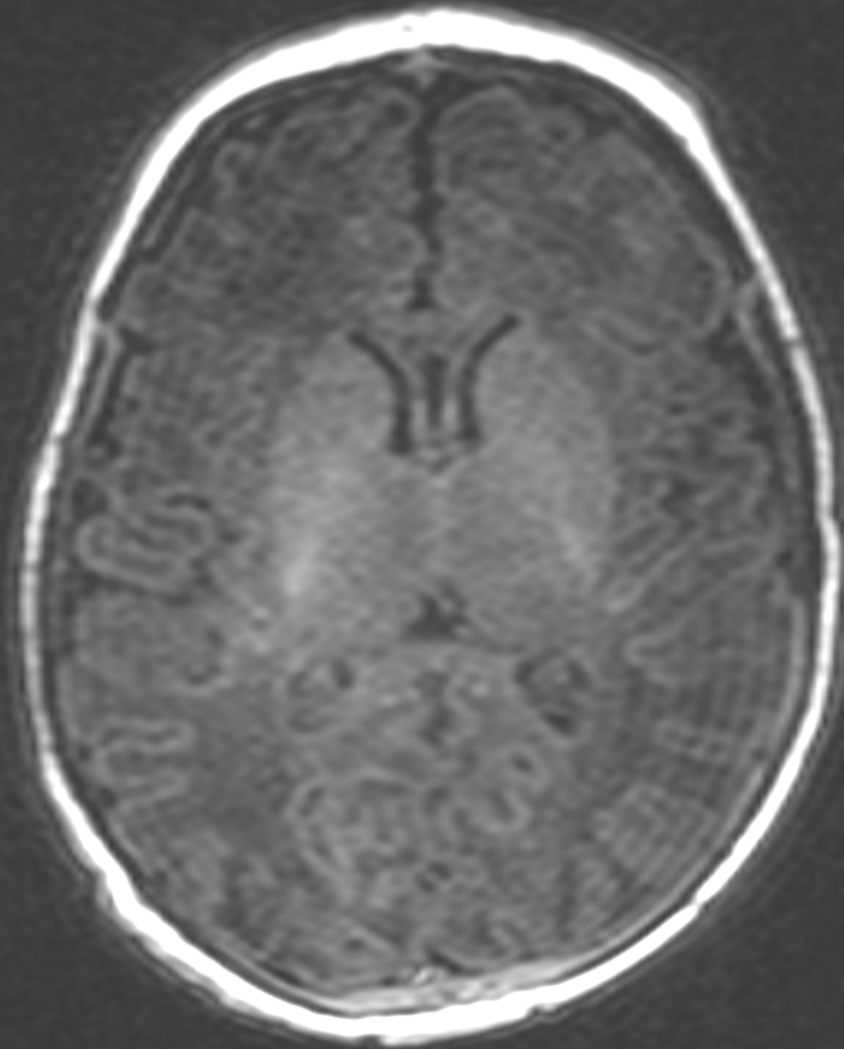


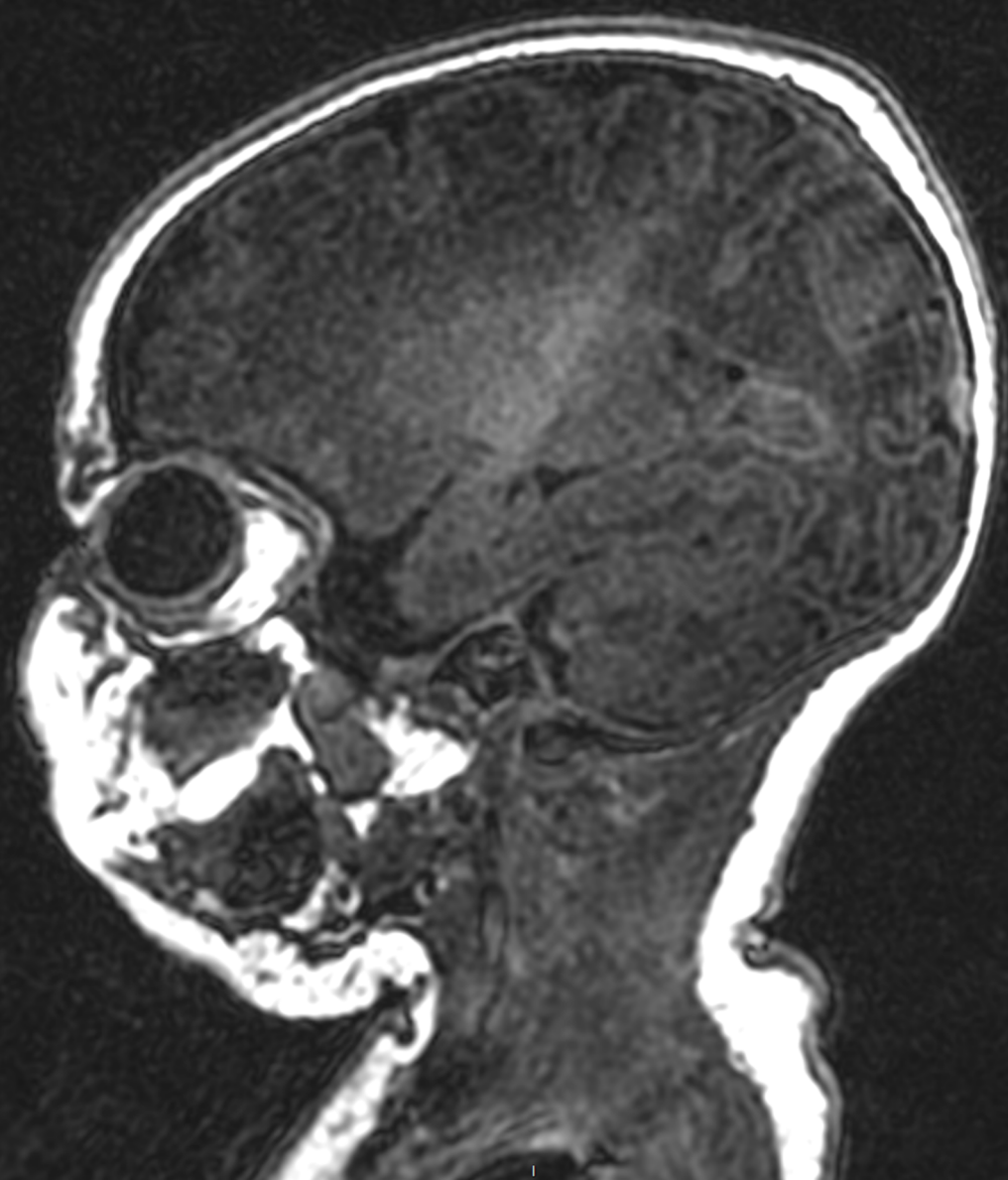
Sensitivity (TPR)

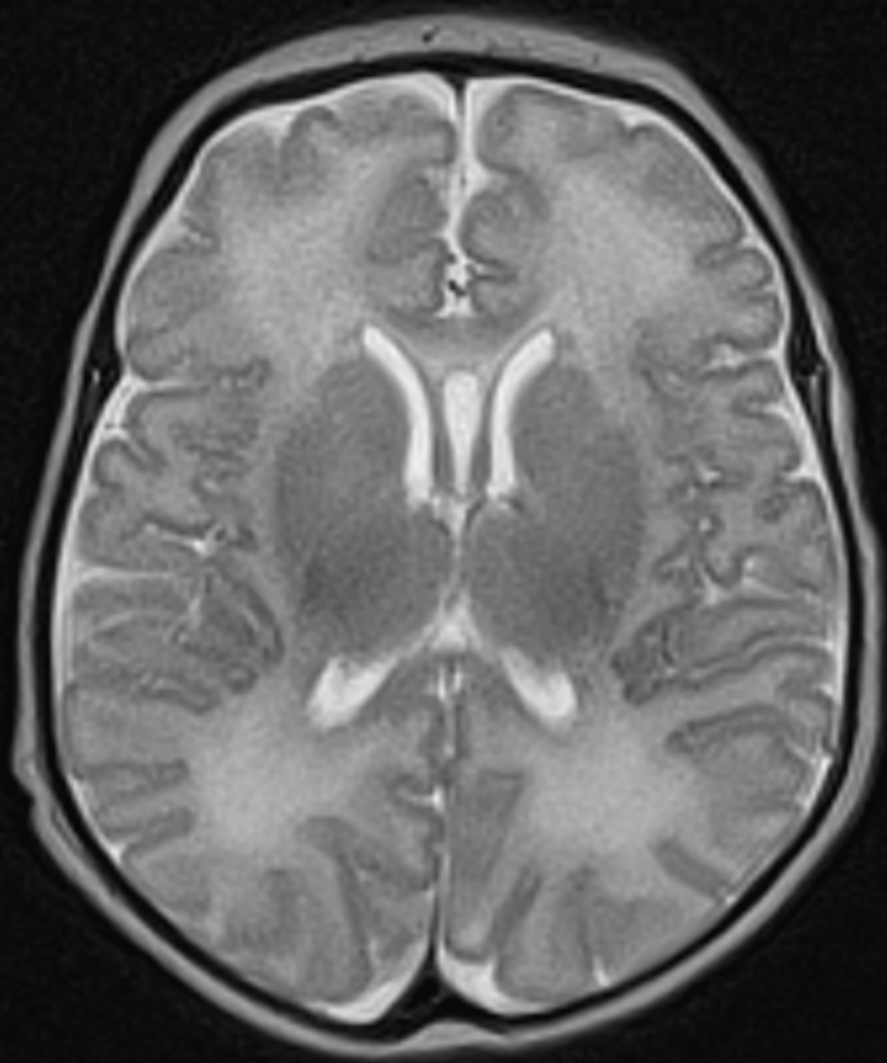


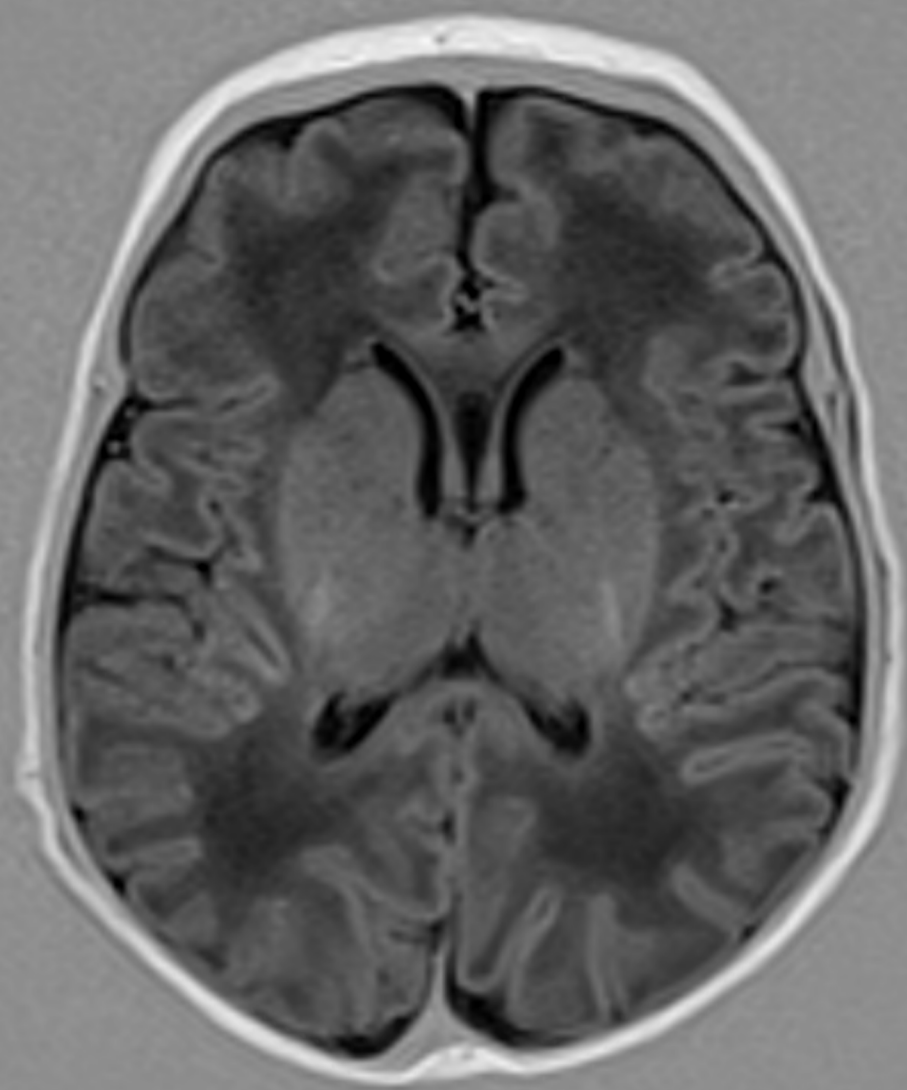
1-Specificity (FPR)

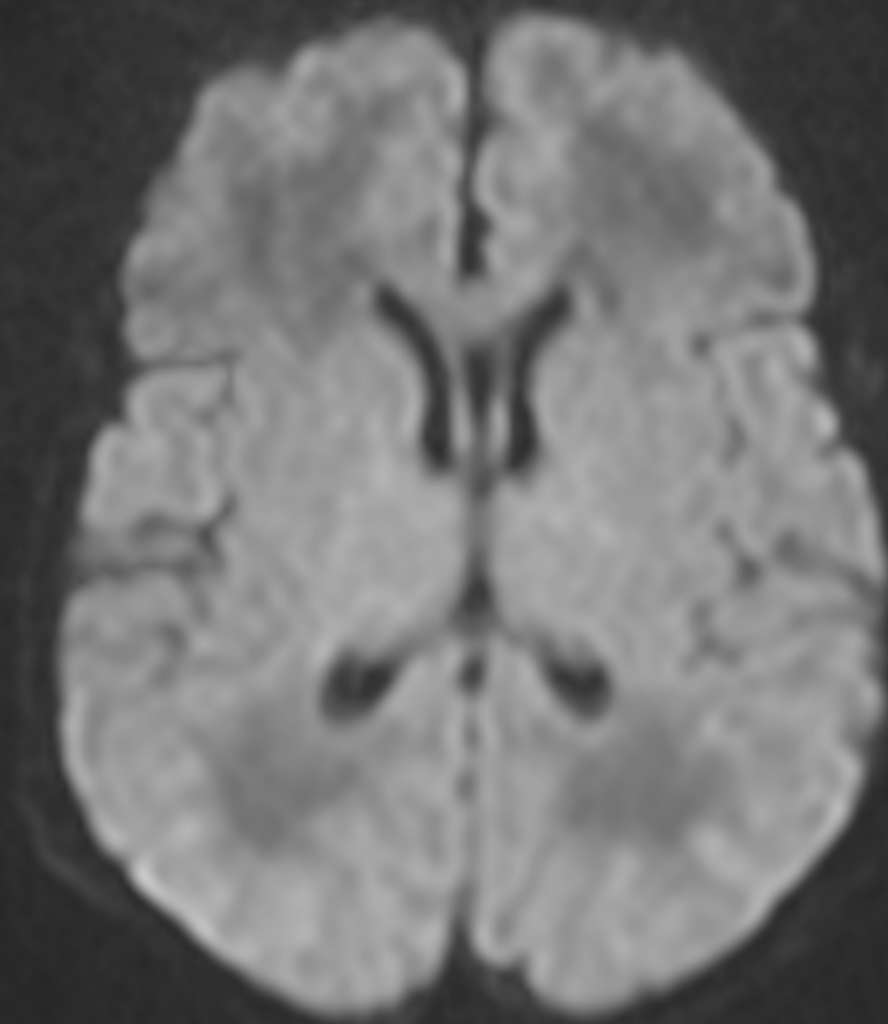




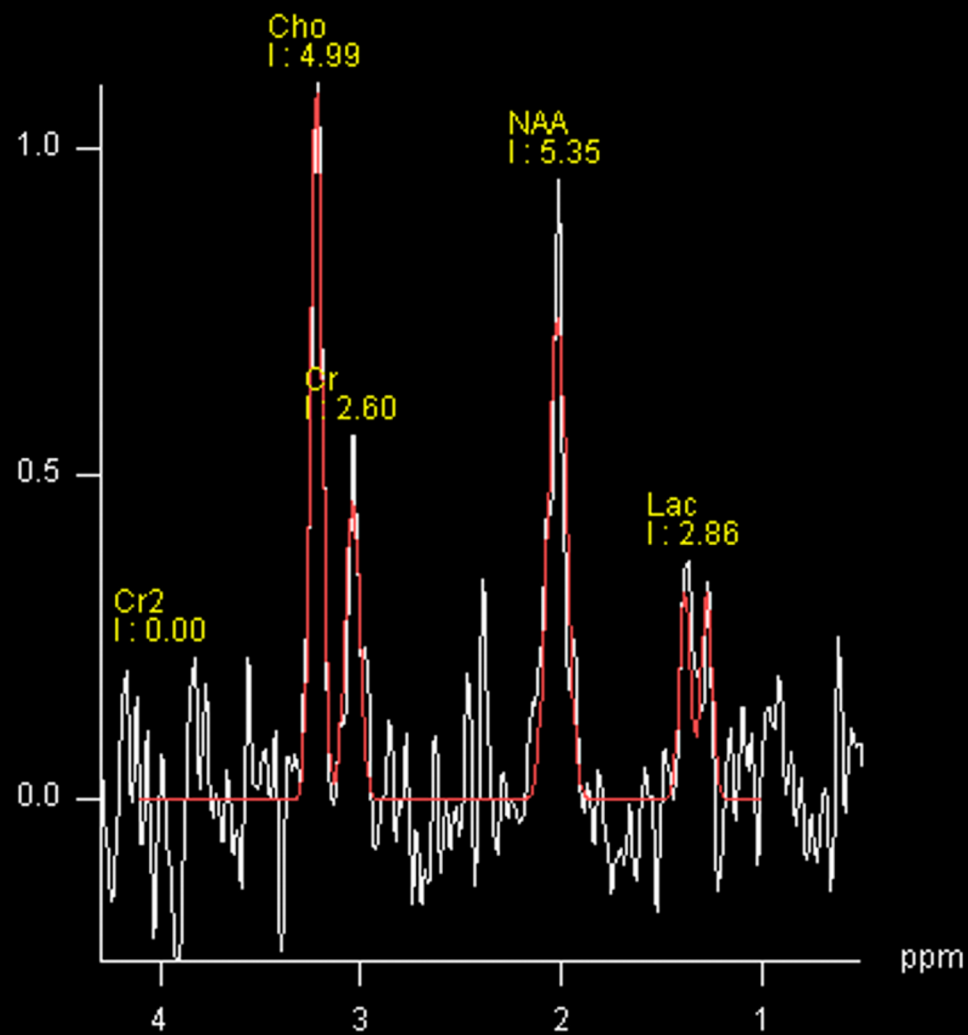








I : Intégrale



MRI systems	Sequence	Acquisition plane	TE (ms)	TR (ms)	flip angle (°)	Matrix	FoV (cm x cm)	Thickness (mm)
(1) 1.5 Tesla Siemens Avanto	T1 sag SE/IR (TI 900)	sagittal	47	2130	150	256 x 256	39.9 x 24	4
	T2 ax blade SE	axial	144	4500	141	320 x 320	33.2 x 20	3
	T2 coro SE	coronal	128	4900	150	378 x 448	36.6 x 22	2.5
	T2 ax GE	axial	26	1060	20	256 x 256	33.2 x 20	3
	T1 ax SE/IR (TI 400)	axial	70	5390	150	224 x 256	29.9 x 18	3
	Diffusion b800	axial	95	7400	90	308 x 308	38.2 x 23	3
	CSI long TE	axial				512 x 512		
(2) 1.5 Tesla Philips Medical Systems Achieva	T1 sag SE	sagittal	17	540	90	256 x 256	38.2 x 23	4
	T2 ax SE	axial	120	6751.26	90	256 x 256	26.6 x 16	3
	T2 coro SE	coronal	120	7956	90	512 x 512	24.9 x 15	3
	T1 ax SE	axial	15	541	69	256 x 256	38.2 x 23	5
	T1 IR (TI 400)	axial	14	3424	90	512 x 512	33.2 x 20	2
	T2 FFE	axial	23	554	16	256 x 256	33.2 x 20	4
	Diffusion b800	axial	70	4444	90	256 x 256	38.2 x 23	3
	CSI long TE	axial				1515 x 1114		
(3) 3 Tesla GE Medical Systems Discovery MR750w	3D T1 bravo GE (TI 450)	sagittal	2.8	7.7	15	512 x 512	33.2 x 20	1.4
	Ax T2 propeller SE	axial	96	10421	150	512 x 512	29.9 x 18	4
	Coronal T2 SE	coronal	89.46	8000	111	512 x 512	29.9 x 18	3
	Ax T2* GE	axial	18	600	15	256 x 256	29.9 x 18	4
	Ax T1 SE	axial	6.77	400	111	512 x 512	39.9 x 24	4
	Diffusion b800	axial	73	5445	90	256 x 256	39.9 x 24	4
	CSI long TE	axial				926 x 715		
(4) Siemens Aera 1,5 T	Sag T2 TSE	sagittal	86	4760	150	384 x 384	38.6 x 23	3
	Sag T1 SE/IR (TI 400)	sagittal	44	2040	150	256 x 256	39.9 x 24	4
	Sag T1 SE	sagittal	8.9	489	90	256 x 256	33.6 x 20.2	4
	Ax T2 TSE	axial	87	5970	150	350 x 448	38.6 x 23	4
	T2 ax blade SE	axial	136	4500	141	320 x 320	33.2 x 20	3
	Coronal T2 SE	coronal	133	4900	150	378 x 448	36.9 x 22	2.5
	Ax T2 GE	axial	20	399	20	320 x 320	38.6 x 23	4
	Ax T1 SE	axial	9.2	462	82	250 x 320	36 x 21.5	4
	Ax T1 SE/IR (TI 400)	axial	67	5390	150	224 x 256	29.9 x 18	3
	Diffusion b1000	axial	64	6560	180	194 x 194	41.3 x 24.6	4
	CSI long TE					512 x 512		

Type of sequence	Abnormalities	Score
T1 and T2 sequences	Cerebral edema (hypersignal of white matter on T2, compared to CSF)	0 = no, 2 = yes
	White matter/cortical grey matter differentiation	0 = present, 1 = missing in 1 location, 2 = missing in > 1 location
	T1 hyperintensity of the PLIC	0 = normal, 1 = decreased, 2 = missing
	T1 hyperintensity of BGT	0 = absent, 1 = present in 1 location, 2 = present in > 1 location
	T2 abnormalities of BGT	0 = absent, 1 = present in 1 location, 2 = present in > 1 location
	T1 or T2 brainstem signal abnormalities	0 = no, 1 = yes
	T1 cortical hypersignal	0 = absent, 1 = present in 1 location, 2 = present in > 1 location
	Punctate hypersignal abnormalities of white matter on T1	0 = absent, 1 = present in 1 location, 2 = present in > 1 location
	Extra-axial hemorrhage	0 = no, 1 = yes
Diffusion sequences	White matter water restriction	0 = absent, 1 = present in 1 location, 2 = present in > 1 location
	BGT water restriction	0 = absent, 1 = present in 1 location, 2 = present in > 1 location
	Cortical water restriction	0 = absent, 1 = present in 1 location, 2 = present in > 1 location

Type of sequence	Abnormalities	Unfavorable outcome, n=13	Favorable outcome, n=20	p-value
T1 and T2 sequences	Cerebral edema (hypersignal of white matter on T2, compared to CSF)	10 (76.9)	5 (25.0)	0.01
	Loss of white/grey matter differentiation	10 (77.0)	2 (10.0)	<0.001
	Loss of T1 hyperintensity of the PLICs	8 (61.5)	5 (25.0)	0.036
	T1 hyperintensity of BGT	8 (61.5)	3 (15.0)	0.006
	T2 abnormalities of BGT	9 (69.2)	2 (10.0)	<0.001
	T1 or T2 brainstem signal abnormalities	2 (15.4)	0 (0.0)	0.148
	T1 cortical hyperintensity	4 (30.8)	0 (0.0)	0.03
	Punctate high signal abnormalities of white matter on T1	3 (23.1)	3 (15.0)	0.175
	Extra-axial hemorrhage	3 (23.1)	9 (45.0)	0.363
	Diffusion sequences	White matter water restriction	9 (69.2)	7 (36.9)
BGT water restriction		9 (69.2)	1 (5.0)	<0.001
Cortical water restriction		4 (30.8)	0 (0.0)	NR

	Edema (n=15)	No edema (n=18)	p-value
Right T2 ratio (median, IQR)	0.79 (0.74 – 0.83)	0.71 (0.67 – 0.74)	<0.001
Left T2 ratio (median, IQR)	0.79 (0.76 – 0.82)	0.68 (0.66 – 0.74)	<0.001