A Study of Temporal Evolution of Morphological Brain Changes on Conventional MRI Sequences and Brain Metabolites on MR Spectroscopy in Infants with Neonatal Hypoxic Ischemic Encephalopathy

Viram Singh Rathod¹, Kirti Chaturvedy², Divyangi Mishra³, Manish Parakh⁴, Bhupendar⁵, Deepak⁶, Raghunath⁷, Balakrishna⁸, Devashish⁹

¹-⁹ Department of Radiodiagnosis, Dr. S.N. Medical College, Jodhpur

Article Info: Received 28 January 2022; Accepted 28 March 2022
doi: https://doi.org/10.32553/ijmbs.v6i4.2512
Corresponding author: Viram Singh Rathod
Conflict of interest: No conflict of interest.

Abstract
Magnetic resonance imaging (MRI) and Proton magnetic resonance spectroscopy (1HMRS) plays an important role in assessment and prognostication of the brain damage due to perinatal hypoxic-ischemic encephalopathy (HIE). Serial imaging is superior and is more useful especially in the prognostication. The aim of the present study was to assess the Temporal evolution of morphological brain changes on conventional MR imaging sequences and brain metabolites on MRS in deep gray matter as early as possible after birth, their status on follow up MRI scan in first 6 months of life. A prospective observational study was performed between October 2020 and September 2021. 31 full-term neonates with HIE, were included. Two sequential MR studies were performed; a conventional MR imaging, and proton MR spectroscopy for observation in the deep gray matter. Morphological brain changes were studied in the form of MRI scoring system. Followup with clinical examination for neurodevelopmental delay was done in our pediatric neurology clinic at 6 to 7 months of age. Mean MRI score in the first scan was found out to be 5.58 and in the second scan it was around 2.25. 30 subjects out of 31 showed lactate peak in the first scan and on followup imaging 8 out of 30 infants showed persistence of lactate peak (P value < 0.0001), 27 (87.1 %) out of 31 subjects showed increase in NAA/Cr ratio on followup scan and 4 (12.9%) subjects showed decrease in NAA/Cr ratio. 5 out of 31 infants showed developmental delay, one infant expired and 25 infants (80 %) had no significant developmental delay. In conclusion there is significant correlation between persistence of lactate peak, decrease in NAA/Cr ratio and increased MRI score with neurodevelopmental delay.

Keywords: Hypoxic-ischemic encephalopathy, Magnetic resonance spectroscopy, Lactate peak, NAA/Cr ratio, neurodevelopmental delay, serial MRI.

Introduction

Perinatal asphyxia and consequential hypoxic-ischemic encephalopathy (HIE) remains one of the leading causes of perinatal brain injury, affecting more than two million neonates yearly worldwide [1]. Although full recovery is possible, HIE can also lead to permanent mental or psychomotor disability [2]. Perinatal asphyxia is defined as the failure to initiate and sustain breathing at birth [3].

Advanced MRI techniques, including diffusion tensor imaging (DTI) and magnetic resonance
spectroscopy (MRS) are increasingly being used to help fine-tune prognostication \[4\].

For the purpose of prognostication in neonatal HIE, standard MRI protocols include conventional T1WI, T2WI and diffusion-weight imaging (DWI). Conventional MRI identifies the region of injury and extent of injury through variations in signal intensity seen on the MRI images. DWI is a more advanced technique that further depicts the region and extent of injury, but also adds to the understanding of onset and progression of injury.

When interpreting conventional MRI and DWI, two main patterns of injury are distinguishable. The first pattern of injury is the basal ganglia–thalamus pattern (BGT), in which the primary injury involves the basal ganglia, thalamus, and peri-rolandic cortex. The outcome of the BGT pattern of injury tends to be severe cerebral palsy, hence severe motor disability. The second pattern of injury is the watershed predominant pattern (WS), in which the primary injury involves the water shed zone territories, affecting mainly the cerebral white matter and extending into the cerebral grey matter (cortex) with more severe injury.

MRS measures the biochemical makeup of the brain, specifically comparing the biochemical composition of normal brain with areas of brain injury. The key metabolites present in healthy brain are choline (Cho), creatine (Cr), and N-acetylaspartate (NAA). In the context of neonatal HIE brain injury results in elevated lactate (Lac) levels. In fact, many believe that reduced NAA and elevated Lac are highly predictive of adverse neurodevelopmental outcome in neonatal HIE.

The NAA metabolite studied in the form of NAA/Cr in the brain parenchyma represent the neuronal maturation. The level of increase or decrease in it is very useful in predicting the outcome in later part of life in the form of neurodevelopment.

In this study we correlated MR findings seen in HIE to establish temporal evolution of brain metabolites and morphological changes seen in brain in the first six months of life and to predict probable neurological outcome.

**Material and methods:**

The study was conducted in the Department of Radiology and Pediatric Neurology Clinic, Dr. S.N. Medical College, Jodhpur, Rajasthan from October 2020 to September 2021. It was an observational study with a prospective design. The study was approved by our institutional ethical committee. All patients were term neonates evaluated in the departments of pediatrics and were diagnosed clinically as hypoxic ischemic encephalopathy, after which they underwent MR imaging. The sample size was estimated as 31 according to relevant formula.

All the study subjects underwent two MR imaging studies, one within the neonatal period of 28 days and the second scan was done within two months to six months of age. Follow-up with clinical examination for neurodevelopmental delay was done in our pediatric neurology clinic at 6 to 7 months of age.

All the patients included in our study were having history of difficult resuscitation, Apgar score < 7 at 5 minutes of life, delayed cry or born with documented evidence of fetal distress. All the babies who were having congenital anomalies, intracranial hemorrhage, suspected to be having an inborn error of metabolism were excluded from the study.

MRI MACHINE: All the MRI imaging in this study were performed using 1.5 Tesla scanner (PHILIPS Achieva, The Nederlands) with PHILIPS intellispace portal, windows work station and software.
Method:
This was a single institutional observation study of patients with clinically diagnosed hypoxic ischemic encephalopathy.

After enrolment the caregiver’s were explained the aim and objectives of the study along with the methodology in hindi and an informed consent to participate in the study was taken. Any caregiver who was not willing to participate in the study was given the liberty to withdraw at any time during the study. All epidemiological data including registration number, name of baby, mother’s name, father’s name, detailed address, contact telephone number, date and exact time of birth, date and exact time of admission, date and exact time of sampling were recorded on the predesigned proforma.

Detailed antenatal history was recorded to include history suggestive of any maternal morbidity during pregnancy including history of pregnancy induced hypertension, Gestational diabetes mellitus, hyper emesis gravidarum, onset of quickening and fetal movements, infections during pregnancy, etc. Detailed Perinatal history including duration of rupture of membranes, history suggestive of obstructed/difficult labour, failed progress, evidence of intrapartum asphyxia in the form of decreased fetal movements, meconium stained liquor, positive non stress test, sonological evidence of reverse diastolic flow or absent diastolic flow in the umbilical artery was also noted. The time period between the onset of labour pains and delivery, significant intervention by the obstetrician during this period was also taken into account.

MRI and MRS Procedure:
During the MRI procedures, all neonates were sedated with chloral hydrate 10 mg/kg (Sigma-Aldrich, St. Louis, MO, USA) or rectally as a suppository. Vacuum pillows were used to prevent patients movement during MR examinations. Ear protection to noise exposure was provided by using neonatal ear muffs. A paediatrician was present throughout the imaging. The neonates were monitored by MR-compatible pulse oximetry during the examination procedure.

Acquisition protocols:
Conventional MRI methods: MRI protocols included 3.0 mm transverse and sagittal T1-weighted spin-echo sequences; 3.0 mm transverse T2-weighted fast spin-echo sequence; and an echo-planar imaging technique was used for diffusion weighted imaging, 3.0 mm section thickness and b values of 0 and 1,000 sec/mm2.

Proton MR-Spectroscopy methods: MR spectroscopy was performed similarly to the routine MR protocol. Spectra was acquired by using a multi voxel technique and voxel placed in the deep gray matter. The basal ganglia and thalamus are most sensitive to the effects of acute anoxia. This region can reflect the global disturbances, such as cortical gray matter and the frontal and occipital white matter. Placement was performed carefully to avoid contact with cerebral spinal fluid.

The parameters of multivoxel MR spectroscopy was as follows: TR, 1,500 ms; TE, 35 ms; 128 signals acquired; and 8NEX. Water suppression was achieved by applying chemical shift selective saturation pulses. Metabolites of biologic importance, such as N acetylaspartate (NAA), creatine (Cr), and choline (Cho) peaks were identified at 2.02, 3.02 and 3.24 ppm, respectively. When present, lactate (Lac) was identified as a doublet at 1.33 ppm.

Continuous monitoring of transcutaneous oxygen saturation was provided for all neonates during the MR scan, using MR Monitoring System.

Interpretation:
Conventional MRI:
The MR images obtained in all neonates were analyzed by two radiologists, one with an
experience of 16 years and the other with one year of experience in neonatal neuroimaging and findings were recorded by consensus. Findings of MRI and MRS were recorded as stated in the proforma.

The following predefined structures were analyzed: Basal ganglia regions (including thalamus); cerebral cortex; peri-ventricular and sub-cortical white matter; corpus callosum volume; and brainstem. For each structure, any MR signal intensity abnormality irrelevant to injury was documented as a high signal intensity (SI) lesion on T1 weighted image (WI). Each finding noted was assigned a score as per the proforma (Table 1). Each of the findings were assigned score as 0, 1 and 2. The maximum possible score was 28 and minimum being 0.

**MR-Spectroscopy.** The spectra were reviewed by an MR specialist. All 1H MR spectroscopic data was included in the analysis and all findings were pooled. Creatine was used as a reference to measure the ratios of NAA/Cr and for presence/absence of lactate peak.

| Category | Score criteria                                                                 | 1st scan | 2nd scan |
|----------|---------------------------------------------------------------------------------|----------|----------|
| A        | Brain swelling: 0, Not present; 2, present                                      |          |          |
| B        | Grey/white matter differentiation: 0, Present; 1, absent in one localization; 2, absent in more than one localization |          |          |
| C        | High signal in the posterior limb of the internal capsule on T1WI: 0, Normal; 1, mild decrease; 2, absent |          |          |
| D        | Hyperintensity on T1WI sequences on PP and T: 0, None; 1, one localization; 2, more than one localization |          |          |
| E        | Hyperintensity on T2 sequences on PP and T: 0, None; 1, one localization; 2, more than one localization |          |          |
| F        | Brain stem abnormalities on T1WI and/or T2WI sequences: 0, None; 1, present     |          |          |
| G        | Cortex abnormalities on T1 and/or T2 sequences: 0, None; 1, one localization; 2, more than one localization |          |          |
| H        | White matter petechial abnormalities: 0, None; 1, one localization; 2, more than one localization |          |          |
| I        | Subarachnoid hemorrhages: 0, None; 1, present                                   |          |          |
| J        | White matter abnormalities in DWI: 0, None; 1, one localization; 2, more than one localization |          |          |
| K        | Basal ganglia abnormalities in DWI: 0, None; 1, one localization; 2, more than one localization |          |          |
| L        | Cerebral cortex abnormalities in DWI: 0, None; 1, one localization; 2, more than one localization |          |          |
| M        | Corpus callosum volume : normal,0; thinning in one region,1; thinning in >1 region,2 |          |          |
| N        | White matter volume : normal,0; loss in one region,1; loss in >1 region,2      |          |          |

T1WI, T1 weighted image; T2WI, T2 weighted image; DWI, diffusion weighted imaging; PP, putamen and pallidum; T, thalamus.
Observation and Results:
A total of 31 infants were included in our study out of which 20 (64.5%) were male and 11 (35.5%) were females, who met our inclusion criteria (Chart-1).

The minimum gestational age was 36 weeks and maximum was 39 weeks, 5 newborns (16%) were in the category of 36-37 weeks, majority that is 20 newborns (65%) were in the category of 37-38 weeks of gestation and 6 newborns (19%) were in the category of 38-39 weeks of gestation (Chart-2).

The majority 23 (74%) of the infants did not have any antenatal complications, 4 (13%) had a history of obstructed labour, 2 (6%) had history of PIH and 2 (6%) had history of meconium stained liquor (Chart-3).

We used sarnat and sarnat staging to categorise the HIE staging clinically. Out of 31 studied infants we found that 4 (13%) were of stage I, majority , 19 (61%) were of stage II (26%) and 8 were in stage III (Chart-4).

MR-spectroscopy findings were as described in charts 5, 6 and table-2.

Conventional MRI findings were as described in charts 7, 8 and table-3.

Conventional MRI-score and MR-spectroscopy findings were as described in table 4-6.

Discussion:
The conventional MRI is a very important tool for early understanding of the hypoxic insults and proton- MRS adds more value to the imaging investigation in the evaluation of neonatal hypoxia.

The current study was therefore conceived to evaluate the evolution of brain lactate peak, NAA/Cr ratio, their trends, various morphological changes in asphyxiated neonates in the first 6 months of life and the correlation of brain lactate peak and MR SPECTROSCOPY with neurological outcome at 6 months of age.

Lactate peak trends and its correlation with neurodevelopmental outcome.
The characteristic appearance of 1HMRS in neonates suffered from HIE is the rise of lactate peak. The steep rise in lactate relative to the other metabolites is presumably largely due to the excessive production of lactic acid in cerebral tissue, which is attributable to reduced oxygen supply resulting in decreased oxidative phosphorylation, causing enhanced glycolysis. The lactate level in the brain, probably rising immediately after the hypoxia-ischemic insult, may finally fall if the accumulation of lactate not exceeding definite levels within 2-3 weeks after the insult. The reason for that may be the removal of lactic acid from the brain either by local metabolism or by transport such as Na+/H+ exchange. If the lactates persist increasing to a definite level, it may result in poor outcome due to energy failure and irreversible insult of neuron.

In the first scan out of 31 infants 30 showed the presence of lactate peak and 1 infant did not show any lactate peak. As we were studying the evolution of lactate peak in the our study we selected the cases which showed elevated lactate peak in the first scan and those infants were followed up and a repeat scan was done in them. Out of the 30 infants, 8 (26%) showed persistence of lactate peak in the second scan, in the remaining 22 infants the lactate peak disappeared. The mean age of the infants at the second scan was 3.5 months. The mean age at the time of second scan in the group which showed persistence of lactate peak was 3.3 months. The mean age of no lactate peak group at the time of second scan was 3.42 months which was slightly higher than the lactate peak yes group.

Study done by J Donacha et al, they found that in severely asphyxiated neonates lactate peak may persist after one month of age. Lactate was
detected later than the 1st month after birth in seven of eight infants with abnormal neurodevelopmental outcome. No lactate was detected later than the 1st month after birth in infants with normal neurodevelopmental outcome, nor in five of six control subjects, although a small amount of lactate was detected in one control infant. These results suggest that the pathologic post asphyxial process, indicated by persistent cerebral lactate, may not be confined to the period immediately after injury. The results of this study are in concordance with our study [6].

In our study we found that there is strong association with lactate peak and neurodevelopmental outcome, out of 8 infants who had lactate peak on second scan 6 infants had adverse outcome, 6 infants had neurodevelopmental delay at 6 to 7 months follow-up, 1 infant expired at the age of 6 months, even that child had developmental delay.

Our findings of adverse neurodevelopmental outcome in lactate peak positive group is supported by a study done by Donacha et al, in their study they found that 14 out of 19 infants with persistent lactate peak beyond 1 month of age had adverse neurodevelopmental outcome at 1 year of age [6].

Hanrahan j, I Jane, et al, in their Study also found an association between the persistence of lactate more than 4 wk after hypoxia-ischemia and neurodevelopmental impairment at 1 Y of age [6].

NAA/Cr ratio trends and its correlation with neurodevelopmental delay.

In our study it was found that mean NAA/Cr ratio in the first scan was 0.94 with a SD of 0.13 and in the second scan the mean NAA/Cr ratio was 1.16 with a SD of 0.24. There was significant increase in the mean NAA/Cr ratio in the follow-up scan. It is very well understood that with the brain maturation there is increase in NAA concentration.

In our study we found that 27 (87.1 %) out of 31 subjects showed increase in NAA/Cr ratio on followup scan and 4 (12.9%) subjects showed decrease in NAA/Cr ratio in the interval scan.

Guoguang Fan et al, in their study found that 24 out of 26 full term neonates with HIE had increase in NAA/Cr ratio and in two infants it showed a fall [7].

M S Vander knap et al in their study found that Proton spectroscopy revealed an increase in the ratios of N-acetylaspartate (NAA) to choline (Cho) and NAA to creatine (Cr) and a decrease in Cho/Cr with increasing age. The most rapid changes were noted during the first 3 years of life, but changes were still observed at the age of 16 years [8].

Haznalka Barta et al, in their study of one hundred and sixty-nine newborns with moderate-to-severe HIE, having ≥1 H-MRS scan during postnatal days 0-14 and known neurodevelopmental outcome (Bayley-II score/cerebral palsy/death) found that In HIE, NAA/Cr and ml/NAA give most accurate outcome prediction throughout postnatal days 0-14 [9].

In our study it was observed that the mean NAA/Cr in the infants who developed a developmental delay was 0.93 in the first scan and 0.96 in the second scan. The mean NAA/Cr in the infants who did not have developmental delay in the first scan was found to be 0.94 in the first scan and 1.23 in the second scan.

It is observed that in the first scan there is no significant difference with P value of 0.903 in the mean NAA/Cr ratio in the two groups with developmental delay and the group with no developmental delay. Where as in second scan we found significant difference in the mean NAA/Cr ratio of the two groups with a P value of 0.082, hence it is observed that the actual difference in mean NAA/Cr ratio occurs at later age in the two groups with normal development and adverse outcome.
Christopher G Filippi et al, in their study found in children older than 2 years there was significant difference in the NAA/Cr ratio in between two groups with normal and adverse neurodevelopmental outcome. The group with adverse neurodevelopmental outcome had significantly lower metabolite concentrations as compared with the group with normal outcome. They also found that there was no significant difference in the metabolite concentrations in both the groups at younger age\textsuperscript{[10]}.

In our study we observed that the all infants in which there was decrease in NAA/Cr ratio showed neurodevelopmental delay that is 4 infants with decrease in NAA/Cr ratio showed developmental delay, overall 27 infants showed increase in NAA/Cr ratio in which only one infant showed developmental delay. Our test was tested upon by Chi square test and had a P value of $<0.0001$, validating the significance of our observation.

Manami Akasaki et al, in their study found strong positive correlation between neurodevelopmental outcome and NAA/Cr ration in basal ganglia/thalamus region. They showed it quite evidently increases in the infancy period in case of normal neurodevelopmental outcome and less in infants with adverse neurodevelopmental outcome\textsuperscript{[11]}.

Reina Hyodo et al, in their study found that Decreased NAA/Cr and NAA/Cho ratios in the thalamus was associated with neurodevelopmental delay at 18 months corrected age in preterm infants\textsuperscript{[12]}. Nicolas Fayed et al, In children with developmental delay, found a significant decrease of the following ratios: NAA/Cr (P $<0.016$) in relation to controls. The mean NAA/Cr ratio in children with developmental delay was 1.92 (SD 0.14), and in controls it was 2.09 (SD 0.14); $t = 2.62$, $fd$ (freedom degrees) = 21, P $<0.016$. No differences were seen in the remaining ratios. The lower NAA/Cr ratio in children with developmental delay in relation to controls may be a promising marker of this disorder and supports the hypothesis of delayed myelination\textsuperscript{[13]}.

**Conventional MRI**

Magnetic resonance imaging has been demonstrated to be a useful tool for evaluation of brain damage in asphyxiated infants. Because of higher sensitivity and specificity to maturational changes such as evaluation of myelination, magnetic resonance imaging has had an enormous impact on neurologic imaging. Especially serial imaging can identify specific patterns of injury accurately. Several studies have tried to establish the predictive value of magnetic resonance imaging in children with perinatal asphyxia. There are few reports that document serial magnetic resonance imaging findings in infants with hypoxic-ischemic encephalopathy in association with long-term neurologic assessment.

There is a dynamic evolution of any hypoxic-ischemic injury, and the magnetic resonance imaging pattern develops gradually until the final stage is achieved. The early neonatal magnetic resonance imaging findings include brain swelling and abnormal signal abnormalities within basal ganglia, thalamus, posterior limb of internal capsule, periventricular and sub cortical white matter.

In our study the mean age of the study participants at the first scan was about 8.5 days with 5 subjects having age less than 5 days, 12 subjects having age in the range of 6 to 10 days, 4 subjects having age in the range of 11-15 days and 6 subjects having age greater than 15 days. All the infants had brain swelling in the first scan. 27 infants out of 31 showed abnormal T1 and T2 signal intensities in our study. 10 infants showed diffusion restriction and 21 did not have any diffusion restriction in the first scan. Out of 31 infants only one had signs of brain atrophy.
In our study the mean age of the study participants at the second scan was about 3.5 months with 10 subjects having age less than 2 months, 14 subjects having age in the range of 3 to 4 months, 6 subjects having age in the range of 5 – 6 months and 1 infant had age greater than 6 months. None of the infants had brain swelling in the second scan. 11 infants out of 31 showed abnormal T1 and T2 signal intensities in our study. None of the infants had brain swelling in the second scan. Out of 31 infants 26 had signs of brain atrophy and 5 infants did not show any signs of atrophy.

We basically studied the morphological changes in four major domains that is brain swelling; T1 & T2 signal abnormalities, diffusion restriction and brain atrophy. Rest of all findings were also included in the designed MRI score as mentioned in the proforma as mentioned earlier.

In our study we found that all the subjects showed brain swelling in the first scan. So it is quite evident that brain swelling is seen in almost all the forms of asphyxial brain injury, irrespective of severity. Brain swelling is the earliest finding seen in any form of brain injury. It is very well understood by pathophysiology that it is an acute finding and it naturally disappears in later course of disease evolution. In our study none of infant showed brain swelling in the second scan. This is easily explained by the pathophysiology and various literatures available to support it.

Mary Rutherford, Jacqueline Pennock, et al, in their study also found that all the neonates had brain swelling in the first scan and which disappeared in the follow-up scan [14].

In our study it was observed that 10 (32.6%) out of 31 subjects showed diffusion restriction in the first scan. The average age of all the neonates who did not show diffusion restriction at the time of first scan in our study was 8.5 days. The average age of neonates at the time of first scan which showed diffusion restriction was 8 days. None of the subjects showed persistence of diffusion restriction in the second scan.

It is very well known that diffusion restriction is an early finding on MRI imaging in the hypoxic injury, there are several studies to support this.

Floris Groenendaal & Linda S. de Vries in their study found that introduction of diffusion weighted imaging (DWI), has enabled detection of cell swelling ("cytotoxic edema"). Using DWI, changes in the thalamus during the initial days after HIE, and basal ganglia slightly thereafter could be demonstrated, days before they could be identified with conventional T1 and T2 weighted imaging. Furthermore, quantification of apparent diffusion coefficient (ADC) values helped to further improve prediction of outcome after HIE. However, ADC values pseudo normalize after the first week, which restricts the value of DWI to the first week [16].

In our study we found that one out of 31 subjects showed brain atrophy in the first scan and 26 out of 31 subjects showed atrophy in the second scan.
It was observed that atrophy is a predominantly late finding in the infants affected with HIE.

Mary Rutherford, Jacqueline Pennock, et al, also had findings in concordance with our study, out of 13 subjects 8 infants signs of atrophy in the follow-up scan done near 2 to 3 months of age.

Nursen Belet MD, Umit Belet, MD, et al, in their study found that in first scan 11 out of 20 neonates had signs of atrophy in follow-up scan at 4 months. This study is in concordance with our study findings[15].

As explained in the methodology we formulated a MRI scoring system to evaluate the conventional MRI findings in our study for better understanding and quantification of findings. In our study we found that mean MRI score in the first scan was found out to be 5.58 and in the second scan it was around 2.25. There was significant sequential decrease in the mean MRI score.

In our study it was observed that the mean MRI score in the infants who developed a developmental delay was 9 in the first scan and 6 in the second scan. The mean MRI score in the infants who did not have developmental delay in the first scan was found to be 4.6 in the first scan and 1.2 in the second scan. P value being <0.03. It is observed that the decrease in mean MRI score in the group with no developmental delay had a significant decrease compared to the group which had developmental delay.

Thomas Alderliesten, MD Linda S. in their study observed The combination of MR imaging score with ADCs or Lactate/NAA ratios in the basal ganglia has a better association with outcome of asphyxiated term neonates than does MR imaging alone[17].

Mary Rutherford, Jacqueline Pennock, et al, in their study also used similar scoring system to tabulate the findings. The findings in their study is in concordance with our study in which the decrease in mean MRI score in group with good neurological outcome was high compared with the poor outcome group[14].

**Conclusion**

The purpose of this study was to study the evolution of NAA/Cr ratio, lactate peak and morphological brain changes in the first six months of life in neonates with hypoxic ischemic encephalopathy (HIE) and their correlation with neurodevelopment outcome at 6-7 months of follow-up.

In majority of cases there was significant increase in the NAA/Cr ratio in follow-up scans which suggest an adequate neuronal maturation and good neurodevelopment outcome at 6-7 months of follow-up.

In few cases where there was decrease in the NAA/Cr ratio in follow-up scans which suggest a poor neuronal maturation and adverse neurodevelopment outcome at 6-7 months of follow-up.

In follow-up scans majority of the infants showed disappearance of lactate peak which suggest good neurodevelopment outcome at 6-7 months of follow-up. In few cases which had persistence of lactate peak on the follow-up scans had poor neurodevelopment outcome. So there is positive correlation between lactate peak persistence in follow-up scans and neurodevelopment outcome.

None of the scans showed restricted diffusivity and white matter edema on follow-up scans, neuroparenchymal atrophy was predominantly demonstrated in follow-up scans, signal abnormalities in deep grey matter and perirolandic region were demonstrated in both the scans, however less in the follow-up scans.

In the early (neonatal period) scans there was no significant difference in the mean NAA/Cr ratio between the two groups, one with the developmental delay and other one with no developmental delay. However, in the follow-up scans there was significant difference in the mean NAA/Cr ratio between the two groups. So we
recommend that the difference in the NAA/Cr ratio is a late feature, an increase in the NAA/Cr ratio is more important than the mean value in the early MRI scans.

Chart-1: Gender distribution of the study subjects.

Chart-2: Gestational age of the study subjects.
ANTENATAL COMPLICATIONS

Chart-3: Antenatal complication.

HIE STAGE DISTRIBUTION OF THE STUDY SUBJECTS (SARNAT AND SARNAT STAGING)

Chart-4: HIE stage distribution of the study subjects.
Chart 5: Lactate peak.
Lactate Peak Findings

Chart 6: NAA/Cr ratio changes in sequential scans.
Table 2: Change In Mean Naa/Cr Ratio In The Sequential Scans

| MRI findings | NAA/CR | Mean | SD | Mean difference | t value | p value |
|--------------|--------|------|----|----------------|---------|---------|
| 1st scan     | 0.94   | 0.13 |    | -0.227         | 5.315   | <0.0001 |
| 2nd scan     | 1.16   | 0.24 |    |                |         |         |

Chart 7: Conventional MRI findings at first scan.

Chart 8: Conventional MRI findings at second scan.
Table 3: Change in MRI Score in the Sequential Scans

| MRI findings | MRI Score | Mean difference | t value | p value   |
|--------------|----------|-----------------|--------|----------|
| 1st scan     | 5.58     | 2.99            | 3.323  | 11.87    | <0.0001  |
| 2nd scan     | 2.25     | 2.86            |        |          |          |

Table 4: Correlation of MRI Score with Developmental Delay

| Development delay | MRI Score | 1st scan | 2nd scan | 1st scan | 2nd scan |
|------------------|----------|----------|----------|----------|----------|
| Mean             | Mean     | SD       | Mean     | SD       |          |
| Yes              | 9        | 2.91     | 6        | 2.91     |          |
| No               | 4.6      | 2.02     | 1.12     | 0.78     |          |
| p value          | 0.032    |          | 0.02     |          |          |

Table 5: Correlation of NAA/CR Ratio with Developmental Delay

| Development delay | NAA/CR | 1st scan | 2nd scan | 1st scan | 2nd scan |
|------------------|--------|----------|----------|----------|----------|
| Mean             | Mean   | SD       | Mean     | SD       |          |
| Yes              | 0.93   | 0.14     | 0.96     | 0.25     |          |
| No               | 0.94   | 0.13     | 1.23     | 0.19     |          |
| p value          | 0.903  |          | 0.082    |          |          |

Table 6: Correlation of Change in NAA/CR Ratio with Developmental Delay

| Development delay | NAA/CR | Increase | Decrease | Total |
|------------------|--------|----------|----------|-------|
|                  |        | N        | %        | N     | %     |
| Expired          | 1      | 3.70     | 0        | 0.00  | 1     | 3.23  |
| Yes              | 1      | 3.70     | 4        | 100.00| 5     | 16.13 |
| No               | 25     | 92.59    | 0        | 0.00  | 25    | 80.65 |
| Total            | 27     | 100.00   | 4        | 100.00| 31    | 100.00|
Case-1: Axial T1WI without IV contrast image (A) demonstrates absent T1 hyperintensity in posterior limb of internal capsule – absent PLIC sign. Axial T2WI without IV contrast image (B) demonstrates diffuse neuroparenchymal atrophy with diffuse white matter edema. DWI image (C) demonstrates high signal intensity in posterior putamen, posterior limb of internal capsule and ventro-lateral thalamus. MR-Spectroscopy (D) done at low TE (31) demonstrates increased choline with reduced NAA peak (NAA:CR ratio – 0.76) and lipid-lactate peak. Follow-up MR-Spectroscopy (E) after 2 month done at low TE (31) demonstrates increase in NAA:CR ratio – 1.05.

Case-2: Axial T1WI without IV contrast image (A) demonstrates high T1 hyperintensity posterior putamen and ventro-lateral thalamus. Axial T2WI without IV contrast image (B) demonstrates diffuse neuroparenchymal atrophy, diffuse white matter edema and hyperintensity in posterior putamen and ventro-lateral thalamus. DWI image (C) demonstrates high signal intensity in posterior putamen, posterior limb of internal capsule and ventro-lateral thalamus. MR-Spectroscopy (D) done at low TE (31) demonstrates increased choline with reduced NAA peak (NAA:CR ratio – 0.77) and lipid-lactate peak. Follow-up MR-Spectroscopy (E) after 2 month done at low TE (31) demonstrates increase in NAA:CR ratio – 0.96.
References

1. Kurinczuk JJ, White-Koning M, Badawi N. Epidemiology of neonatal encephalopathy and hypoxic-ischaemic encephalopathy. Early Hum Dev. 2010;86:329–38.

2. Mwaniki MK, Atieno M, Lawn JE, Newton CRJC. Long-term neurodevelopmental outcomes after intrauterine and neonatal insults: a systematic review. Lancet. 2012;379:445–52.

3. Eric C.AnneR. Cloherty and stark’s manual of neonatal care.8th.philadelphia.LWW.2016,Chapter 55,Perinatal Asphyxia and Hypoxic-Ischemic Encephalopathy,791p.

4. Lisa Anne Rasmussen, Prognostication in neonatal hypoxic ishmemic encephalopathy: A qualitative research study. Mc gill university Montreal, Cananda.2017.

5. Gupta BD, Sharma P, Bagla J, Parakh M, Soni JP. Renal failure in asphyxiated neonates. Indian pediatrics. 2005 Sep 1;42(9):928.

6. Hanrahan JD, Cox IJ, Edwards AD, Cowan FM, Sargentoni J, Bell JD, Bryant DJ, Rutherford MA, Azzopardi D. Persistent increases in cerebral lactate concentration after birth asphyxia. Pediatric research. 1998 Sep;44(3):304-11.

7. Fan G, Wu Z, Chen L, Guo Q, Ye B, Mao J. Hypoxia-ischemic encephalopathy in full-term neonate: correlation proton MR spectroscopy with MR imaging. European journal of radiology. 2003 Feb 1;45(2):91-8.Beken S, Aydin B, Dilli D, Erol S, Zencirolu A, Okumuş N. Can biochemical markers predict the severity of hypoxic-ischemic encephalopathy?. Turkish Journal of Pediatrics. 2014 Jan 1;56(1)

8. van der Knaap MS, van der Grond J, van Rijen PC, Faber JA, Valk J, Willems K. Age-dependent changes in localized proton and phosphorus MR spectroscopy of the brain. Radiology. 1990 Aug;176(2):509-15.

9. Lakatos A, Kolossvary M, Szabó M, Jermendy A, Barta H, Gyebnár G, Rudas G, Kozák LR. Neurodevelopmental effect of intracranial hemorrhage observed in hypoxic ischemic brain injury in hypothermia-treated asphyxiated neonates-an MRI study. BMC pediatrics. 2019 Dec;19(1):1-1.

10. Filippi CG, Uluğ AM, Deck MD, Zimmerman RD, Heier LA. Developmental delay in children: assessment with proton MR spectroscopy. American journal of neuroradiology. 2002 May 1;23(5):882-8.

11. Tanifuji S, Akasaka M, Kamei A, Araya N, Asami M, Matsumoto A, Sotodate G, Konishi Y, Shirasawa S, Toya Y, Kusano S. Temporal brain metabolite changes in preterm infants with normal development. Brain and Development. 2017 Mar 1;39(3):196-202.

12. Hyodo R, Sato Y, Ito M, Sugiyama Y, Ogawa C, Kawai H, Nakane T, Saito A, Hirakawa A, Kidokoro H, Natsume J. Magnetic resonance spectroscopy in preterm infants: association with neurodevelopmental outcomes. Archives of Disease in Childhood-Fetal and Neonatal Edition. 2018 May 1;103(3):F238-44.

13. Fayed N, Morales H, Modrego PJ, Muñoz-Mingarro J. White matter proton MR spectroscopy in children with isolated developmental delay: does it mean delayed myelination?. Academic radiology. 2006 Feb 1;13(2):229-35.

14. Rutherford M, Pennock J, Schwieso J, Cowan F, Dubowitz L. Hypoxic-ischaemic encephalopathy: early and late magnetic resonance imaging findings in relation to outcome. Archives of Disease in Childhood-Fetal and Neonatal Edition. 1996 Nov 1;75(3):F145-51.

15. Belet N, Belet U, ütfi İncesu L, Uysal S, Özinal S, ülay Keskin T, Sunter AT, ükrü Küçüködük S. Hypoxic-ischemic encephalopathy: correlation of serial MRI and outcome. Pediatric neurology. 2004 Oct 1;31(4):267-74.
16. Groenendaal F, de Vries LS. Fifty years of brain imaging in neonatal encephalopathy following perinatal asphyxia. Pediatric research. 2017 Jan;81(1):150-5.

17. Cebeci B, Alderliesten T, Wijnen JP, van der Aa NE, Benders MJ, de Vries LS, van den Hoogen A, Groenendaal F. Brain proton magnetic resonance spectroscopy and neurodevelopment after preterm birth: a systematic review. Pediatric Research. 2021 May 5:1-2.