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Original Article

Radiology Section

Correlation of Magnetic Resonance Imaging and Magnetic Resonance Spectroscopy of Basal Ganglia with APGAR Score in Perinatal Asphyxia: A Cross-sectional Study

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ABSTRACT

Introduction: Birth asphyxia is leading cause of perinatal and neonatal mortality and morbidity especially in developing countries. Around 20% of neonatal deaths in India are due to birth asphyxia. There are around one million cases of birth asphyxia per year worldwide. Majority of deaths and disabilities can be prevented by timely identification of pathologies and early initiation of rehabilitation. Magnetic Resonance Imaging (MRI) and Magnetic Resonance Spectroscopy (MRS) plays a vital role by helping in identification of such pathologies.

Aim: To assess the severity of injury to brain in hypoxic ischaemic encephalopathy infants using MRI and MRS which helps in prognosticating the disease outcome.

Materials and Methods: A cross-sectional study was conducted on 30 term infants with low Appearance, Pulse, Grimace, Activity, and Respiration (APGAR) score in the Department of Radiodiagnosis, from all the Hospitals attached to Bangalore Medical College and Research Institute, Bengaluru, Karnataka, India from November 2018 to May 2020. Patients were subjected to brain MRI and basal ganglia MRS. All MR imaging examinations were performed on a SIEMENS magneto Avanto 1.5 Tesla system. Conventional MR imaging findings were documented and MR spectroscopy values of Basal Ganglia (BG) N-Acetyl Aspartate (NAA), Creatinine (Cr), Choline (Cho) and lactate were obtained. Metabolite levels were correlated with APGAR scores by performing Pearson correlation. Chi-square test was applied with Fisher's-exact correction to see the association between lactate peak and diffusion changes in brain.

Results: A total of 30 term neonates with low APGAR score at birth were selected, of which 12 were females and 18 were males. Babies with APGAR score of 2 at one minute showed only subcortical and parasagittal areas of diffusion restriction. Basal ganglia diffusion restriction is noted only in babies with very low APGAR score of 1 at one minute. Positive correlation was noted between APGAR score and BG-NAA and BG-Cr. Negative correlation was noted between BG-Cho and APGAR score. Hence, BG-NAA:Cr, NAA:Cho and Cho:Cr can be used to assess severity of hypoxic ischaemic encephalopathy (p-value <0.001).

Conclusion: Basal ganglia is a sensitive region in defining asphyxia related metabolite abnormalities. Involvement of basal ganglia and thalamus indicates severe asphyxia. BG metabolite levels may alter even in the absence of brain changes on MR imaging. Presence of lactate peak indicates severe asphyxia. Thus, MRS helps in early diagnosis of birth asphyxia, grading of its severity and prognostication.

Keywords: Appearance pulse grimace activity and respiration score, Hypoxic ischaemic encephalopathy, N-acetyl aspartate, Perirolandic area

INTRODUCTION

Birth asphyxia is leading cause of perinatal and neonatal mortality and morbidity especially in developing countries. Around 20% of neonatal deaths in India are due to birth asphyxia. Worldwide birth asphyxia accounts for 920,000 neonatal deaths every year. Hypoxic ischaemic encephalopathy in newborns is a devastating disease which accounts for death and severe neurological deficits [1].

Hypoxic injury leads to diminution of Adenosine Triphosphate levels (ATP) in brain. ATP is produced by a non chemical process which takes place in mitochondria. Since basal ganglia have very high neurotransmitter level and metabolic activity, ATP requirement is enormous. Hence, they are susceptible to injury when there is any insult which alters the cerebral metabolism [2]. Changes may be seen in basal ganglia alone or in combination with cerebral changes. MRI has increased ability to image these changes [3]. It allows visualisation of signal changes, morphological changes and changes in metabolic contents in basal ganglia and cerebrum. Further normal myelination and cortical development process can also be evaluated using MRI.

Magnetic Resonance Imaging (MRI) along with MR spectroscopy and diffusion weighted imaging will help improving proper characterisation of the disease and narrowing down differential diagnosis [4]. Early diagnosis of Hypoxic-ischaemic encephalopathy (HIE) is possible by a combined clinico-radiological and laboratory data [5].

Early diagnosis of HIE will help in proper planning and initiation of specific rehabilitation which results in better neurological outcome in patients [6]. The radiologist by contributing imaging features to clinical, biochemical and genetic data plays a vital role in creating a perfect picture of systemic and metabolic disease in patients [2]. The present study objectives were to evaluate MRI and MRS findings in infants with perinatal asphyxia and to correlate the basal ganglia metabolite ratios with the APGAR scores in infants with perinatal asphyxia.

MATERIALS AND METHODS

A cross-sectional study was conducted on 30 newborns, who were referred to Department of Radiodiagnosis from all the Hospitals attached to Bangalore Medical College and Research Institute, Bengaluru, Karnataka, India over a period of 18 months from November 2018 to May 2020. After obtaining approval and clearance from the Institution Ethics Committee, the patients fulfilling the inclusion criteria were enrolled for the study after obtaining informed consent.

Sample size calculation: Based on previous study done by Pavlakis SG et al., APGAR score for perinatal asphyxia infants was 6.0±2.1 at 5 minutes [7]. Using this the minimum sample size required was calculated as 30 and hence 30 newborn babies were included in this study.

Inclusion criteria: Term newborn babies (within 28 days) with history of perinatal asphyxia, with either 1 minute APGAR score <3 or 3. 5 minutes APGAR score <6 and whose parents/guardians are willing to give informed consent were included in the study.

Exclusion criteria: New born babies who were born in other health facility and admitted to NICU, preterm neonates, who had major congenital malformations (hydrops, NTD), metabolic disorders and brain structural abnormalities, in whom cooling has been done were excluded from the study. New born babies with history of maternal analgesia (h/o drug abuse) and infections (may cause depression of the APGAR score) were excluded. New born babies for whom parents/guardians not willing to give informed consent were excluded from the study.

Study Procedure

A detailed history was taken and clinical examination was done. The MRI examination was performed after birth (within 28 days). Sedation was given. All MR imaging examinations were performed on a SIEMENS magneto Avanto 1.5 Tesla MR system in the Department of Radiology. MRI brain protocol includes axial T1 and T2-weighted images (T1: TR is 300-600, TE is 10-30, T2: TR is 2000-6000, TE is 50-80) with slice thickness of 3 mm, T2-Fluid attenuated inversion recovery (FLAIR) images, Sagittal T1-weighted images, coronal T2-weighted images, T1 Inversion Recovery (T1 IR) and FLAIR coronal oblique (for seizures), Susceptibility Weighted Imaging (SWI), Diffusion-Weighted Imaging (DWI), MRS.

STATISTICAL ANALYSIS

Data was analysed by descriptive statistics such as mean, median, standard deviation, inter-quartile range, percentages, tables and graphs wherever necessary. Chi-square test was applied with Fisher's-exact correction to assess the relationship between quantitative variables. The p-value <0.05 was considered statistically significant. Pearson's correlation was done between basal ganglia metabolites, their ratios and APGAR score to check the correlation. In correlation, r-value near ±1 indicates perfect correlation. Near to +1 indicates positive correlation and near to -1 indicates negative correlation. Data was entered in Microsoft (MS) Excel and analysed by Statistical Package for the Social Sciences (SPSS) Version 24.0.

RESULTS

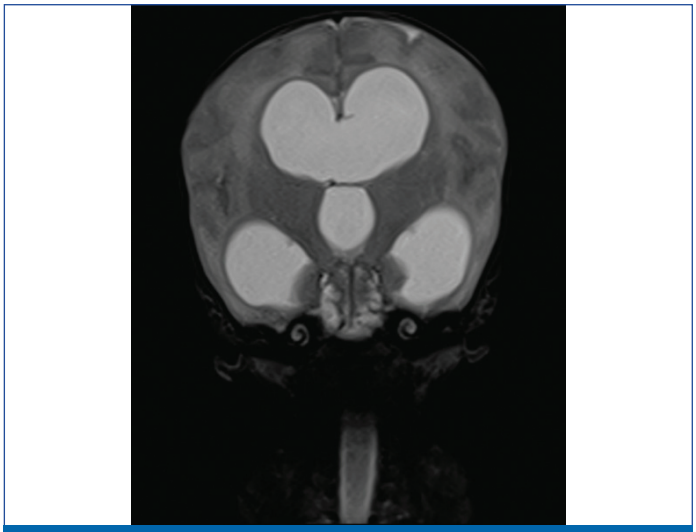
Study was conducted on 30 term neonates with low APGAR score at birth. Out of 30 babies 12 were females and remaining 18 were males. Mean APGAR score of the study population is depicted in [Table/Fig-1].

Time	APGAR score (Mean±SD)
At 1 minute	2±0.8
At 5 minute	4±1.07

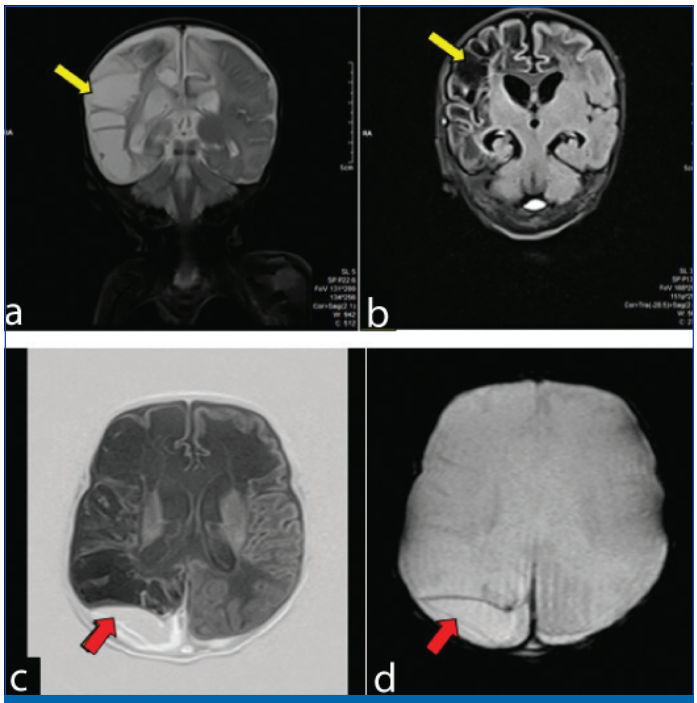
[Table/Fig-1]: Mean APGAR score of study population.
APGAR: Appearance, pulse, grimace, activity, and respiration; SD: Standard deviation

Abnormal brain findings include hydrocephalus with periventricular Cerebro Spinal Fluid (CSF) seepage [Table/Fig-2], crescent shaped T1 hypointense and T2 hyperintense collection along right parieto-occipital and left occipital convexities with no evidence of blooming on SWI suggestive of subdural collection [Table/Fig-3], areas of T1 hypointensity and T2 hyperintensity with facilitated diffusion in right cerebral hemisphere and left frontal lobe suggestive of cystic encephalomalacia [Table/Fig-3].

Among 18 males, only four babies (13.3% of study population) had diffusion restriction areas and among 12 females, only three



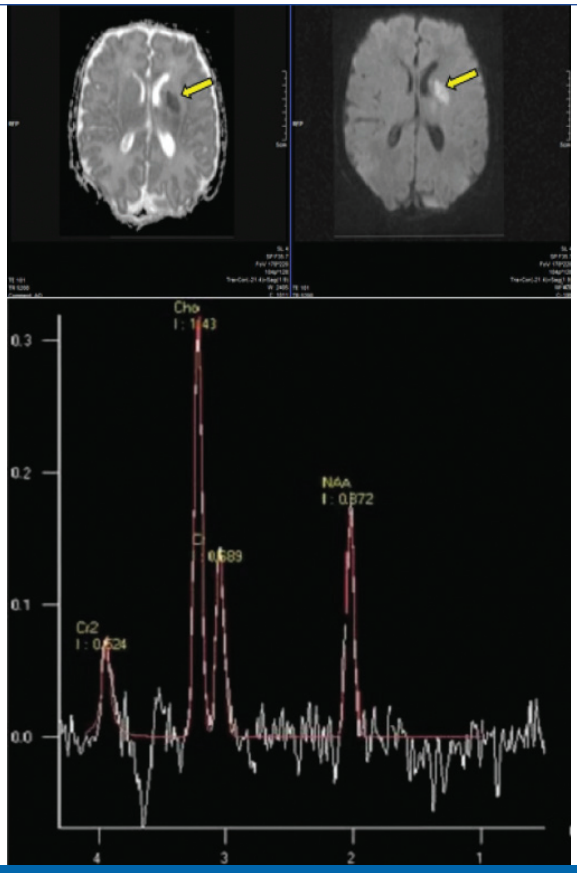
[Table/Fig-2]: A 12-day-old male baby with low 1-minute APGAR score diagnosed with hypoxic ischaemic encephalopathy-Coronal T2WI showing gross dilatation of bilateral lateral ventricles and 3rd ventricles.



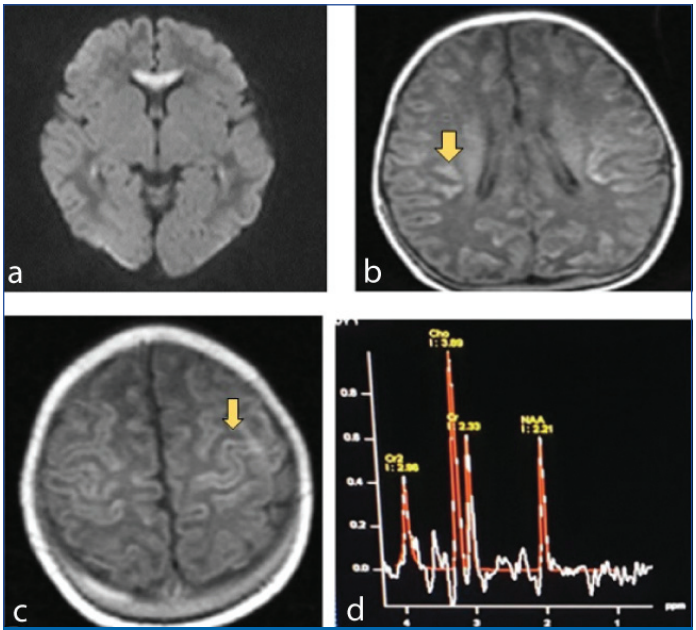
[Table/Fig-3]: A 14-day-old male baby with low 1-minute APGAR score diagnosed with hypoxic ischaemic encephalopathy (a, b) Coronal T2W image showing well defined hyperintense areas in right temporal and parietal lobes (Yellow arrow). Corresponding areas shows inversion on T2 FLAIR. Features are suggestive of cystic encephalomalacia. (c,d) T2 FLAIR image showing hyperintense subdural collection along right parietooccipital and left occipital convexities (Red arrow). Corresponding SWI image shows no evidence of blooming. The findings are suggestive of subdural collection. Cystic encephalomalacic changes noted in right cerebral hemisphere and left frontal lobe.

babies (10% of study population) had diffusion restriction areas. So, a total of seven babies (23.3%) of the study population showed diffusion restriction changes on brain MRI. Diffusion restricted areas noted predominantly in subcortical white matter, perirolandic area and basal ganglia [Table/Fig-4,5]. Corresponding areas of T1 hyperintensity was noted in few cases. T2 hyperintensity and restricted diffusion involving genu of corpus callosum was noted in one patient [Table/Fig-5].

In the study population, the peaks of metabolites of biologic importance, such as NAA (2.02 ppm), Cr (3.02 ppm) and Cho (3.24 ppm) were identified. The Cr was used as a reference to measure NAA/Cr and Cho/Cr. Lactate peak was identified in nine babies, the values of NAA/Cr, NAA/Cho and Cho/Cr in these babies were 1.99±0.14, 0.96±0.13 and 2.08±0.21, respectively and values of NAA/Cr NAA/Cho and Cho/Cr in 21 babies without lactate peak were 2.69±0.27, 1.90±0.34 and 1.44±0.18, respectively [Table/Fig-6]. Restricted diffusion was identified in seven babies, the values of NAA/Cr, NAA/Cho and Cho/Cr in these



[Table/Fig-4]: A 24-day-old male baby with low 1-minute APGAR score diagnosed with hypoxic ischaemic encephalopathy Axial DWI and Apparent diffusion coefficient (ADC) images showed diffusion restricted in left lentiform nucleus (Yellow arrow). MRS images of the basal ganglia; Low levels of N-acetyl aspartate and high levels of choline were detected.



[Table/Fig-5]: A four-day-old male baby with low 1-minute APGAR score diagnosed with hypoxic ischaemic encephalopathy; a) Axial DWI image showing diffusion restriction in genu of corpus callosum; b) T1WI showing hyperintensity in deep white matter (yellow arrow in image; c) T1WI showing hyperintensity in perirolandic area (yellow arrow in image; d) Basal ganglia MR spectroscopy image depicting reduced NAA level and increased Cho level.

babies were 1.98±0.16, 0.93±0.13 and 2.11±0.20, respectively and values of NAA/Cr NAA/Cho and Cho/Cr in babies without restricted diffusion were 2.63±0.32, 1.82±0.41 and 1.48±0.23, respectively [Table/Fig-7]. The association between lactate peak and diffusion changes in brain was found to be statistically significant with Fisher's-exact test value of 0.001.

Twenty one (70%) babies without diffusion restriction didn't show lactate peak on MRS whereas all babies with diffusion restriction

Low APGAR	Number	NAA/Cr	NAA/Cho	Cho/Cr
With lactate peak	9	1.99±0.14	0.96±0.13	2.08±0.21
Without peak	21	2.69±0.27	1.90±0.34	1.44±0.18

[Table/Fig-6]: Quantitative analyses of the metabolic compounds with respect to lactate levels in study population.
The association was found to be statistically significant with fisher's-exact test with p-value of 0.001; Data was expressed as the mean±standard deviation; APGAR: Appearance, pulse, grimace, activity, and respiration; NAA: N-acetylaspartate; Cr: Creatinine; Cho: Choline; Lac: Lactate

Low APGAR	Number	NAA/Cr	NAA/Cho	Cho/Cr
With signal on DWI	7	1.98±0.16	0.93±0.13	2.11±0.20
Without signal on DWI	23	2.63±0.32	1.82±0.41	1.48±0.23

[Table/Fig-7]: Quantitative analyses of the metabolic compounds with respect to DWI signal in study population.
The association was found to be statistically significant with fisher's-exact test with p-value of 0.001; Data was expressed as the mean±standard deviation; APGAR: Appearance, pulse, grimace, activity, and respiration; DWI: Diffusion-weighted imaging; NAA: N-acetylaspartate; Cr: Creatinine; Cho: Choline; Lac: Lactate

changes in brain showed lactate peak on MRS. Only two babies (6.67%) with lactate peak on MRS didn't show diffusion changes on MRI. Thus, probability of babies with diffusion restriction having lactate peak on MR spectroscopy was found to be significant in the present study.

On performing Pearson's correlation between variables: One-minute APGAR score and BG-NAA, Cr and Cho, positive correlation was found between APGAR score and BG-NAA, BG-Cr with a p-value of 0.001 indicating statistical significance [Table/Fig-8].

On performing Pearson's correlation between variables: Five-minute APGAR score and BG-NAA, Cr and Cho, positive correlation was found between APGAR score and BG-NAA, BG-Cr with a p-value of 0.001 indicating statistical significance [Table/Fig-8].

Thus, decrease in either 1 minute or 5 minute APGAR score was associated with decrease in BG-NAA and BG-Cr values. Similarly positive correlation was noted between BG-NAA:Cr and BG-NAA:Cho ratio [Table/Fig-9]. Negative correlation was found between APGAR score and BG-Cho values and BG-Cho:Cr ratio with p-value of 0.001 indicating statistical significance. Thus, decrease in APGAR score was associated with increase in BG-Cho values and BG-Cho:Cr ratio [Table/Fig-10].

DISCUSSION

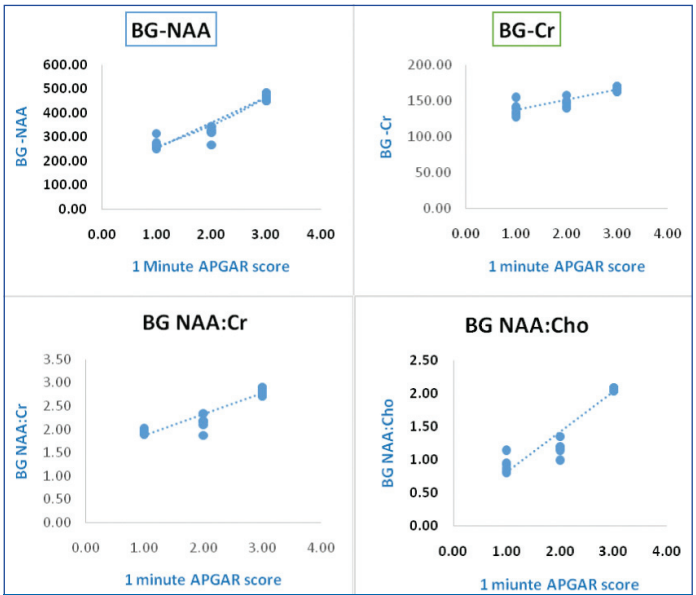
Magnetic resonance imaging is superior to cerebral Computed Tomography (CT) and cranial ultrasonography in diagnosing deep gray matter and white matter lesions [8]. The imaging pattern of HIE can be classified into three types [9,10]- milder type in which lesions are found in cortical and subcortical white matter of parasagittal region, profound type where lesions involve deep gray matter and perirolandic cortex and imaging finding suggestive of multi-cystic encephalomalacia representing chronic sequelae of hypoxia [11].

Findings in the neonate with very low APGAR (1 minute APGAR score=1) who were subjected to MRI in the present study: Increased signal intensity on T1-weighted Images and diffusion restriction of basal ganglia [Table/Fig-4]. A cardinal finding in the neonate who has experienced severe, total hypoxia is abnormally increased signal intensity on T1-weighted images of the basal ganglia with corresponding area of diffusion restriction on DWI. This result most probably shows the fact that the deep gray matter structures (i.e., the basal ganglia and thalamus) are mainly metabolically active in the brain. Therefore, these sites are more susceptible to oxidative stress and demonstrate the effects of hypoxia earlier and to a larger degree than the rest of the brain.

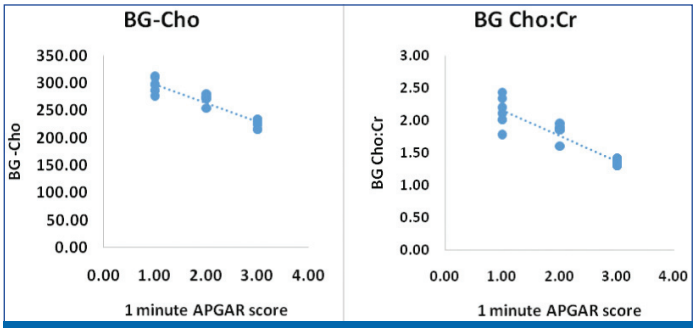
Increased signal intensity on T1-weighted images and diffusion restriction in the thalamus-the second finding of neonatal hypoxic injury is increased signal intensity in the thalamus on T1-weighted images with corresponding area of diffusion restriction on DWI. The thalamus, like the basal ganglia, is another region that is more

Parameters		APGAR 1 min.	APGAR 5 min.	BG-NAA	BG-Cr	BG-Cho	BG-NAA:Cr	BG-NAA:Cho	BG-Cho:Cr
APGAR 1 min.	Pearson correlation	1	0.939**	0.956**	0.911**	-0.953**	0.950**	0.961**	-0.939**
	Significant (2-tailed)		0.001	0.001	0.001	0.001	0.001	0.001	0.001
	N	30	30	30	30	30	30	30	30
APGAR 5 min.	Pearson correlation	0.939**	1	0.922**	0.934**	-0.940**	0.895**	0.922**	-0.955**
	Significant (2-tailed)	0.000		0.001	0.001	0.001	0.001	0.001	0.001
	N	30	30	30	30	30	30	30	30

[Table/Fig-8]: Pearson correlation between basal ganglia metabolites, their ratios and APGAR score.
**p-value <0.001- Extremely signigicant; APGAR: Appearance, pulse, grimace, activity, and respiration; BG: Basal ganglia; NAA: N-acetylaspartate; Cr: Creatinine; Cho: Choline; min: Minute; N: Number of subjects



[Table/Fig-9]: Positive correlation between APGAR score, basal ganglia NAA, Cr, NAA:Cr and NAA: Cho levels.
BG: Basal ganglia; NAA: N-acetylaspartate; Cr: Creatinine; Cho: Choline



[Table/Fig-10]: Negative correlation between APGAR score and basal ganglia Cho and Cho: Cr ratios.
BG: Basal Ganglia; Cr: Creatinine; Cho: Choline

susceptible to hypoxic injury, making this finding a relatively sensitive and specific sign of hypoxic injury. The normal subtle increase in signal intensity of the postero-lateral quadrant of the normal neonate (corresponding to normal myelination of the ventro-lateral nucleus of the thalamus) must be distinguished from the more diffuse increase in signal intensity of the abnormal thalamus in the neonate with hypoxia. The abnormal signal intensity on T1-Weighted Images (T1WI) was more subtle than that seen in the basal ganglia, in such cases sagittal T1-weighted images can be especially helpful in detecting signal abnormalities when volume-averaging artifacts are suspected on axial or coronal images. Axial diffusion weighted images are even more helpful in such cases. A range of increased intensity can be seen, from the very subtle to the overtly hyperintense.

Findings on diffusion-weighted imaging: The third finding of neonatal hypoxic injury is restricted diffusion in the basal ganglia and the thalamus manifested by bright signal on diffusion-weighted images and reduced apparent diffusion coefficient values on apparent diffusion coefficient maps. Diffusion-weighted imaging sequences can be overtly abnormal when other signs are only subtly abnormal or even normal. Studies using serial diffusion imaging of term neonates with hypoxic injury show the appearance of regions of restricted diffusion is a dynamic process, beginning on day 1 of life and progressing over the next week [12]. Restricted diffusion can be seen in the first 24 hours after birth, but the degree of restricted water diffusion often increases over the first few days of life, frequently achieving maximum decrease in apparent diffusion coefficient values at approximately five days. In addition, new regions of restricted diffusion that are not seen on day 1 may evolve in the first week of life. Nonetheless, diffusion-weighted imaging has limitations. For instance, increased signal intensity on diffusion-weighted images and concomitant decreased apparent diffusion coefficient values are typically seen for only 10-12 days after tissue death [8]. Beyond that time, diffusion-weighted images appear normal despite the presence of tissue injury. In some instances, diffusion-weighted images again begin to attain a normal appearance early as four days after the tissue injury [12]. Stated differently, diffusion-weighted imaging is informative when abnormal findings are present. However, normal diffusion weighted imaging findings do not exclude hypoxia; in such cases, when hypoxia is suspected, reliance on the above two findings should be increased. These findings should be systematically reviewed in each term neonate with a possible history of hypoxia.

In addition to the above three major findings described in this study, in severe hypoxic injury two additional findings of cerebral injury may be seen. The first additional finding is that of profound global injury involving both the gray matter and the white matter, a finding that is much less common than any of the focal injury patterns outlined previously. In the present study out of 30 cases profound injury leading to cystic encephalomalacic changes was noted only in two cases [Table/Fig-3]. The second additional finding is that of parasagittal gray and white matter injury, which is characterised by the presence of bilateral or unilateral cortical and subcortical white matter necrosis in the parasagittal area. This finding is consistent with study by Campistol J et al., [13]. If severe the parasagittal abnormality may extend to the pre- and postcentral gyrus areas (Perirolandic area) [Table/Fig-5]. Incidental hydrocephalus was noted in a 12-day-old baby with low APGAR score of 1 at 1 minute [Table/Fig-2].

Findings in the neonate with low APGAR (1 minute APGAR score ≥2) who were subjected to MRI in the present study: Most of the neonates with 1 minute APGAR score 3 have no abnormal brain findings on MR imaging. Some of the neonates with 1 minute APGAR score 2 also showed abnormal brain findings in the form parasagittal cortical and subcortical areas of diffusion restriction on DW imaging.

MR spectroscopy findings: MR spectroscopy findings in full-term infants with hypoxic-ischaemic injury included in this study are elevation of choline relative to creatinine, decreased N-Acetyl Aspartate (NAA), and the presence of a lactate peak. Decrease in ratios such as NAA/creatinine and NAA/Choline and increase in Cho/Cr ratio. The metabolites are noted to alter in babies even though there are no abnormal brain findings on conventional MR study.

Positive correlation was noted between APGAR score and basal ganglia NAA, Cr metabolites. Negative correlation was noted between APGAR score and Basal ganglia Cho metabolite. Elevated lactate levels are more sensitive in determining poor neurological outcome when

compared to NAA/Cr ratio [14]. When convention MRI fails to diagnose hypoxic ischaemic encephalopathy in term neonates MRS acts as a problem solving tool. Establishing normal basal ganglia metabolite levels by more studies will improve further the disease diagnosing efficacy [15].

The results of the present study was found correlating with a study conducted by Pavlakis SG et al., on 20 infants with low APGAR, where basal ganglia region NAA-Cho and NAA-Cho Cr ratios correlated with the 1 minute and 5 minute and strongest predictions exist between the 1 minute Apgar scores and the NAA-Cho and NAA-Cho Cr ratio [7].

Correlation was also noted with a study conducted by Guo L et al., on 24 full term neonates with HIE and five normal neonates, where basal ganglia NAA/Cr, Choline/Cr and Lac/Cr in HIE group were significantly different compared with normal neonates. In their study NAA values were noted to decrease with increase in severity of HIE and Cho values were noted to increase with increase in severity of HIE. However, Cr values were found to be constant with no variation with severity of HIE [16].

The findings of the present study was also found consistent with prospective study conducted by Cheong JLY et al., on 17 term neonates with HIE and 10 healthy neonates. Based on neurodevelopmental outcome at the end of one year, infants with HIE were classified into two outcome groups namely normal/mild and severe/fatal. After MR spectroscopy analysis it was found that there was decrease in NAA and increase in Cho, Cr and Lac in severe/fatal group when compared to control group [17].

In the present study, babies with borderline low APGAR scores of 3 at 1 minute have no abnormal brain findings or lactate peak. Those babies with APGAR score of 2 at 1 minute showed only subcortical and parasagittal areas of diffusion restriction. Basal ganglia diffusion restriction is noted only in babies with very low APGAR score of 1 at 1 minute. The findings in this study is consistent with “MRI imaging of HIE in term neonates- pearls and pitfalls” a study conducted by Ghei SK et al., [18]. If APGAR score indicates severity of asphyxia, the present study results suggest that there is a correlation between brain metabolite levels and perinatal asphyxia. But further studies are necessary to establish normal basal ganglia metabolite levels.

In conclusion, combined approach using clinical variables, MRS derived basal ganglia metabolite levels, routine and diffusion weighted MRI will define an asphyxiated population with high risk for poor neurodevelopmental outcome. Such infants should be targeted for brain resuscitation measures in future treatment trials which help reducing the risk for cerebral palsy, hence improving the outcome.

Limitation(s)

Performing the study on babies is a difficult task. Because of long scan duration sedation is must. Difficulty in monitoring vitals of severe hypoxic babies during MR study is another restraint. The above results of the study does not hold good for preterm babies, term neonates with congenital malformations like hydrops, neural tube defects and babies with metabolic disorders. Non availability of normal basal ganglia metabolite level is a setback, establishing this value with further studies will improve the diagnostic value of MRS in perinatal hypoxia.

CONCLUSION(S)

Basal ganglia NAA- metabolite ratios (p-value <0.001) are directly related to the one and 5 minute APGAR score and BG-Cho: Cr ratio (p-value <0.001) is indirectly to the one and 5 minute APGAR score. The use of routine and diffusion weighted MRI assists in defining focal brain insults and MRS has added benefits to it.

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