Original Research Paper

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Radiology

MRI IN HYPOXIC ISCHEMIC ENCEPHALOPATHY WITH CLINICAL FOLLOW UP

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ABSTRACT

Introduction: HIE is often clinically suspected in the setting of a known perinatal stress event arising from a complicated or difficult delivery. The most sensitive and specific imaging technique for examining infants with suspected hypoxic-ischemic brain injury is MR imaging. It also gives information about the timing and specific patterns of injury and also suggest diagnoses other than HIE such as metabolic disorders and developmental disorders of the brain. MRI is also a useful tool in the determination of prognosis and also follow-up of HIE.

Aim: This study was undertaken to evaluate the various MRI appearances of hypoxic ischemic encephalopathy in term and preterm neonates and to correlate the MRI appearances with clinical outcome.

Materials and Methods: All neonates with history of birth asphyxia, referred for MRI examination to the Department of Radio-Diagnosis, K. R. Hospital attached to Mysore Medical College and Research Institute, during January 2018 to January 2019. All MRI scans were performed on GE optima MR360 1.5 Tesla. Sequences used were T1W axial, T1 FLAIR axial, T2W axial, T2 FLAIR axial, T1W sag, T2W coronal, T2W GRE axial, DWI axial and ADC maps.

Results: 30 babies with clinically suspicion of HIE and positive findings on MR imaging were evaluated in our study. Out of 30 babies, 18 were term and 12 babies were preterm. Periventricular luecomalacia is most common MRI pattern in preterm and central pattern in term neonates. 16 babies had abnormal developmental outcome at 6 months follow up study. 16 babies with diffusion restriction in corpus callosum, 12 had abnormal outcome. 7 out of 10 babies with loss of normal signal in internal capsule had abnormal outcome. Babies with diffusion restriction in basal ganglia had gross developmental delay.

Conclusion: MRI is the modality of choice for evaluation of HIE because of excellent gray – white matter resolution, well-depiction of myelination pattern and multi-planar imaging capabilities. There is a strong relation between the MRI appearances of birth asphyxia and the clinical outcome. Therefore MRI has a strong role in prognosticating lesions.

KEYWORDS : Basal ganglia and thalamus, Corpus callosum, Posterior limb of internal capsule, Periventricular luecomalacia, Germinal matrix haemorrhage

INTRODUCTION:

Hypoxic ischemic encephalopathy (HIE) is one of the most common causes of cerebral palsy and other severe neurologic deficits in children, occurring in two to nine of every 1000 live births. Hypoxic-ischemic encephalopathy (HIE), which is also known as hypoxic-ischemic injury, refers to the subset of neonatal encephalopathy that results from a hypoxic or ischemic event, often in the setting of perinatal asphyxia, which leads to hypoxemia and hypercapnia (1).

Imaging evaluation of HIE with ultrasonography (US), computed tomography (CT), and magnetic resonance (MR) is widely beneficial in evaluating the cause and severity. The most sensitive and specific imaging technique for examining infants with suspected hypoxic-ischemic brain injury is MR imaging. It also gives information about the timing of the injury, and specific patterns of abnormality may suggest diagnoses other than HIE such as metabolic disorders and developmental disorders of the brain.

Imaging findings in HIE are highly variable and depend on a number of factors, including brain maturity, severity and duration of insult, and type and timing of imaging studies. (2,3)

Diffusion-weighted imaging (DWI) is very useful for the early identification of ischemic tissue in the neonatal brain but may underestimate the final extent of injury, particularly basal ganglia and thalamic lesions. MR imaging is an excellent predictor of outcome following perinatal brain injury and can therefore be used as a biomarker in interventional trials designed to reduce injury and improve neurodevelopmental outcome (4).

Conventional MRI sequences (T1W and T2W) provide information on the status of myelination and pre-existing developmental defects of the brain. When performed after the first day (and particularly after day 4), conventional images may accurately demonstrate the injury pattern as areas of hyperintensity. Conventional images are most helpful at 7-10 days of age when the diffusion-weighted imaging (DWI) findings have pseudo-normalized.

MRI is also used for follow-up. In any newly diagnosed case of cerebral palsy, MRI should be considered because it may help establish the cause (5).

MATERIALS AND METHOD:

A hospital based descriptive study with sample size of 30 patients. These cases were referred from the Department of pediatrics, Mysore Medical College And Research Institute, KR Hospital, Mysore, during the period from January 2018 to January 2019. The MRI examination of the spine was performed using a standard surface coils and body coils, of GE Optima MR360 1.5 Tesla

The MRI examination was performed using a standard surface coils and body coils, of GE Optima MR360 1.5 Tesla

The MR imaging protocol as part of the routine protocol comprised of T2W (axial and coronal), T1W (axial), T1 FLAIR (axial), T2 FLAIR (axial), DWI (axial), and GRE(axial). Data was analysed for age, sex, gestational age distribution, birth weight, clinical staging, overall patterns in HIE, patterns in preterm, patterns in term, distribution of other lesions, outcome of patients. Further the lesion in corpus callosum, basal ganglia and thalami and posterior limb of internal capsule is correlated with outcome. Approval of the research proposal was sought from the Ethical and Research Committee of Mysore medical college and research institute.

STATISTICALANALYSIS

The results of the study were tabulated and evaluated descriptively by Microsoft excel 2016. Also the results were presented in figures, tables, frequency graphs and pie charts.

RESULTS:

The age of patients in the study group ranged from 1 to 30 days. Most of the patients were in the ages 6 to 10 days (Table / Fig 1). Out of a total of 30 patients, 18 (60%) were male and 12 (40%) were female showing a slight male preponderance for HIE (Table/ Fig 2). Out of 30 patients, 18 patients were term patients (60%) and 12 (40%) were preterm, showing HIE to be more common in term patients in our study (Table/ Fig 3). Out of 30 patients, about 73.3% of the patients included in our study were normal weight. Only 26.6 % patients were classed as low birth weight (Table / Fig 4). Out of 30 babies who were part of the study, 14 patients (46.7%) were clinically staged as Stage II, 11 patients were graded Stage I (36.7 %) and 5 patients out of 30 were categorized as Stage III, corresponding to 16.7 % of the total study population (Table / Fig 5).

Mixed pattern of HIE changes is found in 11 patients (36.67%), followed by deep gray matter injury in 10 patients (33.33%) (Table / Fig 6). Periventricular injury in 6 (20%) and cortical injury in 3 (10%Out of 12 preterm patients with hypoxic ischemic encephalopathy, 6 patients (50%) had periventricular luecomalacia changes which constituted as most common finding in preterm babies. Germinal matrix hemorrhage was seen in 3 (25%) patients. Two patients showed signal changes in deep gray matter (16.67%). One patient had cerebellar hemorrhage (8.3%) (Table/Fig 7).The largest group demonstrated changes in the central structures only, 8 (44.4%) patients out of 18 term neonates. These structures included the thalami, basal ganglia, internal capsules and the corpus callosum. Most of the patients showed signal changes in corpus callosum. The next significant group by numbers was the patient population with mixed findings. 6 patients out of 18 (33.33%) patients had findings that categorized them in the mixed category. Watershed pattern of changes was seen in 3(16.67 %) patients. And one patient had cerebellar hemorrhage (5.56%)(Table/Fig 8). Out of 30 patients included in the study, 16 (53.3 %) had abnormal outcomes at 6 months follow up, 10 (33.3%) had normal outcomes at 6 months and follow up of 4 (13.3%) were lost. Among 16 patients with abnormal outcome, 6 patients have developed cerebral palsy, 6 patients have delayed milestones, and two patients have gross developmental delay and two patients died because of severity of hypoxic ischemic encephalopathy (Table / Fig 9). This study recognizes the limitations of a six-month follow up as many of the neurological sequelae of birth asphyxia are known to manifest in a delayed fashion. Out of 30 neonates, 16 neonates showed presence of restricted diffusion within corpus callosum involving varying regions like body, splenium and genu of which 12 neonates (75%) had abnormal outcome(Table / Fig 10). Out of 10 patients had restricted diffusion in the posterior limb of the internal capsule, 7 (70%) patients, had abnormal clinical outcome. Two patients were normal and follow up of one patient was lost (Table /Fig 11). Four patients had restricted diffusion within the basal ganglia and thalami, of which three (75%) had abnormal outcomes and follow up of one patient been lost. The clinical outcomes associated with lesions of the basal ganglia included gross developmental delayed in two patients and one patient died on follow up and one patient the follow up was lost (Table / Fig 12).

DISCUSSION

Out of 30 neonates, most of the neonates included in our study belonged to the age group of 6 to 10 days. In a study done by Priyanka et al[6] most of the neonates included in the study belonged to the age group of 6 to 10 days. Out of a total of 30 patients, 18 (60%) were male and 12 (40%) were female showing a slight male preponderance for HIE. In a study carried out by Azhar Munir Qureshi[7] et al 79.6% were males and 20.4% were females. In another study done by Basavaraj Patil[8] et al, among the 37 cases included in the study, 22 were males, 15 were females. The study was done by Cheung et al[9] in 15 neonates, 11 male and 4 female neonates. Thus, our findings corroborate well with the above studies.

Out of 30 patients, 18 patients were term patients (60%) and 12 (40%) were preterm, showing HIE to be more common in term patients in our study. In a study by Ramachandran et al[10] in 50 neonates with HIE, 41 neonates were term infants and nine neonates were preterm. Out of 30 patients, about 22 (73.3%) patients included in our study had normal birth weight. Only 8 (26.6 %) patients were classed as low birth weight. In the study by Ramachandran et al[10] study total of 33 neonates had normal birth weight (>2.5kg at birth), 13 had low birth weight (1.5-2.5kg) and four had very low birth weight.

Out of 30 babies who were part of the study, 14 babies (78.3%) were clinically staged as Stage II, 11 patients were graded Stage I (36.7 %) and 5 out of 30 were categorized as Stage III, corresponding to 16.7 % of the total study population.

The number of subjects with Grade III injuries that who could be included in the study was less due to the unstable clinical picture associated with the same and the difficulties in obtaining MRI in patients on respiratory support. The findings of our study correlated with Priyanka et al[6], out of 45 babies who were part of the study, 35 babies (77.8%) were clinically staged as Stage II, 6 patients were graded Stage I (13.3%) and 4 out of 45 were categorized as Stage III, corresponding to 8.9% of the total study population. Concluded that the number of subjects with Grade III injuries that who could be included in the study was less due to the unstable clinical picture associated with the same and the difficulties in obtaining MRI in patients on respiratory support.

Overall most common MRI finding in our study group is deep gray matter seen in 11 patients (33.6%) followed by mixed pattern injury in 10 patients (33.3%) (Table/ Fig 18). Periventricular injury in 6 patients (Table /Fig 14) (20%) and the cortical injury was seen in 3 patients (10%). James Barkovich et al[11] undertook a study in 16 neonates to detect changes of Neonatal Hypoxic-Ischemic Encephalopathy and most common pattern in their study is deep gray matter injury, seen in 9 patients. The mixed pattern in 3 patients, watershed injury in 3 patients and periventricular injury in one patient.

- **MRI FINDINGS IN PRETERM:**

In our study, periventricular leukomalacia changes constituted as the common finding in preterm babies, seen in 6 preterm babies accounting for 50% (Table /Fig 14). Basal ganglia thalami pattern is seen in severely asphyxiated patients (Table / Fig 15).

Barkovich and Sargent[11] described five profoundly asphyxiated preterm infants. The characteristic pattern of basal ganglia thalami injury was found in 5 patients. Thus concluding profound asphyxia results in basal ganglia-thalamic injury.

Barkovich & Turvit[12] found partial asphyxia generally results in damage to the periventricular white matter with relative sparing of gray matter structures

In our study babies with partial asphyxia had the predominant periventricular injury and severely asphyxiated babies had the basal ganglia-thalamic injury. The finding of our study correlated with the above studies.

Another study done by Logithraj et al[13] in 55 preterm infants, found white matter changes as most common finding in 42 infants (89%), associated with followed by basal ganglia-thalamic injury.

Another study done by Sie et al[14] periventricular leukomalacia was seen in 51 patients (73%)

Our study correlated well with the study done by Khalandkar et al[15], with 26 preterm HIE patients and showed periventricular leukomalacia as the most common pattern.

- **MRI FINDINGS IN TERM:**

Central pattern of injury is most commonly seen in our study followed

by the mixed and watershed pattern (Table /Fig 16).

Our study correlated with Priyanka et al[6], studied 36 patients positive for HIE, reported central pattern (17 patients – 37.78%) as the most common pattern followed by mixed pattern constituting 14 cases.

The study done by Sie et al[14], central pattern of injury was most common in term patients constituted about 20% of total cases (21/104 patients).

- **DISTRIBUTION OF FOLLOW UP OF HIE PATIENTS IN STUDY GROUP**

Among 16 patients with abnormal outcome in our study, 6 patients have developed cerebral palsy, 6 patients have delayed milestones, and two patients have the gross developmental delay and two patients died because of the severity of hypoxic-ischemic encephalopathy.

In our study, basal ganglia injury patient had a severe developmental delay. The outcome was better in patients in patients with the periventricular injury.

Two babies died on follow up in our study, one patient with cerebellar hemorrhage and another patient had severe basal ganglia and thalami injury.

The study was done by Logithraj et al[13] also found infants with white matter abnormality were associated with better outcome and severe outcome or death in infants with basal ganglia and brainstem injury

COMPARISION OF MRI FINDINGS WITH CLINICAL OUTCOME:

- **LESIONS IN THE POSTERIOR LIMB OF THE INTERNAL CAPSULE :**

70% of patient with restricted diffusion in the posterior limb of internal capsule had an abnormal outcome.

This is in partial concordance with the observations provided by Mary A. Rutherford et al[16] examined 73 term neonates with HIE between 1 and 17 days after birth with cranial magnetic resonance imaging and correlated the findings to neurodevelopmental outcome at 1 year of age. All infants with abnormal signal intensity in the PLIC developed neurodevelopmental impairment. A normal signal intensity was associated with a normal outcome in all except 4 cases; 3 of these infants had minor impairments and 4th infant with abnormal signal intensity on day 2 died before a further image could be obtained.

Priyanka et al[6] studied 45 patients, showed 55 % of patients with loss of the normal signal in the posterior limb of the internal capsule had abnormal outcomes at 5 months.

- **LESIONS WITHIN THE BASAL GANGLIA AND THALAMUS REGION:**

In our study patients with restricted diffusion in basal ganglia and thalami had global developmental delay and death of one patient. Many studies have found the basal ganglia watershed score to be an excellent predictor of the neurological outcome.

Kaufman et al[17], have shown that more basal ganglia involvement in MRI correlates with more severe encephalopathy.

Steinman et al[18] only children with no functional motor impairment were included. When all children were examined at 30 months, injury predominating in the basal ganglia /thalamus was associated with the worst cognitive and motor outcomes.

In the study conducted by Mary Rutherford et al[16] also concluded that bilateral basal ganglia abnormalities are associated with severe developmental delay, but infants with mainly white matter and cortical abnormalities have less severe problems despite extensive tissue loss.

In a study done by Priyanka et al[6], Seven patients had restricted diffusion within the basal ganglia, of which five (71.4%) had abnormal outcomes and 2 patient (28.5%) had a normal outcome.

Our study matches with the above studies where it was found that outcome was severe in patients with basal ganglia abnormalities

In the study done by Logithraj et al[13], Severe BGT and brainstem injury was associated with a severe outcome or death in infants (95%). One infant had a moderate outcome. Isolated WM signal abnormalities were associated with a normal outcome in two infants and a mild outcome in one. Infants with mild BGT lesions in the absence of WM or brainstem lesions had a normal outcome.

- **IMPORTANCE OF CORPUS CALLOSAL LESIONS :**

In our study, about 75%neonates showed abnormal outcome with restricted diffusion within corpus callosum involving varying regions like body, splenium, and genu.

A study by Takenouchi et al[19] is the only published study to document diffusion restriction in the corpus callosum in HIE. Authors reviewed images of 34 infants in the study. Ten of the 34 (29%) infants demonstrated restricted diffusion within the splenium of the corpus callosum, with a significantly higher incidence of severe developmental delay or death, compared to infants without restricted diffusion in the splenium of the corpus callosum.

Another study done by Kale et al[20] restricted diffusion on DWI was noted in 16 out of 40 patients (40%). Patients with the restricted diffusion of the entire corpus callosum, as well as those with isolated involvement of the splenium and the genu were documented. Corpus callosum injury was associated with more severe clinical presentations.

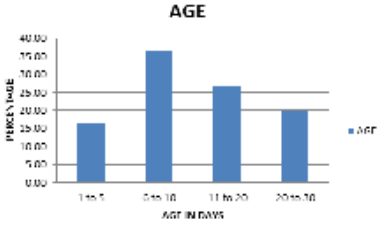
CONCLUSION:

This is a prospective study done with clinically suspected hypoxic brain damage from antenatal and perinatal insults including both term and preterm infants. This study attempted to evaluate the various magnetic resonance imaging changes in hypoxic-ischemic encephalopathy in term and preterm neonates. It set out to categorize and suitably classify the various MRI patterns of disease in these patients. It was found that MRI is superior to other imaging modalities in the evaluation of neonatal hypoxic-ischemic encephalopathy. There is a strong and consistent correlation between the various MRI findings and the final clinical outcome. MRI has a high sensitivity and specificity in the evaluation of the above condition. It is non-invasive and has no radiation hazards. It offers excellent gray-white matter differentiation and well depiction of the pattern of myelination for which Computed Tomography is incapable. Diffusion-weighted imaging adds sensitivity and provides information not seen on the other conventional sequences. Many of the signs of hypoxic-ischemic encephalopathy are based on diffusion-weighted imaging. MRI findings can further predict the outcome of the patients and help in accessing the prognosis of the patients affected with HIE. MRI findings likely periventricular pattern in preterm and watershed pattern in term patient has the good prognosis and central pattern of injury involving basal ganglia and thalami, corpus callosum and loss of normal signal in the posterior limb of internal capsule had the bad prognosis on follow-up in our study. Though CT is considered the initial imaging modality, that is easily available, multi-planar MRI has is the modality of choice for HIE. The main limitation of this study is the lack of systematic follow-up neuroimaging. Also, patients could be followed up for a maximum of 6months time at follow up clinics and it has been recognized that subtle neurodevelopmental abnormalities can occur years after birth asphyxia. It was found in our study that MRI has significant advantages over other imaging modalities in the evaluation of neonatal HIE. The drawbacks with this modality are few if any. One of them being prolonged scan times as well as the difficulty in obtaining seams in patients with severe birth asphyxia.

TABLES/ GRAPHS

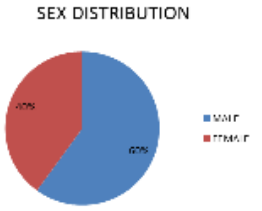
Table/Fig-1: Age distribution of patients

Age (days)	No	Percentage
1 to 5	5	16.67
6 to 10	11	36.67
11 to 20	8	26.67
20 to 30	6	20



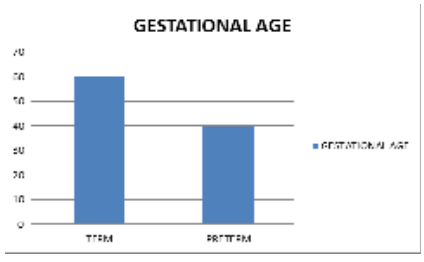
Table/Fig-2: Gender distribution of patients

Sex	Frequency	Percentage
M	18	60
F	12	40
Total	30	100



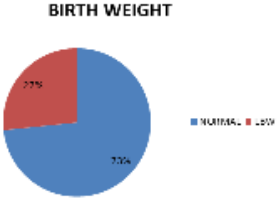
Table/Fig-3 : Gestational age distribution of patients

GESTATIONAL AGE	NO	PERCENTAGE
TERM	18	60
PRETERM	12	40
TOTAL	30	100



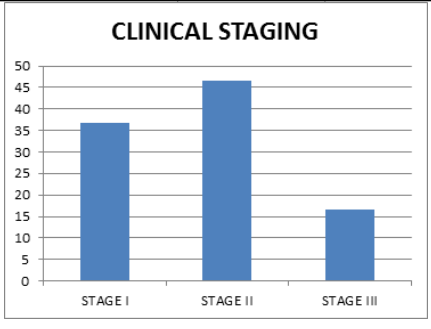
Table/Fig-4 : Distribution of birth weight of patients

BIRTH WEIGHT	NO	PERCENTAGE
NORMAL	22	73.33
LBW	8	26.67
TOTAL	30	100



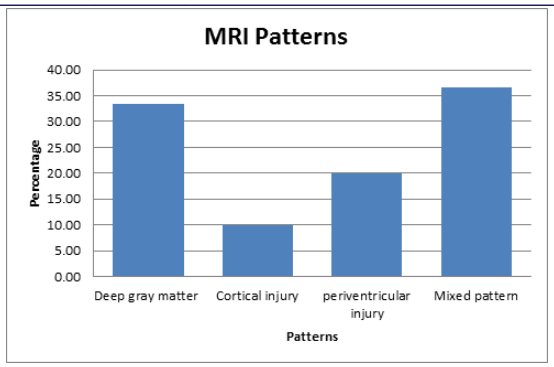
Table/Fig-5: Distribution of clinical staging of patients

CLINICAL STAGING	NO	PERCENTAGE
STAGE I	11	36.7
STAGE II	14	46.7
STAGE III	5	16.7
TOTAL	30	100



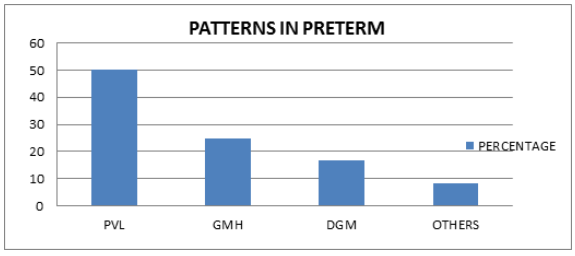
Table/Fig-6: Distribution of patterns of HIE in patients

MRI Patterns of HIE		
MRI Patterns	No	Percentage
Deep gray matter	11	33.67
Cortical injury	3	10
periventricular injury	6	20
Mixed pattern	10	36.33
Total	30	100



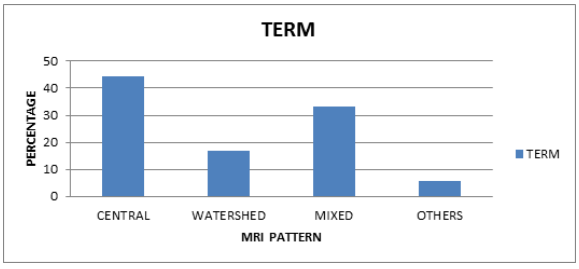
Table/Fig-7: Distribution of patterns of HIE in preterm patients

MRI PATTERN	NO	PERCENTAGE
PVL	6	50
GMH	3	25
DGM	2	16.67
OTHERS	1	8.33
TOTAL	12	100



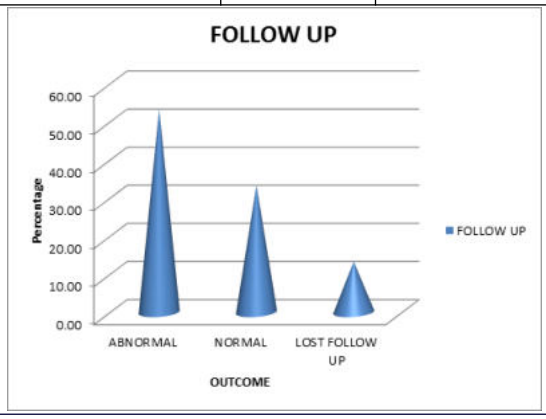
Table/Fig-8: Distribution of patterns of HIE in term patients

MRI PATTERN	NO	PERCENTAGE
CENTRAL	8	44.44
WATERSHED	3	16.67
MIXED	6	33.33
OTHERS	1	5.56
TOTAL	18	100



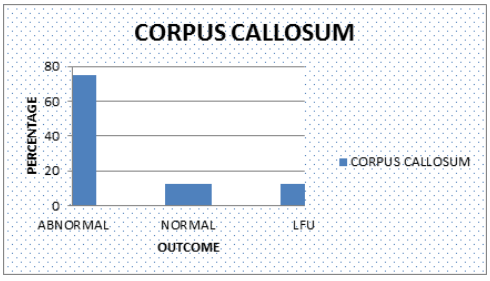
Table/Fig-9: Distribution of follow up of HIE patients

FOLLOW UP	NO	PERECNTAGE
ABNORMAL	16	53.33
NORMAL	10	33.33
LOST FOLLOW UP	4	13.33
TOTAL	30	100



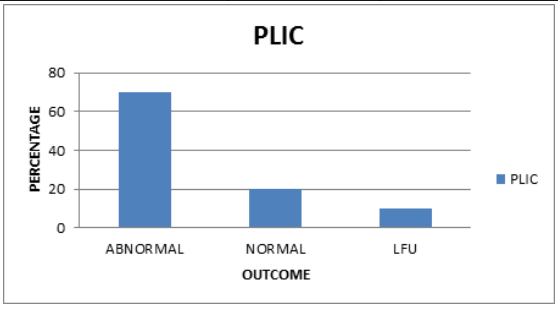
Table/Fig-10: Distribution of correlation of restricted diffusion in corpus callosum with outcome HIE patients

Outcome	NO	Percentage
Abnormal	12	75
Normal	2	12.5
LFU	2	12.5
Total	16	100



Table/Fig-11 : Distribution of correlation of restricted diffusion in PLIC with outcome HIE patients

Outcome	No	Percentage
Abnormal	7	70
Normal	2	20
Lost follow-up	1	10
Total	10	100



Table/Fig-12: Distribution of correlation of restricted diffusion in BGT with outcome HIE patients

Outcome	No	Percentage
Abnormal	3	75
Normal	0	0
Lost follow-up	1	25
Total	4	100

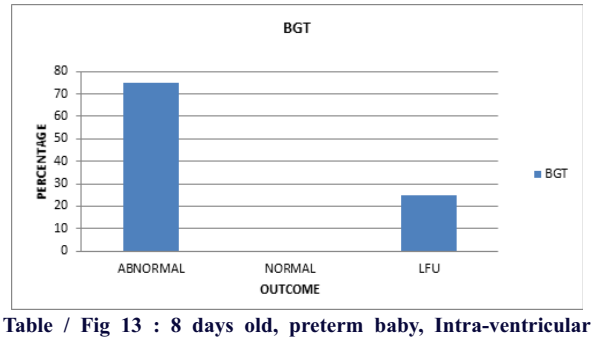
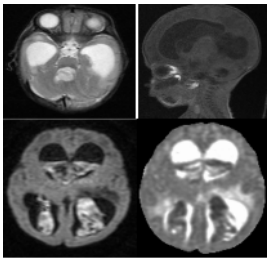
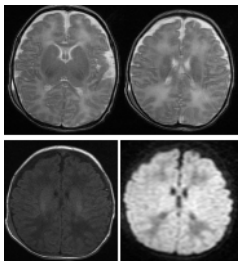


Table / Fig 13 : 8 days old, preterm baby, Intra-ventricular hemorrhage



Axial T2W and Sag T1W shows bilateral lateral third and fourth ventricles are dilated with hyper-intense foci on T2. DWI there is e/o restriction within ventricles. Grade 3 germinal matrix hemorrhage.

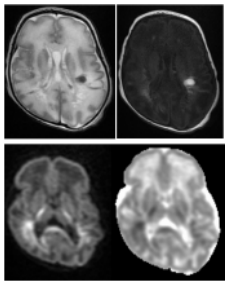
Table / Fig 14 :7days old preterm baby with Periventricular pattern of injury.



Axial T2W images shows diffuse periventricular hyperintensities, hypointense on T1W.

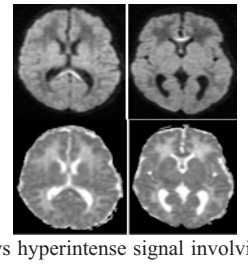
DWI shows no evidence of restriction.

Table / Fig 15 : 16days old, Term baby with severe grade HIE changes.



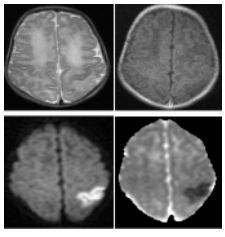
Axial T2W MR: shows periventricular hyperintensities with hypointense focus, hyperintense on T1W images s/o hemorrhage. On DWI diffusion restriction seen in corpus callosum and periventricular parieto-occipital lobes.

Table / Fig 16 : 20 days old term baby with Central pattern of injury



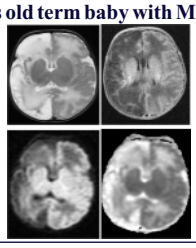
DWI images shows hyperintense signal involving corpus callosum body and splenium. Corresponding ADC maps shows low signal s/o diffusion restriction.

Table / Fig 17 : 28 days old term baby with Watershed pattern of injury



Axial T2W and T1W images shows subtle hyperintense signal in left parietal lobe on T2, hypointense on T1. On DWI with corresponding ADC maps shows diffusion restriction.

Table / Fig 18 : 22 days old term baby with Mixed pattern of injury



Axial T2W images shows hyper-intense signal in bilateral fronto-temporo- parietal and occipital lobes, hypointense on T1. On DWI with corresponding ADC maps shows no evidence diffusion restriction.

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