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# MRI changes of brain in newborns with hypoxic ischemic encephalopathy clinical stage ii or stage iii- a descriptive study

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## Abstract

**Objectives:** The aim of the study was to estimate the proportion of MRI changes in newborns with HIE, to compare the findings of term and preterm babies and to identify if there is any clinical stage specific MRI findings

**Methods:** After obtaining clearance from ethical committee, 30 newborns with either stage II or stage III HIE are included in the study. MRI brain was taken between one to two weeks of age once the vitals of the babies are stable & after ensuring euthermia.

**Results:** Out of the 30 babies, 19 were male babies and 11 female babies. 16 of them were term and 14 of them preterm babies.27 of the total 30 patients had MRI changes of HIE, which accounts for 90%. 17of the 30 mothers were primi mothers which accounts for 56.7%. Most important antenatal factors associated with HIE are gestational hypertension and UTI. Gestational diabetes mellitus and placental/cord factors are also found to be important contributing factors. 33.4% had a history of UTI, 30% gestational hypertension, 23.4% gestational diabetes mellitus in the antenatal period.

**Conclusion:** Basal ganglia and/or thalamus were affected in 50% of term babies. 87.5% of babies with periventricular leucomalacia are preterms. Intracranial hemorrhage was seen in 7.4% of the babies and all of them were preterms. Out of the four babies with clinical stage III HIE, 50% of them had bilateral basal ganglia involvement. 25% had thalamic involvement. In stage II HIE, no specific change could be found.

**Keywords:** HIE; MRI brain; Basal Ganglia Thalami; periventricular leukomalacia

## Introduction

Perinatal asphyxia is one of the common problems encountered in NICU. HIE is the most important consequence of perinatal asphyxia.(1) It has a spectrum of clinical manifestations ranging from mild to severe, which correlates with severity of insult and gestational age.(2) Cerebral injuries in newborns with HIE are associated with different clinical and neuro developmental outcome.(3) Perinatal asphyxia can be diagnosed from careful history and thorough clinical examination.(4) According to sarnat & sarnat clinical staging, hypoxic ischemic encephalopathy is divided into three stages. MRI is the most sensitive imaging technique for depicting developing brain. It can provide important diagnostic and prognostic information needed for optimal treatment and appropriate counseling.

According to recommendation of American Association of Neurology MRI should be performed at the end of 1st week of life, in order changes were evident in 75-100% of babies with HIE stage I-III with MRI taken at the end of 1st week or beginning of 2nd week of life.(7,7,8) Early MRI finding in HIE are – brain edema and hyper intensity within the basal ganglia, periventricular white matter, subcortical white matter and the cortex.(9) Cortical lesions, in frontal lobes and precentral gyrus, along with basal ganglia or thalamic injury is typical of severe perinatal asphyxia.(10) Unfavorable outcome is seen in patients with injuries of posterior limb of internal capsule.(7) MRI findings are not included in sarnat & sarnat staging. There are no changes in MRI which are specific to clinical stages. In this study, the aim is to identify whether there is any particular MRI finding that can be correlated with the clinical stages.

## Aim and Objectives

1. To identify whether there is any particular MRI finding in stage 2 and in stage 3 HIE.
2. To estimate the proportion of newborns with HIE having MRI changes.
3. To compare the MRI changes of term and preterm babies with HIE.

## Review of Literature

Perinatal asphyxia is a condition of impaired gas exchange that leads, if persistent, to fetal hypoxemia and hypercarbia.(11) WHO defines perinatal asphyxia as 'failure to initiate and sustain breathing at birth'.(12) HIE is characterized by clinical and laboratory evidence of acute or subacute brain injury due to asphyxia leading to hypoxia and acidosis. Multiple markers including, low apgar score, biochemical markers and the need for neonatal resuscitation reflects intra partum fetal and neonatal distress.(13-16) Which can lead to a process of neurological cell injury and brain damage. The incidence of acute neurological symptoms within the first hour of life is 1- 3 per 1000 live births,(17,18) low socioeconomic areas the rate is approximately10 times higher.(19) The incidence of HIE varies between countries and different studies depending on the inclusion criteria and study population.(20) Maternal age at delivery did not appear to be significant.

A number of antepartum risk factors are identified which includes gestational hypertension, post term,

abnormal appearance of placenta, maternal thyroid disease, neurological disorder, treatment for infertility. Premature infants are more prone to ischemic injuries of the white matter. Neonatal brain injury is difficult to diagnose in premature infants because either obvious signs are absent or if present, are attributed to developmental immaturity.[24] Regional cortical volumes are significantly smaller in preterm brains.[25] This may lead to neurological findings, which may be difficult to differentiate from HIE and thus to missed diagnosis in this particular group of neonates.

**Diagnosis:** HIE is a clinical syndrome of disturbed neurological function manifested by difficulties with initiating and maintaining respiration, depression of tone and reflexes, subnormal level of consciousness and seizures.[26] Evidence of fetal distress and depression must also be present at birth. It is extremely important to distinguish hypoxic -ischemic event from other causes of neonatal encephalopathy.[27]

**Classification:** In clinical practice, the purpose of a classification system is to help diagnose, assess prognosis and be able to collect and compare research data.[28] Sarnat and sarnat described their HIE grading system in a study relating electroencephalographic findings to the clinical condition of the infants.[16] Since then it has been used by several authors and is now the basis for most modern evaluation schemes.[21,19] The classification system modified by Levene has three stages – mild (I), moderate (II), severe (III) - are based on clinical observation. During resuscitation, the infant is often hypotonic, apnoeic and lethargic. Infants with mild HIE (I) usually recover within 12-24 hours. They do not have seizure activity and present a normal a EEG /EEG pattern. Prognosis is uniformly good. Infants that deteriorate with altered levels of consciousness and clinical/subclinical seizure activity 12-24 hours after the hypoxic ischemic event have developed moderate-severe HIE (II-III). Electrophysiological abnormalities are common, including seizure activity and abnormal background pattern on a EEG.

**Clinical Markers:** Prospective studies show a correlation between intrapartal hypoxic ischemic events and neurological symptoms at birth. In two studies, conventional imaging techniques have reviewed the intrapartum events a) with ultrasound combined with autopsy.[33] and b) MRI combined with scoring of HIE,[9] predominant brain injury pattern and outcome.[34,35]

**Investigations-MRI:** Magnetic resonance (MR) imaging is non-invasive and non-ionizing type of imaging. It provides excellent soft tissue differentiation, making it the modality of choice for investigating numerous diseases of the brain.

**Timing the MR imaging:** Conventional scans performed within the first 24 hrs may appear normal even when there has been severe perinatal injury to the brain. Early imaging will help to differentiate antenatal from perinatal lesions. Perinataly acquired abnormalities 'mature' and become easier to identify by the end of the first week. For information on the exact pattern of injury a scan between1and 2weeks of age is usually ideal.

**Preparation for scanning:** Neonates can often be scanned without sedation during natural sleep. For those who need sedation, we usually use trichlofos orally. All neonates and infants undergoing MR scanning are monitored with ECG and pulse oximetry and a paediatrician is in attendance throughout.

**MR imaging of the normal neonatal brain:** In the neonatal brain, unmyelinated white matter (WM) has a low signal intensity (SI) onT1weighted images and high SI on T2 weighted images. Cerebrospinal fluid (CSF) is hypointense onT1 weighted imaging and hyperintense onT2 weighted imaging. Myelination begins at around 20weeks gestational age (GA) and continues up to around 2years of age. As myelination progress, the water content of WM decreases, causing a reduction in SI onT2 weighted imaging. There is a corresponding increase in glycolipids, cholesterol and proteins which causes an increase in SI on T1 weighted imaging.[37]

**MR imaging assessment of brain injury in term infants:** Term infants that develop HIE following a well-defined acute hypoxic-ischemic insult (e.g. placental abruption, uterine rupture) typically sustain bilateral lesions within the basal ganglia and thalami (BGT).[45] In term infants with HIE the main sites of abnormality are the posterior and lateral lentiform nucleus and the ventrolateral nuclei of thalami. More extensive lesions may involve all of the basal ganglia and medial areas of thalami and there may be spread downwards to involve the midbrain and the dorsal aspects of the medulla. Additional abnormalities associated with BGT lesions include early brain swelling, with diminished extra cerebral spaces and slit like ventricles. Abnormal, mainly short T1, appearances in the cortex so-called 'cortical highlighting' almost always accompany significant BGT lesions at term. The predominant sites are the central fissure, the interhemispheric fissure and the insula. The depths of the cortical sulci are preferentially affected.

Severe BGT lesions are also associated with abnormalities in the medial temporal lobe. These are not immediately obvious but by the end of the second week, there are often definite short T1areas within the hippocampal region and dilatation of the temporal horn as a result of adjacent tissue atrophy. In some infants with severe BGT, there are additional widespread abnormalities in the white matter with appearance of infarction giving rise to multicystic leucomalacia. The clinical outcome of the infant is dependent on the severity of the BGT lesions. Severe BGT lesions are associated with a spastic[18] or mixed dystonic/spastic quadriplegia, secondary microcephaly and marked intellectual impairment. In infants with a combination of BGT and multicystic leucoencephalopathy, the neurodevelopmental outcome is determined mainly by the severity of the BGT, particularly in terms of motor

impairment. Less severe BGT lesions are associated with the development of an athetoid quadriplegia usually with good preservation of intellect and normal head growth. Mild BGT lesions may be associated with late onset tremor, and mild but often transient abnormalities of tone.

**MRI assessment of brain injury in preterm infants:** The developing brain is highly susceptible to injury including periventricular leucomalacia (PVL), intraventricular haemorrhage/germinal layer hemorrhage (IVH/GLH) and parenchymal hemorrhagic infarction. The majority of preterm infants demonstrate some abnormality on brain MR imaging in the early neonatal period.[40] Additionally, quantitative MRI has revealed delayed myelination in adolescents who were born preterm[49] and reduced cortical folding.[43] In the preterm brain at term equivalent age compared with term born infants.[50]

## Materials and Methods-Study Design:

Descriptive study

**Study Population:** All newborns admitted in NICU, department of pediatrics, Govt. T.D. Medical College, Alappuzha with hypoxic ischemic encephalopathy-clinical stage II or stage III who survives beyond 7days.

**Study Setting:** Babies admitted in In Born Nursery or Out Born Nursery of the Department of the department of pediatrics, T.D. Medical College, Alappuzha.

**Period of Study:** November 2013 to November 2014.

**Sample Size:** According to study by Rutherford et al, incidence of MRI changes in stage II and stage III HIE is 93%. Using this information, sample size has been estimated to be 7 by the formula $Z\alpha 2pq/d2$ where, $Z\alpha=1.96$, p=93, q=7, d is the precision, 20% of p. As the incidence of HIE is low, all the newborns admitted with the above criteria will be included in my study.

**Inclusion Criteria:** Preterm and term neonates with clinical stage II or stage III hypoxic ischemic encephalopathy who survives beyond one week

**Exclusion Criteria**

1. Neonates with HIE stage I.
2. Neonates with major congenital malformation, CCHD, intracranial infection.

**Study Procedure:** After obtaining written consent from one of the parents, all the newborns fulfilling the inclusion criteria were enrolled in the study. Clinical staging of hypoxic ischemic encephalopathy in term neonates was done based on Sarnat & Sarnat staging system, and preterm babies were staged based on Levene (modified Sarnat & Sarnat) scoring system. Those newborns aged 1 week or more, MRI brain was taken from the department of radiology. Thermo neutral environment was ensured with blankets during the transport and while doing the procedure. A resident doctor accompanied the babies for the procedure. Our hospital has 1.5 Tesla MRI machine by hind labs. Changes in brain image were interpreted by chief radiologist. MRI changes in HIE were hyper intensity in basal ganglia, periventricular white matter, sub cortical white matter, cortex, internal capsule, insula, and intracranial hemorrhage.

According to our hospital protocol, MRI brain should be done in all babies with HIE stage II or stage III. MRI scan is done in medical college and is done free of cost for all newborns according to JSSK scheme by Govt. of India, if indicated. Proportion of newborns with MRI changes were assessed.

**Statistical Analysis:** Epi info statistical software was used for the descriptive data analysis. Qualitative data was analyzed using percentages and proportions. Quantitative data was analyzed using Mean and Standard deviation.

## Observation and Analysis

Thirty newborns with stage II or stage III HIE, who got admitted in NICU, T. D. Medical College, Alappuzha were enrolled in the study. Of the 30 babies, 19 were males and 11 females, which correspond to 63.3% of male and the rest female babies.

**Gender distribution in the study population**

| Sex | Frequency | Percentage |
|---|---|---|
| Male | 19 | 63.3 |
| Female | 11 | 36.7 |
| Total | 30 | 100.0 |

Out of the 30 babies 16 were term babies, which corresponds to 53.3% and 46.7% of pre-terms.

**Distribution of gestational age in the study population**

| GA | Frequency | Percentage |
|---|---|---|
| Preterm | 14 | 46.7 |
| Term | 16 | 53.3 |
| Total | 30 | 100.0 |

Of the 30 mothers, 56.7% were primi gravidae, 30% second gravidae and 13.3% multigravidae.

**Distribution of maternal parity in the study population**

| Gravid | Frequency | Percentage |
|---|---|---|
| Primi | 17 | 56.7 |
| Gravida 2 | 9 | 30.0 |
| Gravida 3 | 4 | 13.3 |
| Total | 30 | 100.0 |

21 mothers out of 30 belong to low socioeconomic group, which makes 70% of the total mothers. Of the 30 babies with hypoxic ischemic encephalopathy, 27 had MRI changes, which is 90% of the total.

**Distribution of MRI changes in the study population**

| MRI | Frequency | Percentage |
|---|---|---|
| Yes | 27 | 90.0 |
| No | 3 | 10.0 |
| Total | 30 | 100.0 |

Out of the total 7 babies, 40% had PVL, 40% of them had BG or thalamus lesion and the rest 20% had

involvement of occipital region in patients with maternal diabetes.

**Distribution of MRI change in patients with maternal diabetes**

| Site of Lesion | Percentage |
|---|---|
| PVL | 40 |
| BG/ thalamus | 40 |
| Occipital region | 20 |

Out of the 8 babies with a history of maternal hypertension, 37.5% had periventricular leucomalacia. 25% of them had involvement of bilateral basal ganglia. Insula, cortex lesions were seen in 12.5% of the babies. No MRI changes of HIE was noticed in 12.5% of them.

**Maternal Hypertension**

| Site of Lesion | Percentage |
|---|---|
| Bilateral BG | 25 |
| PVL | 37 |
| Insula | 12.5 |
| Cortex | 12.5 |
| No change | 12.5 |

There were 10 babies with history of maternal UTI. Out of the total, 35% of them had MRI changes of HIE in basal ganglia or thalamus. 20% had PVL and 20% had white matter and cortex involvement. Bilateral BG involvement was noted in 10% and bilateral thalami lesion seen in rest of the patients.

**Distribution of MRI changes in patients with maternal UTI**

| Site of Lesion | Percentage |
|---|---|
| BG/thalamus | 35 |
| Bilateral BG | 10 |
| Bilateral thalami | 10 |
| PVL | 20 |
| White matter & cortex | 20 |

Term babies were 16 in number. 37.5% had BG/ thalamus lesion. Bilateral BG lesion, b/l thalami lesion and subcortical involvement was seen in 12.5% each. Out of the total 14 preterm babies, 43% had PVL. Basal ganglia or thalamus involvement was seen in 21%. White matter and cortex involvement was noted in 21% of them. There was no MRI evidence of HIE in 14% of the babies.

In HIE 2 cases, out of the 23 patients 27% had involvement of corpus callosam. 25% had PVL, 23% had basal ganglia or thalamus lesion. There was no MRI evidence of HIE in 11.5%.

**Distribution of MRI changes in study population with stage2 HIE**

| Site of Lesion | Percentage |
|---|---|
| Corpus Callosam | 27 |
| BG/thalamus | 23 |
| No Change | 11.5 |
| PVL | 25 |

Out of 4 babies with stage 3 HIE, 50% had involvement of bilateral basal ganglia. 25% had bilateral thalami lesion and the rest showed subcortical white matter lesion.

**Distribution of MRI changes in study population with stage 3 HIE**

| Site of Lesion | Percentage |
|---|---|
| Bilateral BG | 50 |
| Bilateral thalami | 25 |
| Subcortical white matter | 25 |

## Discussion

The clinical diagnosis of birth asphyxia, along with the closely related conditions of hypoxic ischemic encephalopathy is recognized as an important cause of morbidity and mortality in newborns. Early diagnosis helps in management, prognosis and also in counseling the parents. MRI is the optimum modality of diagnosis in HIE. In our study, out of the 30 patients who were enrolled in the study, 27 had MRI changes seen in HIE. This comes to 90% which is comparable with study done by Rutherford et al, where the proportion was 93%. Our study shows male preponderance. According to a study by Zaneli SA, Stanley DP et al, there was no gender predilection. Male gender being a risk factor for HIE has also been reported by others. In our study, maternal UTI, maternal hypertension and gestational diabetes mellitus are associated with specific MRI changes. PVL is more associated with gestational HTN. Basal ganglia or thalamus lesion are more commonly seen in babies born to mothers with UTI in the antenatal period. Both periventricular leucomalacia, and BGT lesions are of equal proportion in babies with maternal diabetes. Our study shows, that term babies are more affected by MRI than preterms it may be because neonatal brain injury is difficult to diagnose in premature infants because either obvious signs are absent or if present, are attributed to developmental immaturity[36].. Preterm infants can also suffer from hypoxic ischemic encephalopathy, but, most often the change is not recognized early. For preterms findings will be obvious when MRI is done at corrected gestational age. Significantly higher numbers of primi gravida mothers in the affected babies are seen. It may be because the first delivery is more difficult than the subsequent ones. This points to the importance of intrapartum factors in the causation of HIE. In this study 70% of mothers belong to low socioeconomic group which has been found also by other authers. In our study, 65% of term babies had changes in basal ganglia and/or thalamus. Other authors have also observed this finding. This is because basal ganglia and thalami are metabolically very active in the immature brain. Occasionally severe basal ganglia lesions are seen with less obvious precipitating events. This may reflect failure to recognize the severity of asphyxia or due to individual

susceptibility to damage because of previous hypoxic ischemic events or underlying metabolic or thrombotic disorders.

Term infants who develop HIE following a well-defined acute hypoxic injury typically sustain bilateral lesions within the basal ganglia and thalami. In this study, out of the four babies with clinical stage 3 HIE 50% of them had bilateral basal ganglia involvement and 25% had bilateral thalami involvement. In stage 2 HIE no stage specific change in MRI could be found. Preterm brain is highly susceptible to injury including periventricular leucomalacia, intraventricular hemorrhage/ germinal layer hemorrhage and parenchymal hemorrhagic infarction 58. In this study 43% of preterm babies had periventricular leucomalacia. Also, MRI suggestive of hemorrhage was seen in preterm babies only which constitute 7.4% of all babies with positive MRI.

## Conclusion

Bilateral basal ganglia and/or bilateral thalami lesions are the predominant finding in stage 3 HIE. No specific change could be found in stage 2 HIE. Periventricular lesions and intracranial hemorrhage are predominantly seen in preterm babies. In term babies basal ganglia and/or thalamic involvement predominates. PVL is more associated with gestational HTN. BGT lesion predominates in UTI. In maternal diabetes above mentioned lesions shows equal predominance.

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