Correlation of Transcranial Ultrasound and Magnetic Resonance Imaging in Evaluation of Imaging Patterns of Clinically Diagnosed Hypoxic Ischaemic Encephalopathy in Neonates

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ABSTRACT

BACKGROUND
Hypoxic Ischaemic Injury (HII) is an important common cause of neonatal encephalopathy in newborns. Decreased cerebral blood flow and oxygen leads to acidosis, release of inflammatory mediators and excitatory neurotransmitters, and formation of free radicals. Initially, there is primary energy failure followed by a brief period of latency and secondary energy failure. The pattern of brain injury depends on duration, and severity of insult at the time of brain maturation. Clinical staging- Sarnat and Levene classification- was commonly used. Most authors describe a pattern of injury in neonates who are less than 36 weeks’ gestation that is distinct from the pattern in neonates 36 weeks or older. We wanted to determine and compare the role of Transcranial USG and MRI brain, in the evaluation of HIE in neonates with regard to its nature and extent.

METHODS
Consecutive fifty neonates clinically diagnosed with hypoxic-ischemic encephalopathy (HIE) by Levene’s classification were included. All cases had undergone transcranial ultrasound study of the brain. MRI Brain was performed in all patients after USG and findings were compared. The study was conducted between May 2015 and September 2017. They were collected from the Neonatology Intensive Care Unit (NICU) and Sick Newborn Care Unit (SNCU) at Burdwan Medical College & Hospital, Dept of Paediatrics.

RESULTS
Our study found that stages I and II showed predominantly mild to moderate HIE, presented with peripheral pattern and with white matter injuries, while stage III revealed severe HIE presented with predominantly central pattern of injury, i.e. Basal Ganglia and Thalamus (BGT).

CONCLUSIONS
TCUS helps in evaluation of various imaging patterns depending upon gestational age, severity, duration of insult, as depicted above. However, findings need to be corroborated with both conventional and diffusion weighted MRI findings. Both modalities are recommended as diagnostic protocol.

KEYWORDS
HII, HIE, TCUS, MRI, Neonates, Levene Grading

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Neonatal encephalopathy is characterized by disturbed neurological function in the earliest days of life, manifested by feeding difficulties, irritability, abnormality of tone, seizures, and reduced level of consciousness, and often accompanied by difficulty with initiating and maintaining respiration. When it is caused by diffuse hypoxic ischemic brain injury, it is called hypoxic-ischemic encephalopathy (HIE). HIE is one of the most common causes of cerebral palsy and other severe neurologic deficits in children, occurring in 2-9 of every 1000 live births.\(^1\)\(^-\)\(^3\) The incidence rate in premature babies is 60% of all live births. Apart from hypoxia and ischaemia, inflammatory factors (e.g. chorioamnionitis), metabolic conditions (e.g. hypoglycaemia), and heritable predispositions (e.g., COL4A1 gene mutations) play comorbid roles in HIE.\(^2\)

Although the exact pathophysiology of HIE is not known completely, the lack of sufficient blood flow in conjunction with decreased oxygen content in the blood leads to loss of normal cerebral autoregulation and diffuse brain injury. The exact nature of the injury depends on the severity of hypotension and the degree of brain maturation. There is no consensus of the gestational age demarcation at which an infant is considered preterm or term. However, most authors describe a pattern of injury in neonates who are less than 36 weeks’ gestation that is distinct from the pattern in neonates 36 weeks or older.\(^4\)\(^-\)\(^6\)

There are a number of symptoms associated with HIE including:- meconium-stained amniotic fluid (MSAF), low heart rate, poor muscle tone, weak breathing or no breathing at all, bluish or pale skin colour, excessive acid in the blood. Causes of HIE can be divided into intrauterine and post-natal. Intrauterine causes can be further divided into foetal and maternal causes. Important intrauterine foetal causes- Bradycardia, thrombosis, haemorrhage. Important intrauterine maternal causes are preeclampsia, abruptio, maternal hypotension, severe anaemia, chronic vascular disease, cord prolapse. Important post-natal causes -hyaline membrane disease, meconium aspiration syndrome, congenital cardiac disease, pneumonia.

Sarnat staging criteria or Levene staging commonly used to describe the severity of encephalopathy within the first several postnatal days of life in addition with neuroimaging to assess the severity of the encephalopathy for clinical grading.

### Table 1. Sarnat Stages of Neonatal Encephalopathy

| Assessment | Stage 1 | Stage 2 | Stage 3 |
|------------|---------|---------|---------|
| Mental status | Hyperalert | Lethargic | Stuporous |
| Suck reflex | Weak or absent | Weak or absent | Absent |
| Moro reflex | Strong | Weak | Absent |
| Muscle tone | Normal | Hypotonia | Flaccid |
| Autonomic function | Generalized parasympathetic | Generalized parasympathetic | Absent |
| Pupils | Mydriasis | Miosis | Variable |
| Seizures | Absent | Absent | Absent |
| EEG | Normal (awake) | Early: low-voltage theta and delta | Early: periodic pattern with isoelectric phases |
| Duration | < 24 hours | 2-14 days | Hours to weeks |

### Table 2. Levene Staging

| Feature | Mild | Moderate | Severe |
|---------|------|----------|--------|
| Consciousness | Irritable | Lethargy | Comatose |
| Tone | No | Yes | Prolonged or Uncontrolled |
| Seizure | Poor suck | Unable to suck | Absent suck |
| Respiration | Spontaneous | Periodic or irregular | Unable to sustain spontaneous respiration |

To the best of knowledge, this study is the first in West Bengal showing Radiological imaging pattern evaluation in clinically diagnosed and graded HIE neonates using Levene’s Classification.

Pathophysiology and patterns of injury varies with maturation of the brain at the time of injury, severity of insult, duration of insult, and existing comorbidities. The spectrum of brain injury in the preterm and term neonate is broad with distinctive qualities and points of overlap. The full appraisal of injury depends on the timing of imaging and the imaging modality selected.

### Preterm Newborns (Less Than 36 Completed Weeks)

Central or profound injury, perinatal white matter damage, germinal matrix haemorrhage, intraventricular haemorrhagic infarction, and periventricular haemorrhagic infarction, and cerebellar injury. The pattern of severe HII in the preterm newborns is similar to the profound or central pattern of HII in term newborns with a few notable exceptions. The superior cerebellar vermis, posterior limb of the internal capsule, and periorlantic cortex are not involved in preterm severe HII, as these structures normally myelinate at or near term. Severe or profound HII in preterm neonates preferably affects the early myelinating and metabolically active structures, including the thalami, basal ganglia (particularly posterior putamen), and dorsal brainstem, with relative cortex sparing except for the pre- and postcentral gyri. Mild to moderate HII can manifest in one of three general patterns: (1) Haemorrhagic: germinal matrix haemorrhage (GMH), intraventricular haemorrhage (IVH)/periventricular haemorrhagic infarction (PVHI); (2) Perinatal white matter damage (PWMD) Cerebellar injury. These patterns can occur independently or synchronously. Germinal Matrix Haemorrhage can be further graded into four types. Grade I subependymal GMH, typically at caudothalamic groove with no/minimal intraventricular extension. Grade II shows intraventricular haemorrhage with filling <50% of ventricular area with minimal ventriculomegaly. Grade III includes near complete filling (>50%) and distention of ventricle. Grade IV includes periventricular parenchymal haemorrhagic infarction secondary to haemorrhagic ventricular distention, venous ischemia, and haemorrhagic venous infarct. Unlike grade I-III bleeds, PVHI is not true GMH. The prevalence of GMH-IVH in preterm neonates is inversely related to gestational age and birth weight. Perinatal white matter damage (PWMD) is also known as periventricular leukomalacia (PVL). Prevalence is inversely related to gestational age at birth. White matter injury is most common adjacent to the foramen of Monro and lateral ventricle trigones. Three PWMD patterns have been described: diffuse, focal/multifocal-non cavitary, and
focal/multifocal-cavitary. Cavitory PWMD is the least common.

**Term Newborns (36 Completed Weeks)**
Severe HII preferably affects actively myelinating areas where NMDA receptors are highly concentrated. The deep grey matter (e.g. posterior putamina, ventro-lateral thalami), hippocampi, dorsal brainstem, superior vermis, optic radiations, and peri-rolandic cortical regions are most severely affected. Other at-risk regions include subthalamic nuclei, corticospinal tracts, and lateral geniculate nuclei. Severe HII in term infants may also lead to deep white matter injury and para-sagittal and other inter-arterial watershed infarcts. Less severe HII- Partial asphyxia generally spares the brainstem, cerebellum, and deep gray nuclei. Prolonged partial asphyxia causes hypoperfusion in the watershed (e.g. inter-arterial border) zones.

Aim of this study was to evaluate the role of transcranial ultrasonography imaging in assessment of neonatal hypoxic ischemic cerebral injury including the term and preterm infants and correlate the same with the severity of the clinical condition.

### METHODS

#### Study Population
The study was conducted on fifty (50) clinically diagnosed HIE neonates (using Levene’s staging), admitted in the Department of Paediatrics Burdwan Medical College and Hospital, Burdwan and referred to our Dept. of Radiodiagnosis for imaging and evaluation. They were subjected to transcranial ultrasound within 1st week of postnatal life after fulfilling inclusion and exclusion criteria, obtaining due clearance from ethics committee. MRI Brain was performed in all the patients thereafter.

#### Inclusion Criteria
Included neonates clinically diagnosed as cases of HIE and are referred to our Department of Radiodiagnosis for imaging. Neonates whose guardians give valid and informed consent for the study.

#### Exclusion Criteria
Included severely ill neonates with unstable vitals. Those neonates whose guardians not willing to give valid and informed consent for the study. Potential imaging mimics of HII-for ex-Infection (e.g., type II herpes encephalopathy), sepsis, metabolic causes-hypoglycemia, maple syrup urine disease, and nonketotic hyperglycinemia, Head trauma (AHT), cases of neonatal arterial or venous infarction- as there are many other causes of neonatal brain infarct, congenital malformations.

### RESULTS

#### Table 3. Distribution of Cases According to Levene Grading (n=50)

| Stage   | No. of Cases | %    |
|---------|--------------|------|
| Mild    | 17           | 34   |
| Moderate| 26           | 52   |
| Severe  | 07           | 14   |
| Total   | 50           | 100  |

#### Table 4. Distribution of Cases According to Sex (n=50)

| Sex      | No. of Cases | %    |
|----------|--------------|------|
| Male     | 35           | 70   |
| Female   | 15           | 30   |

#### Table 5. Distribution of Cases According to Gestational Age (n=50)

| Gestational Age | No. of Cases | %    |
|-----------------|--------------|------|
| Term- 36 completed weeks | 38 | 76   |
| Pre term- less than 36 completed weeks | 12 | 24   |

#### Table 6. Distribution of Cases According to Positive Findings in Conventional (TCUS) (n=50)

| TCUS    | No. of Cases | %    |
|---------|--------------|------|
| Positive| 36           | 72   |
| Negative| 14           | 28   |

**Figure 1.** Coronal TCUS of a Term Neonate Showing Hyper Echogenecity in Bilateral Basal Ganglia and Thalamic Region with Extension to Brain Stem – Consistent with Central Pattern

**Figure 2.** Axial T2 MRI of a Preterm Neonate Showing T2 Prolongation in Bilateral Posterior Putamina and Thalamus- Consistent with Preterm Central Pattern

**Figure 3.** Coronal and Sagittal TCUS of the Same Neonate Showing Rounded Hyper Echogenecity at Left Caudo Thalamic Groove
preterm newborn babies. In our study and the other studies, there is higher incidence of full term babies compared to preterm babies. We found in our study that there is the usual high incidence of term deliveries compared to preterm deliveries. It is well known that due to incomplete brain maturation in preterm babies, incidence of HIE is higher among the preterm newborn babies compared to full term babies.

In our study, TCUS was normal in 14 cases (28%). Basal ganglia, thalamus (BGT) abnormality was detected in 17 cases (51.51%) and white matter abnormality was seen in 13 cases (39.39%), germinal matrix haemorrhage grade I in 3 cases (2.7%).

In a study, Genedi et al studied 38 neonates presented with HIE. Normal TCUS in 9 cases (23.7%), 15 cases (39.5%) show central pattern injury and white matter injury detected in 12 cases (31.6%). Germinal matrix haemorrhage is seen in 2 cases (5.2). Therefore, our study TCUS findings as regard pattern of injury, our study revealed that central and white matter abnormalities better demonstrate in TCUS than peripheral lesions in patients with HIE. Steggerda et al. in their study showed that TCUS has good sensitivity in detecting central (basal ganglia-thalamus) and white matter injuries in neonates with HIE rather than peripheral injuries, which is concomitant with our study.

In our study, conventional MRI was normal in 8 cases (16%) and the remaining 42 cases (84%) showed abnormalities as follows; central pattern injury in 20 cases (48.78%), white matter injury in 5 cases (12%), peripheral injury is seen in 14 (34.14%). Mixed pattern shown in 1 case (2.4%). Grade 1 germinal matrix haemorrhage (GMH) is seen in 1 case (2.4%). So our study was compatible with the similar study done by Genedi et al. that was conducted on 38 neonates with features of HIE. Conventional MRI was normal in Five cases (13.1%). The remaining 33 cases (86.9%) showed abnormal findings which are as follows; central pattern injury noted in 16 cases (42.5%) and white matter injury is seen in 4 cases (10.5%). One case (2.6%) elicited mixed pattern and the other two cases (5.2%) elicited germinal matrix haemorrhage. Overall sensitivity and specificity of TCUS of our study in detecting imaging findings in 50 neonates with HIE compared to MRI were 78.57% and 62.50% respectively, yielding the overall diagnostic accuracy of TCUS compared to MRI was 76% and the positive predictive value 91.60%, while the negative predictive value was 35.70%.

Genedi et al. found that the overall sensitivity and specificity of TCUS in detecting brain changes compared to MRI were 81.8% and 60% respectively, with overall diagnostic accuracy of 78.9%. The positive predictive value was 93.1 and the negative predictive value was 33.3 (95%). So, our study findings as regards sensitivity, specificity, PPV, NPV and overall diagnostic accuracy are similar to the study of Genedi et al.7

In addition, the study done by Herma et al. matched with our study where they found that Trans cranial USG (TCUS) compared to MRI showed 82% of sensitivity in

**DISCUSSION**

Ramachandran et al. in their study found that from total 50 patients, 82% were term newborn babies and 18% were...
hypoxic-ischemic encephalopathy (HIE) diagnosis. In our study there was statistical difference detected between TCUS and MRI with higher efficacy of MRI in diagnosis of neonatal HIE (P value = 0.03). Babiker et al. reported the results of a study comparing MRI and TCUS in 150 neonates with suspected HIE. Transcranial US was normal in 50%, increased periventricular echogenicity was noted in 32%, germinal matrix haemorrhage in 9% and basal ganglia abnormal echogenicity was detected in 18% of patients. Normal MRI finding in 29% of patients, basal ganglia abnormalities in 18% while germinal matrix haemorrhage in 10.6% of patients.

In our study, 9 cases were false negatively diagnosed normal on TCUS as compared to DW-MRI, but showed restricted diffusion. The pattern of restricted diffusion is as follows; white matter pattern was seen in 6 cases, central pattern seen in 2 cases and mixed pattern of injury was noted in 1 case. So, our study agreed with Genedi et al. as regards high efficacy of DWI in detection of mild to moderate HIE presented with white matter injuries while TCUS was negative.

In agreement with our study Li et al. in their study found positive correlation between MRI and DW-MRI studies (P =0.04) with higher efficacy of DW-MRI in evaluation of HIE. Our study showed statistical difference between TCUS and DW-MR with higher efficacy of DWI in diagnosis of HIE in neonates (P value = 0.004).

**CONCLUSIONS**

Transcranial Ultrasound (TCUS) helps in characterization of different imaging patterns of brain injury depending upon gestational age, severity, and duration of insult, as detailed above. However, findings need to be correlated with both conventional and diffusion weighted MRI findings. We recommend that the ultimate radio-diagnostic protocol for cases of HIE is a combination of both TCUS and MR imaging.

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