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Original research article

A study of neurosonogram findings in new borns with hypoxic ischemic encephalopathy and their correlation with neurodevelopmental outcome

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Abstract

Accurate identification and characterization of the severity, extent, and location of brain injury is essential to predict the neurodevelopmental outcome of newborns. The pattern of brain injury depends on the severity and duration of hypoxia and degree of brain maturation. Various neuroimaging modalities such as neurosonogram, CT, MRI are available which help in identification of severity of brain injury. Initial scans were obtained within 72 hrs of birth and subsequent follow up scans were done on 8-10th day and 30th day so as not to miss the relatively late developing intracranial changes. The infants were then followed up after 6-12 months for a detailed neurological assessment for correlation of clinical outcome with NSG findings using statistical analysis. In our study 66% newborns were term and 34% were preterm where as in a study by Sushmita *et al*., it was 76% term and 24% preterms. In our study 26% neonates had HIE I, 58% were HIE II, 16% were HIE III as compared to another study by Behere A *et al*., in which 11.3% were HIE I, 72.8% were HIE II and 15.95% were HIE III. In our study 90% of cases had abnormal neurosonogram findings and 10% cases had normal neurosonogram.

Keywords: Neurosonogram, hypoxic ischemic encephalopathy, neurodevelopmental outcome

Introduction

Hypoxic-ischemic encephalopathy (HIE) affects 1–3 per 1,000 live births in developed countries and is responsible for a significant burden of morbidity and mortality in the pediatric population [1]. Perinatal asphyxia is the most important cause of HIE, resulting in hypoxemia and hypercapnia. Hypotension and the resulting decreased cerebral blood flow lead to a cascade of deleterious events, including acidosis, release of inflammatory mediators and excitatory neurotransmitters, free radical formation, calcium accumulation, and lipid peroxidation. These biochemical substances result in loss of vascular autoregulation in the setting of cerebral hypoperfusion eventually leading to neuronal cell death. The Sarnat and Sarnat clinical stages are commonly used to estimate the severity of asphyxia insult.

Accurate identification and characterization of the severity, extent, and location of brain injury is essential to predict the neurodevelopmental outcome of newborns. The pattern of brain injury depends on the severity and duration of hypoxia and degree of brain maturation. Various neuroimaging modalities such as neurosonogram, CT, MRI are available which help in identification of severity of brain injury. Neurosonogram has emerged as a powerful screening tool for evaluation of a neonate with suspected HIE as it is inexpensive, portable and imparts no radiation exposure. It has become increasingly effective at determining the pattern, timing, and extent of injury in HIE as well as differentiating these findings from a list of diagnoses that can result in a similarly appearing clinical picture.

Patterns of brain injury

The imaging findings in full term neonates (>36 weeks gestation) differ from those of preterm neonates (<36 weeks gestation) [2]. In preterm neonates with immature brain, periventricular white matter is most vulnerable to hypoxic ischemic injury resulting in periventricular leukomalacia that may be focal or diffuse. Progressive necrosis result in loss of periventricular white matter, passive ventriculomegaly, thinning of corpus callosum. Development of PVL and ventriculomegaly after birth is prone for severe cognitive and motor disabilities [3].

Germinal matrix hemorrhage (GMH) is typically seen in preterm infants with HIE. Depending on severity, GMH can be graded into (Papile grading):

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Grade I: Subependymal hemorrhage,
Grade II: Intraventricular hemorrhage (IVH) without ventricular dilatation,
Grade III: IVH with ventricular dilatation,
Grade IV: IVH with intraparenchymal hemorrhage (Periventricular Haemorrhagic Infarction). Thalami, brainstem, and cerebellum in the immature brain have high metabolic activity and hence are more susceptible to injury in severe HI injury [4, 5].

In term neonates, mild to moderate HI injury produces parasagittal watershed zone infarcts between anterior/middle cerebral artery and middle/posterior cerebral artery. Severe HI injury results in injury to metabolically active tissues such as ventrolateral thalami, posterior putamina, hippocampi, brainstem, corticospinal tracts, and sensorimotor cortex. Severe global hypoxia may also lead to diffuse cerebral edema. Salt and pepper pattern of cerebral hemispheric echogenecity and/ or effacement & obliteration of CSF-containing spaces are early findings in hypoxic injury suggestive of Diffuse Cerebral Edema & can be observed on day 1 itself [6]. Duplex US with spectral analysis of the blood flow curves during systole and diastole allows calculation of the resistive index (RI). It provides a measurement of cerebral dynamics and the integrity of cerebral autoregulation. An abnormal RI (equal to or less than 0.55), in the first 72 h after birth, has been found to be highly predictive of a poor prognosis with either death or severe disability [7].
Although neurosonogram is one of the important imaging modalities in newborns with HIE, there are very few Indian studies which evaluated its efficacy in predicting the neurodevelopmental outcome in neonates. Hence this study is done to determine the efficacy of neurosonogram as an important tool in predicting outcome in neonates with HIE.

Aims and Objectives of this study are
1. To study the various neurosonography findings in neonates with HIE.
2. To evaluate the role of neurosonogram as a reliable tool in assessing the severity of neurological damage & predicting neurodevelopmental outcome.

Methodology
The study was conducted in the Department of Paediatrics in collaboration with Department of Radiodiagnosis in Government Medical College, Ananthapuramu, Andhra Pradesh.

Study Period: January 2021 to December 2021.

Study Design: Prospective observational type

Inclusion criteria
All newborns with Hypoxic Ischemic Encephalopathy who were referred to Department of radiology for neurosonogram were included in the study.

Exclusion criteria
Neonates born with major congenital malformations, chromosomal abnormalities, metabolic disorders, birth trauma or born to mothers who have received magnesium sulfate or opioids within 4 hr before delivery are excluded out of the study.

Methodology
Initial scans were obtained within 72 hrs of birth and subsequent follow up scans were done on 8-10th day and 30th day so as not to miss the relatively late developing intracranial changes. The infants were then followed up after 6-12 months for a detailed neurological assessment for correlation of clinical outcome with NSG findings using statistical analysis. The presence of microcephaly, cerebral palsy, presence of post neonatal seizures, presence of neurodevelopmental impairment and delayed milestones as per Denver Developmental scales were considered as the adverse neurological outcome for the analysis.

Statistical analysis
The statistical analysis of cases is done by comparing the number of cases found in each NSG parameter and their clinical outcome of either healthy or adverse neurological outcome or expired in 2X2 contingency tables and Sensitivity, Specificity, Positive Predictive Value, Negative Predictive Value and their individual statistical significance in the form of p-value were obtained using Fisher's Exact Test.

Results
A total of 138 neonates were initially enrolled in the study after obtaining the informed consent from their parents/guardian. Out of them 11 were excluded from the study based on exclusion criteria. Another 17 were lost to follow-up. Finally 100 patients were considered for statistical analysis of the study.

ISSN:0975 -3583,0976-2833 VOL14, ISSUE 03 2023

Among the 100 neonates 62% were males and 38% were females. 66% were term and 34% were preterm neonates. According to Sarnath and sarnath staging of HIE 26% were mild HIE, 58% were moderate HIE, 16% were severe HIE. The clinical outcome of the neonates was as follows:

Table 1: Clinical outcome of neonates with different grades of HIE

HIE GRADE	Healthy	Adverse neurological outcome	Expired
Mild HIE	2O	6	0
Moderate HIE	10	42	6
Severe HIE	0	12	4
Total	30	60	10

Out of the 100 cases neurosonogram was normal in 10 cases and remaining 90 cases were abnormal. The various neurosonogram findings and their correlation to neurodevelopmental outcome is as follows

Table 2: Subcortical or periventricular increased echogenesity (PVL)

	Adverse neurological outcome or expired	Healthy	Total
Present	60	20	80
Absent	10	10	20
Total	70	30	100

Sensitivity: 86%
Specificity: 33%
Positive predictive value: 75%
Negative predictive value: 50%
P Value: 0.0534 (Not Significant)

Table 3: Intraventricular hemorrhage

	Adverse neurological outcome or expired	Healthy	Total
Present	14	1	15
Absent	56	29	85
Total	70	30	100

Sensitivity: 20%
Specificity: 97%
Positive predictive value: 93%
Negative predictive value: 34%
P Value: 0.034 (Significant)

Table 4: Diffuse cerebral edema

	Adverse neurological outcome or expired	Healthy	Total
Present	46	12	58
Absent	24	18	42
Total	70	30	100

Sensitivity: 66%
Specificity: 60%
Positive predictive value: 80%
Negative predictive value: 43%
P Value: 0.026 (Significant)

Table 5: Abnormal cerebral blood flow velocities

	Adverse neurological outcome or expired	Healthy	Total
Present	53	11	64
Absent	17	19	36
Total	70	30	100

Sensitivity: 76%
Specificity: 63%
Positive predictive value: 83%
Negative predictive value: 53%
P value: 0.0005 (very significant)

ISSN:0975 -3583,0976-2833 VOL14, ISSUE 03 2023

Table 6: Abnormal resistive index (<0.5 OR >0.8)

	Adverse neurological outcome or expired	Healthy	Total
Present	56	2	58
Absent	14	28	42
Total	70	30	100

Sensitivity: 80%
Specificity: 93%
Positive predictive value: 96%
Negative predictive value: 67%
P Value<0.0001 (Very Significant)

Among the five neurosonogram parameters that were studied presence of subcortical or periventricular leukomalacia did not have significant statistical correlation to neurodevelopmental outcome where as IVH and diffuse cerebral edema were significant, abnormal cerebral blood flow velocities and resistive index were extremely significant (p value < 0.001) in predicting adverse neurological outcome.

Discussion

In our study 66% newborns were term and 34% were preterm where as in a study by Sushmita *et al*., it was 76% term and 24% preterms. In our study 26% neonates had HIE I, 58% were HIE II, 16% were HIE III as compared to another study by Behere A *et al*., [8] in which 11.3% were HIE I, 72.8% were HIE II and 15.95% were HIE III. In our study 90% of cases had abnormal neurosonogram findings and 10% cases had normal neurosonogram which is similar to the study done by Bijay Laxmi Malick *et al*. [9] which showed normal study in 13.3% cases. In our study Germinal matrix or Intraventicular hemorrhage is seen in 15% cases, increased subcortical or periventricular echogenecity in 80% cases and cerebral edema in 58% cases where as in study by Barseem NF *et al*. [10] Intraventricular hemorrhage was seen in 10% cases and increased subcortical or periventricular echogenecity in 44.5% cases.

In our study 80 cases showed sub cortical or periventricular increased echogenecity of which 60 cases had adverse neurological outcome or expired. The sensitivity of this finding in predicting adverse neurological outcome is 85% with a positive predictive value (PPV) of 75%. But the p value is 0.0534 which is statistically not quite significant. These findings are similar to that of a study done by Mangaraj N *et al*. [11], which showed a sensitivity of 87% and p value 0.07. In our study diffuse cerebral edema is seen in 58 cases of which 46 cases had adverse outcome with a sensitivity of 66%, positive predictive value of 80% and p value 0.0263 which is statistically significant. The above findings were similar to that of a study done by Jongeling *et al*. [12], which showed 65% sensitivity, 87% positive predictive value and p value of less than 0.001.

In this study Germinal matrix or Intraventicular hemorrhage is seen in 15 cases of which 14 cases had adverse outcome demonstrating a specificity of 97%, sensitivity 20%, PPV 93%, NPV 34% and p value 0.034 which is statistically significant. These findings were comparable to study done by Mangaraj *et al*., which had specificity 96%, sensitivity 28%, PPV 87%, NPV 57% and p value 0.04. Abnormal cerebral blood flow velocities are found in 64 cases of which 53 neonates had abnormal neurological outcome. This finding had sensitivity 76%, specificity 63%, positive predictive value 83%, negative predictive value 53% and p value of 0.0005 which is extremely significant. These results were similar to that of study done by Ilves *et al*. [13] which correlated abnormal cerebral blood flow velocities at 12 hours of life to bad outcome at 3 years of life with p value <0.005. The resistive index abnormalities (<0.5 or >0.8) were found in 58 cases of which 53 cases were neurologically impaired which demonstrated a p value of <0.0001 which is extremely significant. In a study conducted by Kudreviciene *et al*. [14] the neonates with lower RI values demonstrated severe impairment of mental development with p value <0.05. In another study conducted by Kirmi *et al*. [15] neonates with higher RI values had significantly higher incidence of cerebral palsy and severe mental impairment.

As per our study the neurosonogram findings like diffuse cerebral edema, IVH, abnormal cerebral blood flow velocities and abnormal resistive indices have significant correlation with poor neurodevelopmental outcomes. In developing countries like India where higher imaging modalities like MRI are available only at tertiary care centres, there is need for further studies in evaluating the significance of neurosonogram findings in predicting the future outcome in children.

Conclusion

HIE is an important cause of morbidity and mortality in the neonatal period and of cerebral palsy as a late neurologic sequela in the postnatal period. The most common neurosonogram finding in HIE patients are subcortical or periventricular increased echogenicity, abnormal resistive index, abnormal cerebral blood flow velocities, diffuse cerebral edema and Intraventricular hemorrhage. Of the above presence of abnormal cerebral blood flow velocities, abnormal resistive indices, diffuse cerebral edema are very significantly associated with poor neurological outcome. Thus neurosonogram is the cheapest

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and best initial screening modality of choice for HIE for diagnosing and predicting clinical outcome.

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