Original Article

DOI: 10.7860/IJNMR/2023/60764.2373

Paediatrics Section

Early Cranial Ultrasound Changes as Predictors of Outcome during First Year of Life in Infants with Perinatal Asphyxia- A Prospective Cohort Study

SHILPI AGRAWAL[1], RAVANAGOMAGAN[2], SETHI ROHITH SHAMSHER[3], CHAURASIYA RACHNA[4]

ABSTRACT

Introduction: Perinatal Asphyxia (PA) causes impaired exchange of ventilatory gases, or ischaemia that leads to persistent decrease in oxygen levels (hypoxemia) and increase in carbon dioxide levels (hypercarbia). It occurs during the peripartum period can contribute to early neonatal mortality and morbidity.

Aim: To assess the role of early changes in cranial ultrasound a predictor of outcome in babes with PA.

Materials and Methods: This prospective cohort study was conducted in a tertiary care neonatal unit in Maharani Laxmi Bai Medical College, Jhansi, Uttar Pradesh, India, from July 2018 to October 2019. A total of 50 neonates with PA were studied. Cranial ultrasound was performed at or after seven days of life. Neurodevelopment assessment of the subjects were done at three, six, nine and 12 months of life using Development Quotient (DQ). Variables were analysed by student's t-test and categorical variables were analysed by Fisher's-exact probability test using graph pad software.

Results: Out of 50 infants of PA, 29 had an abnormal ultrasound scan and 21 had normal ultrasound scan. A 16 out of 29 patients had abnormal outcome along with abnormal ultrasound scan while rest of the 13 had normal outcome. The mean DQ of the neonates having abnormal ultra sonographic examination was significantly lower as compared to those with normal examination. A six out of 21 neonates had abnormal outcome inspite of having normal ultrasound scan. Cranial ultrasound has a specificity 55%, sensitivity 73%, Positive Predictive Value (PPV) 58% and Negative Predictive Value (NPV) 71% in predicting neurodevelopment outcome of patients with birth asphyxia.

Conclusion: Cranial Ultrasonography (USG) findings in PA babies reveal a strong association with the development severity.

Keywords: Developmental quotient, Hypoxic ischaemic encephalopathy, Neurological outcome

INTRODUCTION

The Perinatal Asphyxia (PA) is one of the leading causes of neonatal mortality and morbidity. It causes impaired exchange of ventilatory gases leading to hypoxia and hypercarbia [1]. As per the statistics of World Health Organisation (WHO), birth asphyxia is one of the leading causes of early neonatal mortality, and accounts for an estimated 900,000 deaths worldwide each year [2]. Birth asphyxia accounts for yearly four million deaths, representing 38% of all deaths of children under five years of age. It was estimated that 3% of all infants (3.6 million) suffer from moderate to severe birth asphyxia in the developing countries, of which 23% (840,000) die, and approximately the same number develop serious squealae [3,4].

Perinatal asphyxia is the largest cause of deaths of children under the age of five following pneumonia, diarrhea, infections of the neonates, and preterm sequelae [5]. Following PA, approximately 15-20% babies die in neonatal period, and surviving 25% newborns are left with permanent neurologic deficit [6]. Hypoxic Ischaemic Encephalopathy (HIE) is one of the major sequelae following PA whose incidence is 1.5 per 1000 live births in developed countries and varies between 2.3-26.5 per 1000 live births in developing countries [7]. The incidence of PA is two per 1000 births in developed countries, but the rate is up to 10 times higher in developing countries, where there may be limited access to maternal and neonatal care [6]. The symptoms of brain form of HIE. The hallmark of resulting encephalopathy following brain injury is seizures [8]. Prolonged seizure results in extensive damage of neonatal brain that may lead to grave prognosis. Outcome and prognosis in a patient of PA is calculated by level of maturity, underlying aetiology and investigations like Electroencephalogram (EEG) and imaging of brain like Computed Tomography (CT), Magnetic Resonance Imaging (MRI), and cranial Ultrasonography (USG) [9]. Though CT and MRI are highly informative but not possible always as these techniques require sedation, patient must be transported to the Radiology Department and finally the hazards associated with ionising radiation are major concern.

Sonographic brain imaging is a particularly attractive application, which can help both haemodynamically stable and unstable neonates because of safety and easy portability of this modality, which also allow clinicians to perform rapid examinations. Cranial ultrasound is implicated to examine the encephalon of the infant after six months of age, when there is a retarded closure of the anterior fontanelle or cranial diastases. Thin temporal bones also act as a medium through which ultrasonic imaging of the brain can be done. USG scans have been very useful in predicting neuro developmental outcome. It is proven to be a dependable modality for detecting most of the haemorrhagic, ischaemic and cystic brain lesions as well as calcifications, cerebral infections and major structural abnormalities in preterm and term neonates [10]. The early prediction of outcome is very important for prognostication and early introduction of neuro protective interventions. Therefore, studies are ongoing to assess the role of cranial USG in PA.

MATERIALS AND METHODS

This prospective cohort study was conducted in a tertiary care neonatal unit in Maharani Laxmi Bai Medical College, Jhansi, Uttar

Pradesh, India, from July 2018 to October 2019. This study was approved by the Ethical Committee of the Institute (Number 278/surgery/17)(30.4.2017). All the neonates were enrolled for first three months and followed-up over a year.

Inclusion criteria: Moderate or severe on the basis of Sarnat HB and Sarnat MS, staging of HIE [Table/Fig-1], or severe PA as manifested by three of the following four criteria [11]:

- Meconium stained amniotic fluid;
- Need for immediate neonatal ventilation with bag and mask or through endotracheal intubation for >2 minutes after delivery;
- Five minute apgar score of <6;
- Base deficit of >15 mEq/l or pH<7 in cord blood or admission arterial blood samples.

Severity	Stage I (mild)	Stage II (moderate)	Stage III (severe)
Level of consciousness	Hyper alert	Lethargic or obtunded	Stupor or coma
Activity	Normal	Decreased	Absent
Neuromuscular control			
Muscle tone	Normal	Mild hypotonia	Flaccid
Posture	Mild distal flexion	Strong distal flexion	Intermittent decerebration
Stretch reflexes	Overactive	Overactive	Decreased or absent
Complex or primitive reflexes			
Suck	Weak	Weak or absent	Absent
Moro's	strong	Weak	Absent
Tonic neck reflexes	Slight	Strong	Absent
Autonomic functions			
Pupils	Mydriasis	Miosis	Variable
Heart rate	Tachycardia	Bradycardia	Variable
Seizures	None	Common	Uncommon

[Table/Fig-1]: Sarnat HB and Sarnat MS, staging of HIE [11].

Exclusion criteria: Babies with severe Intrauterine Growth Restriction (IUGR), metabolic disorders, chromosomal anomalies or congenital malformation were excluded from this study.

All the neonates were clinically evaluated using the HIE score postulated by Thompson CM et al., at the time of admission and at seven day of life [12]. Laboratory investigations included Arterial Blood Gases (ABG) at the time of admission, complete blood counts and blood glucose and serum electrolytes.

Sample size calculation: Based on the sensitivity of the cranial ultrasound 72% [13], and keeping precision of 10%, confidence interval of 95%, error 10%, and by entering it in the End Master Software 2.0, the required sample size was 85. Total 85 newborns were enrolled out of which 10 patients died during hospital stay, four patients died within a month after discharge, 21 patients did not turn up for the revisit and remaining 50 patients were taken in to the study. Finally, 50 neonates admitted to Neonatal Intensive Care Unit (NICU) of MLB Medical College, Jhansi, both inborn and out born were selected for the study.

Study Procedure

Neonatal cranial USG was performed only once between 7-10 days of life during hospital stay, real time unit using a 5 MHz or 7.5 MHz transducer. Through anterior fontanelle five coronal and five parasagittal images were taken. The scans were assessed for anatomy of brain, ventricular morphology and size of the ventricles and evidence of focal or diffuse increased echogenicity of the basal ganglia and cerebral hemispheres during the neonatal period. The radiologist performing the ultrasound was unaware of the birth history of the neonate.

Subjects were divided into two groups:

Group A: Infants having abnormal ultrasonographic findings which commonly included cerebral oedema, Periventricular Leukomalacia (PVL) intracranial haemorrhage.

Group B: Infants having normal ultrasonographic findings. All newborns who have suffered from birth asphyxia and later on progressed were categorised into different stages of HIE based on Sarnat HB and Sarnat MS, staging, 1976 [Table/Fig-1] [11]. The subjects were evaluated for neurodevelopment at the ages of three, six, nine and 12 months. The DQ development and also for individual subscales (gross motor, fine motor, social and adaptive, and language) [13]. Results were classified as normal when the DQ was 80 or above, and abnormal when it was below 80.

STATISTICAL ANALYSIS

Continuous variables were analysed by student's t-test and categorical variables were analysed by Fisher's-exact probability test using graph pad software. Findings associated with a value of $p<0.05$ were considered significant.

RESULTS

This hospital-based study comprised of 50 neonates with evidence of PA who was admitted to NICU. Group A comprised of 29 neonates having abnormal ultrasonographic examination and Group B comprised of 21 neonates having normal ultrasonographic examination. Out of 29 neonates of group A, 23 belonged to HIE grade II and six belonged to HIE grade III. Out of 21 neonates of group B, 19 belonged to HIE grade II and two belong to HIE grade III. There was no statistical difference regarding the gestational age and weight of all the study neonates [Table/Fig-2].

Characteristics	Group A (n=29)	Group B (n=21)	p-value
Place of delivery, n (%)			0.75
Inborn	7 (24)	6 (29)	
Outborn	22 (76)	15 (71)	
Mode of delivery, n (%)			0.140
Vaginal	26 (90)	15 (71)	
Cesarean	3 (10)	6 (29)	
Sex, n (%)			1.000
Male	25 (86)	19 (90)	
Female	22 (76)	15 (71)	
Liquor, n (%)			0.441
Meconium stained	8 (28)	5 (24)	
Non stained	21 (72)	14 (66)	
Encephalopathy, n (%)			1.00
Moderate	23 (79)	19 (90)	
Severe	6 (21)	2 (10)	
Weight (gm), mean±SD	2461.37±469.49	2971±107.35	0.146
Gestational age (weeks), mean±SD	39.069 (2.2)	39.619 (1.83)	0.122
Age at admission (weeks), mean±SD	22.45±23.18	15±23.79	0.273
Apgar score of newborn, mean±SD	4.28±1.49	5.16±1.17	0.266

[Table/Fig-2]: Different variables of both the study groups.

The mean (SD) HIE score of group A was 16 (3.3) and that of group B was 14.25 (2.09) difference was statistically significant. ABG pH of group A was lower than group B and the difference was statistically significant (p<0.05) [Table/Fig-3].

Characteristics	Group A (mean±SD)	Group B (mean±SD)	p-value
pH	7.04±0.17	7.14±0.144	0.038
Base excess value	17.88±4.0	15.05±5.9	0.048
HIE score at admission	16±3.1	14.25±2.09	0.025
HIE score at day seven	8.4±7.2	4.3±4.2	0.023

[Table/Fig-3]: Mean pH value, base excess value and HIE scores of both groups.

In the cranial USG examination maximum numbers of neonates had cerebral oedema [Table/Fig-4] [14]. Three out of the four patients who died within a month of discharge had diffuse cerebral oedema on USG. This shows that cerebral oedema is associated with a bad prognosis as 50% of the patients with cerebral oedema had global developmental delay and 27% of the patients with cerebral oedema died. Neonates having PVL on ultrasound examination have lower DQ on individual subscale and 50% of the patients with PVL had developmental delay at follow-up. All the neonates with haemorrhage had developmental delay at follow-up. There was a statistically significant difference in the DQ of patients of both groups at three, six, nine and 12 months follow-up as depicted in [Table/Fig-5]. The mean DQ of patients with abnormal ultrasound findings was significantly lower than patients with normal ultrasound findings. The [Table/Fig-6] shows the sensitivity, specificity, positive and negative predictive values of cranial ultrasound in relation of neuro developmental outcome when performed in neonates with birth asphyxia. The sensitivity of cranial USG is quite good (73%) and the specificity is 55%. This explains its role in predicting abnormal development in neonates with abnormal ultrasound which can be confirmed at regular follow-up of such patients. The NPV is 71% which corresponds to normal developmental outcome in patients with normal ultrasound findings and thus is helpful in predicting further course of such neonates with asphyxia.

USG findings	Normal outcome (DQ >80) n (%)	Abnormal outcome (DQ <80) n (%)
Cerebral oedema (14)	7 (50%)	7 (50%)
Intracranial haemorrhage (5)	0 (0)	5 (100%)
Periventricular leukomalacia (10)	5 (50%)	5 (50%)
Cyst in caudothalamic groove (3)	1 (33%)	2 (67%)
Normal (21)	15 (71%)	6 (29%)

[Table/Fig-4]: Ultrasound finding of both groups and outcome.

Time interval 3 months	Characteristics	Group A (n=23)	Group B (n=17)	p-value
1	Gross motor	48.8±43.06	77.3±32	0.027
2	Fine motor	49.3±40.8	82.5±22.9	0.024
3	Social and adaptive	46.86±39	77.05±33.44	0.014
4	Language	48.3±39.6	74±36.13	0.042
6 months		**(n=28)**	**(n=9)**	
1	Gross motor	56.5±32.72	75.5±26.9	0.04
2	Fine motor	58.4±34.14	81.1±23.6	0.015
3	Social and adaptive	56.03±33.5	80.02±25.47	0.011
4	Language	48.9±28.9	70.78±31	0.017
9 months		**(n=18)**	**(n=14)**	
1	Gross motor	53.14±32.4	87.7±18.5	0.001
2	Fine motor	55.0±32	85.0±16.5	0.002
3	Social and adaptive	49.57±32.27	85.27±21.3	0.001
4	Language	43.7±26.95	78±25.9	0.001
12 months		**(n=18)**	**(n=14)**	
1	Gross motor	49.1±26.1	77±31.8	0.019
2	Fine motor	47.16±21.26	77.15±21.8	0.001
3	Social and adaptive	42.67±24.6	76.77±25.16	0.001
4	Language	36.6±25.02	72.76±26.2	0.001

[Table/Fig-5]: Neuro developmental outcome in both groups in the form of Developmental Quotient (DQ) (% of DQ) at follow-ups.

USG findings	Abnormal outcome	Normal outcome	Total	Outcome
USG abnormality	17	12	29	PPV=17/29×100=58%
Normal USG	6	15	21	NPV=15/21×100=71%
Total	23	27		
	Sensitivity=17/23×100=73%	Specificity=15/27×100=55%		

[Table/Fig-6]: The PPV, NPV, sensitivity and specificity of cranial USG.

DISCUSSION

The main objective of the present study was to differentiate between a group of apparently normal infants in the new born period but with aberrations on cranial USG, and a cohort of infants with normal USG scans. On follow-up at three, six, nine and 12 months, out of 21 patients having normal scans, six had global developmental delay and out of 29 patients having abnormal scans, 17 had global developmental delay [Table/Fig-5]. Seven out of 14 patients with oedema showed developmental delay, five out of 10 having PVL had global developmental delay, all the five patients had developmental delay in those having haemorrhage, and two out of three had developmental delay at follow-up in those having cyst in cranial ultrasound [Table/Fig-4]. All the eight neonates from both the groups belonging to HIE grade III had marked global developmental delay at follow-up [Table/Fig-7]. In this study, abnormal cranial ultrasound findings were detected in total 17 infants with abnormal outcome and 12 infants with normal outcome. However, in the previous study by Abdulqawi K et al., 24 newborn infants with abnormal outcome and nine newborns with normal outcome had abnormal cranial USG findings out of which 30 had brain oedema and three had intraventricular haemorrhage [14]. In this study, normal sonographic findings were detected in 15 infants with normal outcome and six infants with abnormal outcome as compared to previous study in which normal sonographic finding were detected in 12 newborn infants with normal outcome and seven newborns with abnormal outcome. The PPV and the NPV of cranial ultrasound findings are 58.6% and 79%, respectively. The sensitivity and specificity of cranial USG is 74% and 55%. In the previous study by Abdulqawi K et al., the positive and NPV came to be 78.1% and 58.3% and sensitivity and specificity 73.3% and 58.3% [14].

Characteristics	Abnormal USG	Normal USG	Abnormal outcome	Normal outcome
HIE grade II (N=42)	23	19	15	27
HIE grade III (N=8)	6	2	8	0

[Table/Fig-7]: USG findings and outcome of HIE grade II and III babies.

In the present study, abnormal cranial ultrasonographic findings was also associated with significant increase in HIE score and metabolic acidosis as compared to those with normal scans. These findings were in concordance with another study [14]. Maximum numbers of neonates had cerebral oedema in ultrasonographic examination which seems to be most common finding even in previous studies [14,15]. Three out of the four patients who died within a month of discharge had diffuse cerebral oedema on USG. This shows that cerebral oedema is associated with a bad prognosis as 50% of the patients with cerebral oedema had global developmental delay. This is in concordance to the study by Islam S et al., where 3 (27.3%) of the neonates with cerebral oedema died and 5 (45.4%) of the patients were abnormal neurologically [15]. All the neonates having haemorrhage had developmental delay but neonates having PVL on ultrasound examination have lower DQ on individual subscales as compared to those with haemorrhage. It was in concordance to study by Haataja L et al., whose results show that haemorrhages' was not associated with abnormal outcome and white matter lesions were associated with loco motor delay in four of eight infants [16].

Not much has been commented about cysts in previous study but in the present study, it was found out to be associated with a bad prognosis as two out of the three neonates were neurologically abnormal and out of the four patients who died one had cyst in caudothalamic groove on sonography. Thus, to conclude cranial USG findings are important modality to predict perinatal HIE and its outcome. The optimal use of cranial sonography is a very helpful diagnostic tool and will aid in effective prognostication of the patient as well as updating treatment regimens and neuro protective measures.

Limitation(s)

The study was conducted on a limited number of babies delivered in a tertiary care hospital in an urban area. Studies should be conducted with a larger sample size at the community level to identify the predictors of outcome strongly. There is a lack of evidence to prove that any ante partum insult is happened are not.

CONCLUSION(S)

Cranial USG is a valuable tool for screening and diagnosing the brain changes in newborn period. In the short period of time, it is difficult to get advanced imaging studies due to lack of resources. Early changes in the ultrasound are important predictors of neurobehavioral outcome in neonates with PA and optimal use of cranial sonography in these neonates will definitely have greater impact on the diagnosis, treatment regimens and neuropathologic processes progression. Cranial USG findings in PA babies reveal strong association with the development severity.

REFERENCES

[1] Bhutta BS, Alghoula F, Berim I. Anoxia. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 [cited 2021 May 22]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK482316/.

[2] Spector Jonathan M, Subhash D. Preventing those so-called stillbirths. Bulletin of the World Health Organization. 2008;86(4):315-16. World Health Organization. http://dx.doi.org/10.2471/BLT.07.049924.

[3] Birth Asphyxia- Summary of the previous meeting and protocol overview. Available from: http://www.curoservice.com/health_professionals/news/pdf/10-09-2007_birth asphyxia02.pdf.

[4] State of the World's Children, UNICEF; 2009. https://www.unicef.org/media/84866/file/SOWC-2009.pdf.

[5] Yadav N, Damke S. Study of risk factors in children with birth asphyxia. Int J Contemp Pediatr. 2017;4(2):518-26.

[6] Odd D, Heep A, Luyt K, Draycott T. Hypoxic-ischemic brain injury: Planned delivery before intrapartum events. J Neonatal-Perinat Med. 2017;10(4):347-53.

[7] Namusoke H, Nannyonga MM, Ssebunya R, Nakibuuka VK, Mworozi E. Incidence and short term outcomes of neonates with hypoxic ischemic encephalopathy in a Peri Urban teaching hospital, Uganda: A prospective cohort study. Matern Health Neonatol Perinatol. 2018;4(1):6.

[8] Kharoshankaya L, Stevenson NJ, Livingstone V, Murray DM, Murphy BP, Ahearne CE, et al. Seizure burden and neurodevelopmental outcome in neonates with hypoxic-ischemic encephalopathy. Dev Med Child Neurol. 2016;58(12):1242-48.

[9] Bano S, Chaudhary V, Garga UC. Neonatal hypoxic-ischemic encephalopathy: A radiological review. J Pediatr Neurosci. 2017;12(1):01-06.

[10] Nagaraj N, Berwal PK, Srinivas A, Sehra R, Swami S, Jeevaji P, et al. A study of neurosonogram abnormalities, clinical correlation with neurosonogram findings, and immediate outcome of high-risk neonates in Neonatal Intensive Care Unit. J Pediatr Neurosci. 2016;11(3):200-05.

[11] Sarnat HB, Sarnat MS. Neonatal encephalopathy following fetal distress. A clinical and encephalographic study. Arch Neurol. 1976;33:696-705.

[12] Thompson CM, Puterman AS, Linley LL, Hann FM, van der Elst CW, Monteno CD, et al. The value of scoring system for hypoxic-ischemic encephalopathy in predicting neuro developmental outcome. Acta Pediatr. 1997;86:757-61.

[13] Patil B, Harshangi S, Prabhu B. Clinicoradiological correlation in birth asphyxia. Int J Res Med Sci. 2015;3(3):560-67.

[14] Abdulqawi K, Al-Zohairy YZ, Karam K. Early predictors of neurodevelopmental adverse outcome in term infants with postasphyxial hypoxic ischemic encephalopathy. International Journal of Collaborative Research on Internal Medicine & Public Health. 2011;3(11):822-37.

[15] Islam S, Sarmin M, Ahmed T, Afroze F, Chisti MJ. Factors associated with cerebral oedema in children under 5 years of age admitted in an intensive care unit and their outcome. SAGE Open Med. 2019;7:2050312119874622.

[16] Haataja L, Mercuri E, Cowan F, Dubowitz L. Cranial ultrasound abnormalities in full term infants in a postnatal ward: Outcome at 12 and 18 months. Arch Dis Child-Fetal Neonatal Ed. 2000;82(2):F128-33.

PARTICULARS OF CONTRIBUTORS:

1. Assistant Professor, Department of Paediatrics, Dr. Ram Manohar Lohia Institute of Medical Sciences, Lucknow, Uttar Pradesh, India.
2. Assistant Professor, Department of Paediatrics, Sree Balaji Medical College and Hospital, Chrompet, Chennai, Tamil Nadu, India
3. Former Professor and Head, Department of Paediatrics, Maharani Laxmi Bai Medical College, Jhansi, Uttar Pradesh, India.
4. Professor, Department of Radiology, Maharani Laxmi Bai Medical College, Jhansi, Uttar Pradesh, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Ravanagomagan
G-4, R Block, SBMCH, No 7, CLC Works Road, Chrompet,
Chennai-600044, Tamil Nadu, India.
E-mail: drmgr04@gmail.com

PLAGIARISM CHECKING METHODS: [Jain H et al.]

- Plagiarism X-checker: Oct 20, 2022
- Manual Googling: Jan 09, 2023
- iThenticate Software: Jan 13, 2023 (18%)

ETYMOLOGY: Author Origin

AUTHOR DECLARATION:

- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. Yes

Date of Submission: **Oct 19, 2022**
Date of Peer Review: **Nov 25, 2022**
Date of Acceptance: **Jan 30, 2023**
Date of Publishing: **Mar 31, 2023**