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Cranial ultrasound in high-risk neonates and their neurodevelopmental outcome

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Introduction: With the advancement in neonatal care over the last two decades, neonatal mortality is decreased but simultaneously there is an increase in the adverse outcomes including neurodevelopmental abnormalities in the high-risk neonates. **Purpose:** To evaluate the association between cranial ultrasound findings and the clinical neurodevelopmental outcome among high-risk neonates at 12 months (corrected gestational age in preterm infants) and to assess the various perinatal risk factors associated with neurodevelopmental outcome. **Material and Methods:** 123 high-risk neonates admitted in NICU were enrolled. Cranial ultrasound was performed and morphology was noted. The neurodevelopmental assessment was done using DDST Test II at 12 months age and these neonates were labeled as normal or abnormal based on the findings. Association between the two non-parametric variables was seen using the Pearson Chi-square test. **Results:** There was a statistically significant association between clinical neurodevelopmental outcome and gestational age at birth; birth weight; Apgar score <5 at 5 minutes; neonatal seizures; and abnormal cranial ultrasound findings ($p<0.05$), while the association with all other studied parameters were found to be statistically not significant ($p>0.05$). **Conclusions:** The neurodevelopmental outcome in high-risk neonates was associated with gestational age at birth; birth weight; Apgar score at 5 minutes; neonatal seizures and abnormal cranial ultrasound findings. The current study recommend the use of cranial ultrasound for the prediction of neurodevelopmental abnormalities especially in neonates with above risk factors.

Keywords: Apgar score, cranial ultrasound, gestational age, neonatal seizures, neurodevelopmental outcome

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Introduction

The significant decline in neonatal mortality in India over the last two decades by 44%,[1] has been increasingly associated with the incidence of chronic morbidities and adverse outcome in the survivors. The course of events in the perinatal period of these high-risk neonates has many complications including neurodevelopmental abnormalities. Intact survival is the goal of the current medical scenario. In neonatology, the adverse neurodevelopmental outcome in the form of cerebral palsy, visual, auditory, cognitive, and psychomotor impairment needs to be detected early so that appropriate developmental support is provided timely.

The presence of open fontanelles providing access to the brain, makes cranial ultrasound (CUS) a reliable alternative to other neuroimaging CT/MRI (computed tomography, magnetic resonance imaging). It is non-invasive, cost-effective, reproducible, repeatable, and highly sensitive (75-100%) for depicting normal anatomy and certain intracranial pathological changes in the neonatal brain. Some of the findings of cranial ultrasound in the 1st-week scans are intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL), ventriculomegaly, major malformations (lissencephaly, holoprosencephaly, encephalocele), rarely agenesis of corpus callosum and Vein of Galen malformation. The prevalence of CP (cerebral palsy)was 61% among infants with cystic PVL, 50% in infants with intraparenchymal hemorrhage, 8% in infants with grade I IVH, and 4% in infants without a detectable cerebral lesion [2].

Neurodevelopmental assessment through a standardized test (DDST II), an integral part of the follow-up of all high-risk newborns, helps in early identification of even minor delays/neurological deficits, which can be used for timely guidance and counseling of the parents.

A correlation between the positive cranial ultrasound finding and the neurodevelopmental outcome of high-risk neonates will help us to establish evidence, thereby making CUS a part of regular screening for all high-risk neonates. This prompted us to conduct the study in such cases with the aim of identifying the findings on CUS in high-risk neonates and to establish the clinical association of ultrasonography findings with the neurodevelopmental outcome among neonates by the age of one year (corrected gestational age in case of preterm infants). The current study also Observed a perinatal risk factor associated with abnormal neurodevelopment outcomes.

Material and Methods

Setting: This study was conducted at the tertiary care hospital in Central India.

Duration and type of study: The prospective study was conducted between November 2014 and June 2016.

Sampling methods: A convenient sampling technique was used for the present study.

Sample size calculation: The current study did not calculate the sample size prior to the study but enrolled as many candidates possible available during the study period.

Inclusion criteria: Inclusion criteria were preterm neonates < 34 weeks, birth weight < 1600 gm, perinatal asphyxia with manifestations of HIE (hypoxic-ischemic encephalopathy), ventilated neonates, hyperbilirubinemia requiring exchange transfusion, meconium aspiration syndrome, hyaline membrane disease, intra-ventricular hemorrhage, proven neonatal sepsis, pneumonia, meningitis, symptomatic metabolic disturbances, neonatal convulsions, and major congenital abnormalities.

Exclusion criteria: Neonates not surviving until the completion of the present study and those lost to follow-up were excluded from the study.

Data collection procedure: The data was collected in a predesigned proforma especially made for the present study. One hundred and twenty-three high-risk neonates admitted to the neonatal intensive care unit (NICU) were selected as per the inclusion criteria (excluding the dropouts) and subjected to neuro sonography between 7th to 28th post-natal day.

After obtaining informed consent from the parents/guardian regarding the inclusion of the neonate in the study, assessment of factors placing the neonate in a high-risk category was done taking detailed maternal and perinatal history. Important events during NICU stay was noted (ventilator support, seizures, exchange transfusion, sepsis). The sonograms were performed on a Philips iU22 and GE Vird I ultrasound machine using a small footprint, sector array multi-frequency probe (5-8MHz). A high-frequency linear probe was used for visualization of subarachnoid space and a 2-5 MHz curvilinear probe was used to scan through the

Temple in the axial plane. All ultrasounds were performed by a single radiologist to avoid inter-observer variation. Morphology of cranial ultrasound of the high-risk neonate was studied and recorded.

All of these neonates were followed-up and neurodevelopmental assessment was carried out by 12 months of corrected (in cases of preterm neonates) gestational age using Denver Developmental Screening Test II (DDST II).

Ethical consideration and permission: The protocol of the present study was submitted to the Ethics Committee of the institute and after getting their due approval, the study was initiated.

Statistical analysis: Data was studied in Excel sheet and analysis was done using online statistical software like GraphPad, Epi Info, etc. A Chi-square test was used to find out the significant association between the findings of cranial ultrasound and multiple factors with the neurodevelopmental outcome in the high-risk neonates in our setting.

Results

The current study included 123 neonates who had undergone DDST II neurodevelopmental assessment at the completion of one year of corrected age. 62% neonates were preterm, 37% term, and 0.8% post-term. The mean gestational age of neonates was 36.1 ± 1.3 weeks (preterm 33.2 ± 1.2 weeks and term 39.0 ± 1.5 weeks). 26% of the neonates were having normal birth weight, 32% LBW, 40% VLBW, and 2.5% were in the ELBW group. The mean birth weight of neonates was 1.949 ± 0.668 kg, (preterm 1.555 ± 0.439 kg and term 2.587 ± 0.443 kg). The mean birth weight in neonates with abnormal neurodevelopmental outcomes was 2.282 ± 0.807 kg, while in the neonates with the normal neurodevelopmental outcome it was 1.851 ± 0.614 kg.

The commonest maternal risk factor was preterm delivery without receiving even a single dose of antenatal steroid (41%). The most common neonatal risk factor was prematurity 72% and the least common was hyperbilirubinemia requiring exchange transfusion 5%. On DDST II assessment by 12 months of corrected gestational age, 93 neonates had normal neurodevelopment, while 19 had abnormal and 11 had questionable neurodevelopment. Of the 19 with abnormal neurodevelopment, 58% had a gross motor delay, 79% fine motor delay, 42% language delay, and 47% had social and adaptive domain delay. 1.6% (2 neonates) had cerebral palsy.

Maternal Factors: Comparison of neurodevelopmental outcome at 12 months corrected age with maternal PIH($p=0.3$); and the use of antenatal steroids in premature deliveries showed no significant relationship ($p=0.9$). Abnormal neurodevelopmental outcome was independent of the maternal PIH (pregnancy-induced hypertension) and antenatal steroid use.

Neonatal Factors: Comparison of neurodevelopmental outcome at 12 months corrected age with gestational age at birth; and birth weight showed a significant relationship ($p<0.05$). A higher incidence of abnormal neurodevelopmental outcomes was seen in neonates who were having normal birth weight (57.8%) and also term gestation at birth (68%). Similarly, a significant relationship was seen with Apgar score <5 at 5 minutes and neonatal seizures ($p<0.05$). A higher incidence of abnormal neurodevelopmental outcomes was seen in neonates who have an Apgar score of <5 at 5 minutes (73.7%) and in neonates who had seizures (68.4%).

Comparison of neurodevelopmental outcome at 12 months corrected age with gender ($p=0.3$); weight for gestational age ($p=0.3$); assisted ventilation ($p=0.4$); and neonatal hyperbilirubinemia (NNHB) requiring exchange transfusion ($p=0.06$) showed no significant relationships. Abnormal neurodevelopmental outcome was independent of these neonatal factors.

Comparison of neurodevelopment at 12 months corrected gestational age and duration of NICU stay (</>10 days) showed no significant relationship (p-value = 0.6), showing no dependency on the duration of NICU stay.

On cranial ultrasound study, of the 123 neonates, 103 were found to be normal. Rest 20 neonates had one or other pathological findings. Periventricular leukomalacia (50%) was the commonest abnormal CUS finding in the present study followed by Ventriculomegaly (35%) and GMH (15%). Cavum septum pellucidum which a common normal finding in the developing preterm brain was seen in 25%.

Amongst neonates with abnormal cranial ultrasound findings, 45% were preterm, 25% were SGA, 65% were LBW, 20% had birth asphyxia (Apgar score < 5

At 5 minutes), 5% required assisted ventilation, 10% had seizures and 5% had neural tube defects. None of the patients with NNHB requiring exchange transfusion had any abnormality on CUS.

Neurodevelopment at 12 months corrected gestational age and abnormal CUS findings showed a significant relationship (p-value = 0.0004). A higher incidence (52.6%) of abnormal neurodevelopmental outcome was seen in neonates who had abnormal CUS findings.

Table-1: Comparison of various parameters with neurodevelopmental outcomes.

Parameter	Comparison with neurodevelopmental outcome	P-value	Odd's ratio
Maternal risk factors	PIH in mother	0.3, NS	2.09; 95%; CI: 0.56-7.71
	Antenatal steroids in premature deliveries	0.9, NS	0.96; 95%; CI: 0.18-5.16
Neonatal risk factors	Gestational age at birth	0.004*	5.03; 95%; CI: 1.73-14.57
	Birth weight	0.002*	5.35; 95%; CI: 1.89-15.16
	Apgar score <5 at 5 minutes	0.002*	0.09; 95%; CI: 0.02-0.43
	Neonatal seizures	0.002*	0.12; 95%; CI: 0.03-0.46
	Gender	0.3, NS	1.90; 95%; CI: 0.70-5.17
	Weight for gestational age	0.3, NS	0.35; 95%; CI: 0.07-1.66
	Assisted ventilation	0.4, NS	0.67; 95%; CI: 0.24-1.81
	Neonatal hyperbilirubinemia requiring exchange transfusion	0.06, NS	2.42; 95%; CI: 0.125-45.71
Other factors	Duration of NICU stay (10 days)	0.6, NS	0.68; 95%; CI: 0.25-1.88
Cranial ultrasound findings	Abnormal CUS findings	0.0004*	7.47; 95%; CI: 2.45-22.76

P<0.05 was taken as statistically significant, NS –non-significant

The reliability of CUS was tested against actual neurodevelopmental findings. The sensitivity of CUS was 89.2%, specificity was 47.3%, positive predictive value was 89.2% and the negative predictive value was 47.3%. Cranial ultrasound can be used for screening and confirmation of abnormal neurodevelopmental outcome as it has good sensitivity and positive predictive value, but this test cannot be used to negate the absence of abnormal Outcome (as it has very poor specificity and negative predictive value).

Table-2: Reliability of cranial ultrasound against actual neurodevelopmental delay.

Variable	Value	95% Confidence Interval
Sensitivity	89.2%	0.81-0.94
Specificity	47.3%	0.24-0.71
Positive Predictive Value	89.2%	0.81-0.94
Negative Predictive Value	47.3%	0.24-0.71
Likelihood Ratio	1.696	

Discussion

Despite the wide availability of ultrasound machines in the hospitals, the penetration of CUS in the Indian NICU is less. In experienced hands, CUS is an outstanding tool to detect brain abnormalities in preterm and full-term infants, to follow the progression of these lesions, to assess the timing of brain damage, and to describe the maturation of the infant's brain.

The present study included 123 newborns with a wide range of several high-risk perinatal factors. The mean gestational age on inclusion for preterm neonates (n=76) was 33.2 ± 1.2 weeks. That for term neonates (n=47) was 39.0 ± 1.5 weeks.

PIH was not found to be a risk factor for adverse outcomes in the present study. Backes et al [3] in their review article found that maternal preeclampsia had a protective effect on cerebral palsy regardless of exposure to magnesium sulfate. However, some data suggest infants born to mothers with preeclampsia have lower MDI scores (Bayley II scales of infant development) at 24 months of age compared to infants without maternal preeclampsia. The association between maternal preeclampsia and the worse neurodevelopmental outcome has been challenged by more recent evidence suggesting that infants exposed to preeclampsia have, in fact, higher scores on developmental testing at 18 months corrected age. Another study by Spinillo et al [4] showed an increased risk of minor neurodevelopmental impairment among infants delivered after severe hypertension.

The non-use of antenatal steroids in premature deliveries was not found statistically significant in relation to adverse neurodevelopmental outcomes in this study. But according to a systematic review and meta-analysis by Sotiriadis et al [5] single course of antenatal corticosteroids in women at high risk for

Preterm birth, appears to improve neurodevelopmental outcomes in offspring born before 34 weeks of gestation. Another study by Carlo et al [6] published that among infants born at 23 to 25 weeks' gestation, antenatal exposure to corticosteroids compared with non-exposure was associated with a lower rate of death or neurodevelopmental impairment at 18 to 22 months.

There was no male/female preponderance for adverse neurodevelopmental outcomes as opposed to the study by Beaino et al [7] where male sex was one of the predictors of the development of CP in preterm infants. Although in another study by Romeo et al [8] no gender difference was observed in term-born infants, while male very preterm and late-preterm infants showed lower MDI (Mental Development Index) than peer females at both ages.

In the present study, term babies, who came under high-risk category had a poorer neurodevelopmental outcome which was because the term neonates who were admitted to NICU mostly came with perinatal asphyxia which is a risk factor for adverse neurodevelopmental outcome independently. But most other studies performed on strata of preterm and LBW newborns found that extreme prematurity was commonly associated with adverse neurodevelopmental outcomes. According to a study by Hintz et al [9] who compared neurodevelopmental outcome at 18 to 22 months corrected age of infants born with extremely low birth weight at an estimated gestational age of < 25 weeks during 2 periods: 1999-2001 (epoch 1) and 2002-2004 (epoch 2), concluded that early childhood outcomes for infants born at < 25 weeks estimated gestational age was unchanged and remain guarded between the 2 periods.

In the present study association of birth weight in relation to the abnormal neurodevelopmental outcome was found to be significant statistically, inferring that babies with the normal birth weight falling into the high-risk group had a poorer outcome. Boulet et al [10] who studied the association between the full birth weight distribution and prevalence of specific developmental disabilities, stated although associations were strongest for very low birth weight, children with "normal" birth weights of 2,500-2,999g were more likely than those with birth weights of 3,500-3,999g to have mental retardation, cerebral palsy, learning disability without mental retardation, ADHD and Another developmental delay. Another study by Van et al [11] concluded that lower birth weight is a causal risk factor for child problem behavior, the effects of which may well extend into adulthood using a variation of the co-twin control method. While much research has focused on the health and developmental outcomes of low and very low birth weight children, our findings suggest that additional study of a continuous range of birth weights may be warranted.

In the present study, there was no statistically significant correlation between being small for gestational age(SGA) and having abnormal neurodevelopmental outcome such that only 7% of all SGA infants had an abnormal neurodevelopmental outcome whereas 10% had a questionable neurodevelopmental outcome that was similar to research by Bickle Graz et al [12] who found that out of 342 (76%) premature infants who were assessed, SGA was significantly associated with hyperactivity scores of the Strengths and Difficulties Questionnaire, but not with cognitive scores or neurodevelopmental impairment. Another study by Goldenberg et al [13] states that being born SGA is associated with an increase in various measures of MND (Minimal neurological dysfunction). Major motor and cognitive disability are rare in SGA infants but is probably significantly increased when evaluated in large sample sizes. If the SGA develops early so that affects head growth before 26 weeks, there seems to more of an impact on neurologic function than SGA which develops later. This review suggests that SGA is a heterogeneous condition, at times but not usually associated with various types of neurodevelopment dysfunction.

It was found there was a significant correlation between perinatal asphyxia with adverse neurodevelopmental outcome at one-year age such that 50% of neonates with Apgar score of less than 5 at 5 minutes had abnormal neurodevelopmental outcome, 20% had questionable neurodevelopmental outcome where 30% had normal neurodevelopment at one year of corrected gestational age. This was in concordance with a study by Misra et al [14] where the abnormal outcome at 11 months of age (for term neonates with Apgar score<5 at 5 minutes) was seen in 83%. According to another article by Finer et al [15] infants with five-minute Apgar scores of 0 to 3, seizures within the first day of life, Stage II or III encephalopathy, or a suppressed electroencepha-

Logram had a significantly greater incidence of severe handicap or death.

The outcome of neonatal seizures was significantly poor in the present study. This has been supported by evidence from previous studies. One such study by Tekgul et al [16] where 28% of the survivors of seizures had poor long-term outcomes. Association between seizure etiology and the outcome was strong, with cerebral dysgenesis and global hypoxia-ischemia associated with poor outcome. Another study by Pisani et al [17] on similar grounds shows the unfavorable neurodevelopmental outcome seemed significantly related to the moderate/severe background activity abnormalities, the spread of ictal discharge to the contralateral hemisphere, and the Ictal Fraction when it exceeds 10 minutes.

Amongst abnormal neurodevelopmental outcomes, there were no babies with neonatal hyperbilirubinemia requiring exchange transfusion so correlation could not be done but previous data based on other studies suggest a significant association.

A study was done by Duan et al [18] on two-hundred and eight premature infants. The developmental outcomes of premature infants at the age of 12 months were assessed by the psychomotor developmental index (PDI) scale and mental development index (MDI). The relationship between ultrasonic grayscale value and PDI and MDI was analyzed. The higher grade of periintraventricular hemorrhage and periventricular white matter damage was associated with the worse prognosis of psychomotor and mental development.

O'Shea et al [19] did their study on the association between ultrasound-defined lesions of the brain and developmental delay at 24 months corrected age in 1017 children born before the 28th postmenstrual week and found focal white matter damage, as characterized by echolucent/hypoechoic lesion, and diffuse damage, as suggested by late ventriculomegaly, are associated with delayed mental and psychomotor development.

Pinto-Martin et al [20] stated among perinatal and postnatal factors, CUS abnormalities are by far the most powerful predictors of disabling cerebral palsy in LBW infants. Although parenchymal echodensities/lucencies or ventricular enlargement (PEL/VE) on CUS, germinal matrix/intraventricular hemorrhage (GM/IVH) also appeared to independently contribute to the risk of DCP (disabling cerebral palsy). NDCP (non-disabling Cerebral palsy) in low birth weight infants appears to have a different risk profile than DCP. In particular, it is less closely related to ultrasound evidence of perinatal brain injury.

There was a significant correlation found between abnormal cranial ultrasound with abnormal neurodevelopmental outcome in the present study with sensitivity and positive predictive value of around 89%. Seme-Ciglenecki [21] assessed results of CUS scans done longitudinally from the day of birth until the end of three months of chronologic age for evaluation of psychomotor development of the same children at the corrected age of six years. The validity of the scans was 85%, sensitivity 70%, specificity 90%, positive predictive value 72%, and negative predictive value 89%; for psychomotor development at 6 years of age.

According to a meta-analysis by Ng et al [22], the predictive value of a normal scan for freedom from major disability was 93% and the predictive value for an entirely normal outcome was 88%. Although in the present study the specificity and negative predictive value of cranial ultrasound for adverse neurodevelopmental outcomes were poor (47%) as compared to other studies, the present can safely conclude that cranial USG is a useful tool for prediction of neurodevelopment outcome at later age.

Limitations

The current study could not enroll a large number of newborns as a very long follow up period of one year for neurodevelopment assessment was needed. So a small sample size was the limitation of the study. If a large sample size had been available then study findings could probably be generalized to the whole population.

Conclusion

This study highlights the convenience and diagnostic efficiency of cranial ultrasound as a screening modality among high-risk preterm and term neonates to identify those at risk of the adverse neurodevelopmental outcome. Anticipation is particularly important in the planning of potential preventive, protective, and rehabilitative strategies for the management of critically ill newborns.

Finally, individualized protocols need to be laid down in the NICU for CUS based on the available resources along with neurodevelopmental

Assessment done by a standardized and sensitive test like DDST II at a fixed age for better pick up on regular follow up of high-risk newborns.

What does this study add to the existing knowledge

This study highlights that poor neurodevelopment can be well predicted in smaller setups having only a cranial ultrasound facility without much need of CT scan and MRI, and timely recognition and early intervention can be considered in those newborns having abnormal cranial ultrasound findings. Though these neonates can later be subjected to detailed study with CT scan and MRI. Most of the earlier studies had focused on LBW and preterm newborn but the current study found term neonate and normal birth weight babies are also at risk of the poor neurodevelopmental outcome.

Author's contribution

Dr. Ruby Singh: Formulating aims and objective, data collection, literature review, interpretation of results

Dr. Chandan Shaw: Discussion, interpretation, review of the manuscript

Dr. Shachi Jain Taran- Preparation of manuscript, interpretation of data, discussion, review of the manuscript

Dr. Veerendra Mehar- Concept and study design

Dr. Aman Gupta- Radiological data, literature review, study design

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