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Neurodevelopmental Outcome of High Risk Neonates with Respect to their Neuroimaging Status

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ABSTRACT

Background: Survival of high-risk neonates has improved due to advances in perinatal care, particularly in India. However, this has increased concerns regarding morbidity and developmental outcomes. Early identification of developmental delay in high-risk neonates enables timely intervention during the critical period of brain development, improving long-term outcomes.

Methods: This was a prospective analytical study conducted over a period of 7 years among high- risk neonates admitted and discharged from SNCU/NICU of public and private hospitals of Kottayam District coming for follow up within 3 months of birth in whom neuroimaging was done were followed up till 24 months for their neurodevelopmental outcome. The enrolled babies were followed up to their corrected/completed 24 months of age and detailed neurodevelopmental assessment done using Bayley Scales of Infant and toddler Development edition-III.

Results: 81 out of 375 enrolled children had abnormal imaging of cranial ultrasound/MRI/CT High risks infants with abnormal imaging cohort were having significantly lower neurodevelopmental status scores of all domains, cognitive, communication, motor, and social-emotional at their corrected/completed 24 months of age compared to the group of highrisk babies with normal imaging.

Conclusion: High risk neonates with abnormal neuroimaging after birth or within 3 months of age are having significantly higher chance of developing moderate to severe developmental delay at their corrected/completed 24 months of age.

Key-words: Abnormal neuroimaging, Cerebral palsy, Developmental delay, High-risk newborn, SNCU, NICU

INTRODUCTION

Rapid improvements in the care of high-risk neonates have occurred in recent decades with the availability of skilled personnel and advanced equipment in secondary and tertiary neonatal care units, both in the public and private sectors, in India and the state of Kerala.

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This has resulted in improved survival of an increasing number of high-risk neonates, particularly preterm, low birth weight, and perinatally asphyxiated babies.[1] Along with other modalities, neuroimaging is now routinely used for the screening, diagnosis, and prognostication of these high-risk infants.[2] High-risk conditions expose the developing brain to multiple insults, including prematurity, hypoxia, ischemia, sepsis, hypoglycemia, hyperglycemia, electrolyte imbalance, and multi-organ failure.[3,4]

The objective of the present study was to determine the neurodevelopmental outcome of high-risk newborns at their corrected or completed 24 months of age with respect to their neuroimaging status after birth or within

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the first 3 months of life. Routine neuroimaging in high-risk neonates primarily included cranial ultrasound (CUS), magnetic resonance imaging (MRI) in selected patients, and, rarely, computerized tomography (CT). Cranial ultrasound (neurosonogram) was performed in all high-risk babies and serially in very preterm and extremely preterm infants, usually on postnatal days 3, 7, 14, and 28, as well as within the first 3 months of age. Cranial ultrasound screening was repeated whenever indicated, while MRI was performed only in selected cases. Common abnormal imaging findings included intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL), post-hemorrhagic ventriculomegaly, post-hemorrhagic venous infarction (PHVI), parenchymal hemorrhage, hypoxic-ischemic encephalopathy (HIE)-related encephalomalacic changes, and hypoglycemic parieto-occipital cortical changes. Additional abnormalities detected on MRI included parietal, temporal, occipital, and frontal cortical lesions, subdural hemorrhage, basal ganglia and thalamic hemorrhages, and cerebellar hemorrhage.[2,5]

High-risk neonates included extremely preterm, very preterm, moderate preterm, extremely low birth weight, low birth weight, late preterm, and term babies presenting with respiratory distress, perinatal asphyxia, sepsis, congenital pneumonia, necrotizing enterocolitis (NEC), persistent pulmonary hypertension of the newborn (PPHN), symptomatic hypoglycemia, hyperbilirubinemia, and those admitted to and discharged from the Special Newborn Care Unit (SNCU) or Neonatal Intensive Care Unit (NICU). These infants are particularly vulnerable to repeated insults to the immature developing brain due to hypoxia, ischemia, hypoglycemia, hyperglycemia, electrolyte imbalance, hypotension, hypertension, and sepsis. Several studies have demonstrated the critical role of neuroimaging in the early detection of brain lesions and in predicting subsequent neurodevelopmental outcomes. Abnormal cranial ultrasound and MRI findings at term-equivalent age have been shown to correlate with cerebral palsy, cognitive and motor impairment, visual dysfunction (including peripheral and cortical visual impairment), refractive errors, strabismus, nystagmus, and higher auditory pathway abnormalities.[5,6]

MATERIALS AND METHODS

Research Design- This prospective analytical study was conducted over a period of seven years, commencing in 2017. High-risk neonates admitted with respiratory distress to the SNCU/NICU and subsequently discharged were enrolled during follow-up at term-equivalent age or within the first three months of life. Cranial ultrasound was performed in all enrolled babies after birth or within the first three months of age. MRI was performed in selected babies whenever clinically indicated. Imaging findings suggestive of intraventricular hemorrhage (IVH; Grades II–IV), periventricular leukomalacia (PVL; Grades II–IV), ventriculomegaly/ hydrocephalus, hypoxic-ischemic encephalopathy (HIE) changes, occipital gliosis, basal ganglia changes, and parenchymal hemorrhages were classified as abnormal, while the remaining imaging findings were considered normal. Point-of-care CUS was performed in all babies by the principal investigator and the findings were cross-checked by a specialist sonologist. All enrolled neonates were followed up until their corrected/completed age of 24 months.

Methodology- Neurodevelopmental assessment of all enrolled babies was performed at their corrected/completed age of 24 months using the Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III). The cognitive, motor, and communication domains were assessed by the principal investigator. The social-emotional domain was assessed with the assistance of parents using the English/Malayalam version of the questionnaire. The raw scores obtained for the cognitive, motor, communication, and social-emotional domains were converted into age-specific scaled scores and subsequently into the corresponding composite scores. These composite scores were used for statistical analysis and interpretation.[3]

Inclusion criteria

- Neonates with a gestational age of more than 24 weeks and less than 41 completed weeks admitted for preterm care, perinatal asphyxia, neonatal respiratory distress, hypoglycemia, sepsis, hyperbilirubinemia, extremely low birth weight, fetal growth restriction, and discharged from the SNCU/NICU.

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- Babies evaluated during follow-up at term-equivalent age or within the first three months after birth.
- Babies brought for detailed neurodevelopmental evaluation at their corrected/completed age of 24 months.

Exclusion criteria

- Babies with visible birth defects (VBD), congenital organ defects, chromosomal anomalies, genetic or metabolic disorders, and dysmorphic or syndromic features were excluded.
- Babies who did not attend follow-up at their corrected/completed age of 24 months.
- Babies whose parents refused to provide informed consent.
- Neonates with a gestational age of less than 25 weeks or 41 completed weeks and above were excluded.

Statistical Analysis- Data were entered into Microsoft Excel and analysed using appropriate statistical software. Descriptive statistical methods, including measures of central tendency (mean), standard deviation, coefficient of skewness, and kurtosis, were used to summarize the study variables. Inferential statistical analysis was performed using Student's t-test to compare the mean scores between the normal and abnormal neuroimaging groups. A p-value of <0.05 was considered statistically significant for all analyses.

Ethical Approval- Ethical approval for the study was obtained from the Institutional Ethics Committee, School of Behavioural Sciences, Mahatma Gandhi University, Kottayam, Kerala, India, on 22 September 2017, before the commencement of the study. Written informed consent was obtained from the parents or legal guardians of all enrolled neonates prior to their participation in the study.

RESULTS

Table 1 presents the comparison of the total neurodevelopmental scores according to neuroimaging status. High-risk neonates with abnormal neuroimaging had significantly lower total neurodevelopmental scores (310.91±28.47) than those with normal neuroimaging (364.90±32.33). The difference between the two groups was statistically highly significant (t=13.52, p<0.001).

Table 1: Total neurodevelopmental scores vs Neuroimaging Status

Neuro Imaging Status	No.	Total Neuro Developmental Score		t-value	p-value
		Mean	SD		
Normal	294	364.90	32.33	13.52	0.000
Abnormal	81	310.91	28.47		

Table 2 shows the comparison of cognitive scores between high-risk neonates with normal and abnormal neuroimaging. The mean cognitive score was significantly lower in the abnormal neuroimaging group (76.71±7.55) than in the normal neuroimaging group (87.77±8.05), with a highly significant difference (*t*=11.02, *p*<0.001).

Table 2: Cognitive Scores vs Neuroimaging status

Neuroimaging Status	No.	Cognitive Score		t-value	p-value
		Mean	SD		
Normal	294	87.77	8.05	11.02	0.000
Abnormal	81	76.71	7.55		

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Table 3 depicts the comparison of communication scores according to neuroimaging status. High-risk neonates with abnormal neuroimaging demonstrated significantly lower communication scores (82.22±9.06) compared with those having normal neuroimaging (95.36±9.57). The observed difference was statistically highly significant (t=11.07, p<0.001).

Table 3: Language Scores vs Neuroimaging Status

Neuroimaging Status	No.	Communication Score		t-value	p-value
		Mean	SD		
Normal	294	95.36	9.57	11.07	0.000
Abnormal	81	82.22	9.06		

Table 4 presents the comparison of motor scores between the two neuroimaging groups. The abnormal neuroimaging group had significantly lower motor scores (74.74±10.48) than the normal neuroimaging group (91.96±9.62). The difference was statistically highly significant (t=13.99, p<0.001).

Table 4: Motor Scores vs Neuroimaging Status

Neuroimaging Status	No.	Motor Score		t-value	p-value
		Mean	SD		
Normal	294	91.96	9.62	13.99	0.000
Abnormal	81	74.74	10.48		

Table 5 shows the comparison of social-emotional scores based on neuroimaging status. High-risk neonates with abnormal neuroimaging had significantly lower social-emotional scores (77.16±7.78) compared to those with normal neuroimaging (89.81±10.40). The difference between the two groups was also statistically highly significant (t=11.98, p<0.001).

Table 5: Social -Emotional Scores vs Neuroimaging

Neuroimaging Status	No.	Motor Score		t-value	p-value
		Mean	SD		
Normal	294	91.96	9.62	11.98	0.000
Abnormal	81	74.74	10.48		

DISCUSSION

Advances in critical care, together with the availability of skilled healthcare personnel and supportive equipment for monitoring and management, have significantly improved the survival of extremely preterm, very preterm, moderately preterm, late preterm, intrauterine growth-restricted, and other high-risk neonates in India, particularly in the state of Kerala. However, this improved survival has also been accompanied by an increased risk of morbidity and adverse neurodevelopmental outcomes. Studies from both developed and developing countries have demonstrated a significant association between abnormal neuroimaging findings, such as PVL Grades II–IV, intraventricular hemorrhage (IVH) Grades II–IV, parenchymal hemorrhages involving the major cerebral

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lobes, basal ganglia, thalamus, cerebellum, and other stroke-like cortical lesions, with neurodevelopmental delay in infants and toddlers. Therefore, serial neuroimaging using CUS with Doppler and MRI, whenever indicated, has become an essential tool for the diagnosis, management, and prognostication of preterm and high-risk neonates. Neuroimaging is considered a valuable modality for screening, diagnosis, clinical management, and prediction of neurodevelopmental outcomes in these infants.[4,5]

A study conducted among high-risk neonates with a gestational age of 35 weeks or more and hypoxic-ischemic encephalopathy reported that a lower 5-minute APGAR score, elevated lactate levels at birth, multi-organ dysfunction, and abnormal neurophysiological and neuroimaging findings were significantly associated with adverse neurodevelopmental outcomes, including death, cerebral palsy, severe cognitive impairment, global developmental delay, post-neonatal epilepsy, and feeding difficulties.[6]

In a prospective cohort study of neonates with a gestational age of 36 weeks or more and neonatal encephalopathy, early MRI demonstrated that diffuse, mammillary body, and pontine T2 hyperintensities were not significantly associated with cognitive, language, or motor developmental delay at 3 years of age.[7]

According to a recent study, severe motor deficits, non-ambulatory cerebral palsy, and seizure disorders at 24 months among high-risk term neonates were associated with abnormal neuroimaging showing injury to the deep grey matter, particularly the basal ganglia and thalami. Furthermore, abnormalities involving the watershed regions and peripheral white matter were associated with a significantly higher risk of cognitive and communication delay at 24 months of age.[8]

Another recent study demonstrated that MRI performed at term-equivalent age provides significantly greater diagnostic accuracy than early neonatal scans. Structural markers identified at term-equivalent age, including increased ventricular mid-body size, immature gyration patterns, and bilateral lesion laterality, were found to be strongly associated with gross motor delay and cerebral palsy at 24 months of age.[9]

A systematic review of fetal growth-restricted (FGR) infants reported significant differences in MRI findings compared with term appropriate-for-gestational-age (AGA) infants. A lower total brain parenchymal area on MRI in FGR infants was associated with lower cognitive scores at 12 months of age.[10]

In the present study, all 375 enrolled high-risk neonates underwent cranial ultrasound after birth or within the first three months of age, while MRI was performed in selected babies whenever indicated. Among the enrolled neonates, 81 had abnormal neuroimaging findings and 294 had normal imaging. The abnormal imaging findings included PVL Grades II–IV, IVH Grades II–IV, isolated parenchymal hemorrhages, and other cortical lesions.[4,5] The major high-risk conditions among these babies included prematurity, respiratory distress syndrome, severe fetal growth restriction, perinatal asphyxia, early- and late-onset sepsis, NEC, hypoglycemia, retinopathy of prematurity (ROP), and PPHN.[1]

Neurodevelopmental assessment performed at the corrected/completed age of 24 months using the BSID-III [3] demonstrated that the mean total neurodevelopmental score was significantly lower among high-risk neonates with abnormal neuroimaging than among those with normal neuroimaging. These findings indicate that neonates with abnormal neuroimaging are at a substantially higher risk of developing global developmental delay, which is consistent with previous reports demonstrating the predictive value of abnormal neonatal neuroimaging for adverse neurodevelopmental outcomes.[6-10]

Similarly, the mean cognitive score was significantly lower in the abnormal neuroimaging group than in the normal neuroimaging group, indicating a greater likelihood of significant intellectual disability. The mean language (receptive and expressive communication) score was also significantly lower among babies with abnormal neuroimaging, suggesting a higher risk of moderate-to-severe communication disorders. Likewise, the mean motor (gross and fine motor) score was significantly lower in the abnormal neuroimaging group, indicating an increased risk of developing moderate-to-severe cerebral palsy. In addition, the mean social-emotional score was significantly lower among babies with abnormal neuroimaging, indicating a greater likelihood of developing moderate-to-severe social-emotional and behavioural disorders.

The findings of the present study provide objective evidence of a strong association between abnormal neuroimaging performed at term or within the first three months of life and moderate-to-severe global

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developmental delay at the corrected/completed age of 24 months in high-risk neonates. Abnormal neuroimaging may therefore be considered an important predictor of significant developmental delay, along with other established predictors such as abnormal general movement patterns, abnormal Amiel-Tison tone, and abnormal EEG findings.[11,12] Early identification of these high-risk infants may enable clinicians, neurodevelopmental therapists, physiotherapists, occupational therapists, and speech therapists to initiate timely intervention during the critical window of brain development and maximize the potential benefits of neuroplasticity in the developing brain.

CONCLUSIONS

High-risk neonates with abnormal neuroimaging performed after birth or within the first 3 months of age have a significantly higher risk of developing moderate-to-severe developmental delay in the cognitive, communication, motor, and social-emotional domains at their corrected/completed age of 24 months compared with those having normal neuroimaging. Abnormal neuroimaging may therefore be considered a strong predictor of adverse neurodevelopmental outcomes when interpreted along with other clinical predictors, such as abnormal general movements, abnormal Amiel-Tison tone, and abnormal EEG patterns. Early identification of these abnormalities may facilitate the timely initiation of targeted interventions, including focused physical therapy, auditory stimulation, specific visual stimulation, and combined multisensory and motor stimulation during the critical period of brain development, thereby maximizing neuronal recruitment, neural rewiring, and the neuroplastic potential of the premature and developing brain.

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