Original Research Article

Growth and neurodevelopmental outcome of neonatal intensive care Unit graduates till 1 year at a tertiary care centre in eastern India and identification of the clinical and electrophysiological predictors of adverse developmental outcome

Suman Das[1], Bhattacharya M[2], Sanyal D[3], Basu S[4], Chatterjee A[5], Paul D.K[6], Sen S[7], Bhakta S[8], Aich B[9]

[1]Dr. Suman Das, Resident Pediatrician, [2]Dr. Mala Bhattacharya, Consultant Pediatrician, Dr. B.C. Roy Post Graduate Institute of Pediatric Sciences, Kolkata, [3]Dr. Debashish Sanyal, Consultant Psychiatrist, KPC Medical College, Jadavpur, Kolkata, [4]Dr. Suprit Basu, Resident Pediatrician, [5]Dr. Anish Chatterjee, Consultant Pediatrician, [6]Dr. Dilip Kumar Paul, Consultant Pediatrician, [7]Dr. Sandip Sen, Consultant Pediatrician, [8]Dr. Subhajit Bhakta, Resident Pediatrician, Dr. B.C. Roy Post Graduate Institute of Pediatric Sciences, Kolkata, [9]Dr. Bholanath Aich, Consultant Pediatrician, Behrampore Medical College, Behrampore, India.

Address for Correspondence: Dr. Suman Das, 44, Talpukur Road, Deulpara, Naihati, North 24 Parganas, E-mail-dr.sumands@gmail.com

Abstract

Background: Despite serious neonatal morbidity, the neurodevelopmental outcome of NICU (Neonatal Intensive Care Unit) graduates is often reasonably good. Infants with neurodevelopmental abnormality need to start therapy early, and hence, they should be detected as soon as possible. Therefore we need well designed follow-up services. **Objectives:** To study the outcome of growth and development till one year of age of NICU graduates from a tertiary care centre in eastern India. **Design and setting:** A prospective neurodevelopmental follow-up study on graduates from the Calcutta National Medical College and Hospital NICU. **Methodology:** We selected a cohort of 177 consecutive NICU graduates according to high-risk criteria and followed them up at the high risk clinic of Paediatrics department up to 1 year of age on a predetermined schedule. Growth monitoring (weight, length, head circumference measurements), neurologic examination by Amiel-Tison method, developmental assessment using Denver Development Screening Test (DDST) as screening tool and Developmental Assessment Scale for Indian Infants (DASII) as a definitive test, neuroimaging (cranial ultrasound or magnetic resonance imaging of brain) and electrophysiological investigations visual evoked potential (VEP), brainstem auditory evoked response (BAER), and electroencephalogram (EEG) were done. Early stimulation and physiotherapy were advised as per need. Ongoing illnesses were identified and treated. **Results:** Out of 177 consecutive NICU graduates enrolled in the study, 155 were followed up to 1 year of age. There were no statistically significant difference in the occurrence of growth failure, and neurodevelopmental delay between term and preterm and between appropriate for gestational age (AGA) and small for gestational age (SGA) infants. However growth failure was significantly higher among infants with neurodevelopmental delay. (the word conclusion deleted here) Persistence of abnormalities in tone, BAER, EEG & neuroimaging strongly predicted adverse neurodevelopmental outcome. Recurrent respiratory tract infection was found to be the most common morbidity among NICU graduates followed by seizure disorder.

Key words: High risk newborns, Follow-up, Neurodevelopmental delay, DASII, Early stimulation

Introduction

Improving outcomes beyond survival for high-risk newborns in resource-limited countries is an emerging challenge. As the survival rate of high risk newborns improve with advancing perinatal care services, the total number of infants with unique follow-up needs increase. Numerous studies have shown that despite reduction in neonatal mortality, the incidence of chronic

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morbidities and adverse outcomes have not declined much. Neurodevelopmental impairments include motor function deficits such as cerebral palsy, cognitive delay and sensory impairments such as visual and auditory deficits. This highlights the paramount importance of monitoring the growth and neurodevelopmental outcome of NICU graduates through a multidisciplinary approach [1,2]. In infants with physical, social, adaptive and cognitive developmental delay or having a diagnosed condition with high probability of resulting in developmental delay, early stimulation services need to be initiated. Compensatory mechanisms exist for all cerebral function and this plasticity of brain is encouraged by early stimulation [3].

There are numerous studies evaluating the outcome of asphyxiated babies, preterm babies, and very and extremely low birth infants. However, there are very few studies that evaluate the outcome of a composite high risk cohort. In India, the neurological sequelae of a composite high risk cohort was evaluated by Chaudhari [4] at 3 years and by Paul [5] and Sukumaran [6] at 1 year, and Baburaj [7] evaluated the growth and development of graduates from a rural NICU at 1 year. Luo [8] evaluated the mental and motor developmental scales of high risk infants using Gesell Developmental Scale at 6 and 12 months and performed psychometric test using Wechsler Intelligence Scale- Revised (WISC-R) for Chinese Children at 6-7 years. Molteno [9] assessed and compared perinatal risk rating, the Dubowitz Neurological Assessment and the Infant Neuromotor Assessment in terms of predicting neurodevelopmental outcome of graduates from the Groote Schuur Hospital (GSH) neonatal intensive care unit (NICU) in South Africa at 1 year. Galbraith [10] described a 10 years' experience of neurodevelopmental outcome of high risk neonates till 1 year in Canada.

There are significant gaps in morbidity outcome data in high mortality contexts of low and middle-income countries and global estimates demonstrate the scale of this challenge [2].

This study was thus conducted to document the prevalence of neurodevelopmental impairment in high-risk newborns who were followed up till 1 year in a tertiary referral teaching centre of eastern India.

Objectives: 1) Evaluating the NICU graduates for morbidities like growth failure, developmental delay, visual and hearing deficits and other ongoing illnesses and starting early interventions. 2) To identify the risk factors and clinical and electrophysiological predictors of adverse neurodevelopmental outcome.

Methods and Materials

The observational longitudinal prospective study was performed at the high risk clinic of Department of Pediatrics, Calcutta National Medical College and Hospital over one year, from June 2011 to May 2012 after approval from institutional ethical committee. NICU graduates with the following diagnoses were included in the study- hypoxic ischemic encephalopathy (Sarnat stages II and III), neonatal sepsis with or without meningitis, hyperbilirubinemia >20mg/dl and or requiring exchange transfusion, preterm infants (gestational age<37 completed weeks), infants with birth weight<1800gm, small and large for gestational age infants (SGA and LGA), infants with seizures, shock requiring inotropes, hypoglycaemia, hypocalcemia and those requiring mechanical ventilation. Informed consent was obtained from both the parents before inclusion of any infant in the study. Infants with major congenital anomaly or parental refusal to give consent of participation were excluded.

The team composed of pediatrician, ophthalmologist, otorhinolaryngologist, neurologists, experts in physical medicine and rehabilitation and medical social workers. The follow-up schedule – the cases were examined at 1,3,6,9,12 months corrected age. Infants with birth weight <1800gm and or gestational age <34wks were initially seen more frequently-7 days after discharge and then every 2 weeks till a weight of 3 kg was achieved. Thereafter, they were seen as per the above mentioned schedule.

Growth monitoring (measurement of weight, length, and head circumference) was done and plotted on World Health Organization (WHO) growth charts. Weight was measured on an electronic weighing machine with ±5 gm accuracy. Length and head circumference (HC) was measured using infantometer and nonstretchable tape. Neurologic examination was done by Amiel-Tison technique; adductor, popliteal and dorsiflexion angles were measured and scarf sign examined. Focal neurodeficits, abnormal movements, cranial nerves and primitive reflexes were examined. Developmental assessment was done according to corrected ages of the infants. DDST was used as a screening test, which evaluates the milestones in 4 domains-gross motor, fine motor, language and personal social. The responses were rated as pass (child

passes, fails, or refuses item on which the age line falls between the 25th and 75th percentile), caution (child fails or refuses item on which the age line falls between the 75th and 90th percentile), or delay (child fails or refuses item that falls completely to the left of the age line). Delay in one domain or caution ratings in 2 domains were the criteria for an infant to undergo a formal developmental evaluation using DASII and motor (MoDQ) and mental (MeDQ) developmental quotients were calculated.

For all the infants cranial ultrasound was done prior to discharge and repeated at 1 month of age if initially abnormal. Various abnormalities seen in cranial USG were cerebral oedema, intraventricular, parenchymal and subdural haemorrhage, ventricular dilatation, multicystic encephalomalacia, periventricular echogenicities and echogenecity in caudothalamic groove. Magnetic resonance imaging of brain was done if persistence of abnormality was seen on cranial ultrasound or if the infant had persistent neurological abnormality or developmental delay. EEG was done in all infants who had seizure during NICU stay at 1 month of age and at 6 months of age, if the first EEG was abnormal. Abnormal EEG findings were excessive discontinuity, burst suppression, persistent marked voltage suppression, isoelectric pattern, excessive sharp waves in rolandic / frontal / occipital region, focal periodic lateralized epileptiform discharges. Visual evoked potential (VEP) and BAER was done for all infants within 3 months of post-natal age and, was repeated at 6 months, if initially abnormal. Severity of hearing loss were classified as mild 15-30 dB, moderate 30-50 dB, severe 50-70 dB, profound >70 dB. For persistent severe and profound BAER abnormalities, the infant was referred to Otorhinolaryngology department for fitting of hearing aids. Retinopathy of prematurity (ROP) screening was done for premature infants, following the standard timing schedule based on postnatal age. At 9 months corrected age, the ophthalmologist evaluated the baby for squint, cataract and optic atrophy and adequate interventions were taken.

The infants with tone abnormalities were referred to the department of Physical Medicine and Rehabilitation for physiotherapy. Early stimulation (neurodevelopmental, auditory, visual, tactile and cognitive stimulation) were explained according to individual needs.

Statistical Analysis: Done using SPSS16.0 software. p values were calculated (value<0.05 was considered significant for 95% confidence interval) and an exhaustive chi-square automatic interaction detection (CHAID) analysis was done to identify the most important risk factor for neurodevelopmental delay. Mean and standard deviation were calculated for continuous variables. Chi square test was used for nominal variables.

RESULTS- 177 consecutive NICU graduates were enrolled in the study. However, 17 babies were lost to follow-up and 5 babies died during the study period. Rest 155 infants were followed upto 1 year of age.

Table-1: Characteristics of the infants-

Sex	**Male**	**91(58.7%)**
	Female	64 (41.3%)
Birth weight	<1000gm (ELBW)	2 (1.29%)
	≥1-1.5kg (VLBW)	14 (9.03%)
	≥1.5-2.5kg	48 (30.97%)
	≥2.5-4kg	89 (57.42%)
	≥4kg	2(1.29%)
Gestational age	28-30wks	6 (3.87%)
	31-33wks	16 (10.32%)
	34-36wks	19 (12.26%)
	37-42wks	112 (72.25%)
	>42wks	2 (1.3%)
Weight for gestational age	AGA	113 (72.9%)
	SGA	40 (25.81%)
	LGA	2 (1.3%)

(ELBW- extremely low birth weight, VLBW- very low birth weight.)

Among 40 SGA infants, 14 were preterm SGA and 26 were term SGA. Among 113 AGA infants, 27 were preterm AGA and 86 were term AGA. Both LGA infants were post-term.

Morbidity pattern of the infants- During NICU stay, 55 (35.48%) babies had suffered from a single problem. 37 had HIE, 9 had hyperbilirubinemia >20mg/dl or required exchange transfusion, 4 were admitted in NICU for prematurity, 5 had sepsis with meningitis. Rest 100 (64.52%) babies suffered from multiple problems.

Among babies with HIE, 21 had meconium aspiration syndrome, 14 had sepsis, 5 had shock requiring inotropes, 2 had hypoglycaemia, 2 had early onset hypocalcemia, and all had seizures. Among babies with hyperbilirubinemia, 2 had sepsis, 4 had seizures, and 1 had hypoglycemia. Among preterm babies, 6 were asphyxiated, 25 had sepsis, 4 had septic shock, 5 had hypoglycemia, 2 had early onset hypocalcemia, and 3 had seizures.

Birth Trauma- 1 infant had subdural haemorrhage following forceps delivery. 1 infant had Erb's Palsy following forceps delivery, whose nerve conduction study showed brachial plexopathy. Both these infants were asphyxiated.

Respiratory support- 5 asphyxiated infants and 2 preterm infants had required mechanical ventilation. 7 preterm infants had required continuous positive airway pressure (CPAP) for respiratory distress.

Table-2: Showing growth parameters among the study infants.

Parameters	Term (n=112)	Preterm (n=41)	p value	AGA (n=113)	SGA (n=40)	p value
Normal weight	70 (62.5%)	19 (46.34%)	0.072	71(62.84%)	19 (47.5%)	0.0904
Weight <3rd percentile	42 (37.5%)	22 (53.66%)		42 (37.16%)	21(52.5%)	
Normal HC	65 (58%)	21 (51.2%)	0.54	69 (62%)	18 (45%)	0.068
HC<3rd percentile	47 (42%)	19 (46.3%)		43 (38%)	22 (55%)	
Normal length	96 (85.7%)	33 (80.5%)	0.43	95 (84%)	33 (82.5%)	0.8174
Length <3rd percentile	16 (14.3%)	8 (19.5%)		18 (16%)	7 (17.5%)	

Among 16 infants with birth weight <1.5kg, 3 (18.75%) had normal weight and 13 (81.25%) had weight < 3rd percentiles at 1 year of age. 2 infants who were post term and were LGA had normal weight head circumference and length at 1 year. 1 preterm AGA infant had macrocephaly (head circumference >97th percentile) due to obstructive hydrocephalus as a sequel of meningitis.

Table-3: Comparison of growth parameters among infants with normal outcome and infants with developmental delay

Parameters	Normal outcome (n= 120)	Developmental delay (n=35)	p value
Normal weight	82 (68.33%)	10 (28.58%)	0.00002509
Weight<3rd percentile	38 (31.67%)	25 (71.42%)	
Normal HC	82 (68.33%)	8 (22.86%)	0.000002872
HC <3rd percentile	38 (31.67%)	26 (77.14%)	
Normal length	105 (87.5%)	24 (68.57%)	0.008362
Length <3rd percentile	11 (31.43%)	15 (12.5%)	

Hence it was found that infants with developmental delay had significantly higher incidence of growth failure.

Table-4: Showing distribution of the findings of neurological examination and developmental outcome among the study infants:

Parameters	Term (n=112)	Preterm (n=41)	AGA (n=113)	SGA (n=40)	LGA (n=2)
Normal tone	47 (42%)	14 (34.14%)	41 (36.28%)	20 (50%)	1(50%)
TTA	37 (33%)	20 (48.78%)	43 (38.05%)	14 (35%)	1(50%)
PTA	28 (25%)	7 (17.07%)	29 (25.67%)	6 (15%)	0
Normal development	83 (74.1%)	35 (85.36%)	87 (77%)	31 (77.5%)	2 (100%)
Developmental delay	29 (25.9%)	6 (14.64%)	26 (23%)	9 (22.5%)	0

[TTA-transient tone abnormality, PTA-persistent tone abnormality]

During initial visits, 93 out of 155 infants had tone abnormality. On continued follow-up 58 infants had normalisation of tone (TTA) and rest 35 infants had persistent tone abnormality (PTA). Among them, 27 infants were hypertonic, 7 were hypotonic and 1 had right-left asymmetry. During the follow up, 'Caution' rating on DDST was given to 15 infants and early stimulation was prescribed. Subsequently, 10 infants (66.41%) attained age appropriate milestones with active early intervention in the high risk clinic, but 5 infants had developmental delay.

Table-5: Showing the severity of developmental delay among 35 infants.

Development Quotient	Mild delay (DQ 70-85%)	Moderate delay (DQ 50-70%)	Severe delay (DQ<50%)
MeDQ	5	15	15
MoDQ	1	17	17

The mean motor and mental DQ was 87.98±67.79 and 85.28±68.00. Of the 55 infants suffering from single problem, 10 had developmental delay and 45 had normal outcome. Of the 100 infants suffering from multiple problems, 25 had developmental delay and 75 had normal outcome (p=0.4229).

Table- 6: Showing the results of initial and repeat BAER, CUS and EEG among study infants.

Investigation	Normal outcome	Delay	p value
Normal initial BAER	92 (59.35%)	4 (2.59%)	<0.000001
Abnormal initial BAER	28 (18.06%)	31 (20.0%)	
Normal repeat BAER	27 (45.76%)	1 (1.69%)	0.001147
Abnormal repeat BAER	19 (32.21%)	12 (20.34%)	
Normal initial CUS	96 (61.94%)	16 (10.32%)	0.00003
Abnormal initial CUS	24 (15.48%)	19 (12.26%)	
Normal repeat CUS	22 (51.16%)	9 (20.93%)	0.00065
Abnormal repeat CUS	2 (4.65%)	10 (23.26%)	
Normal initial EEG	72 (63.72%)	21 (18.58%)	0.00001586
Abnormal initial EEG	6 (5.31%)	14 (12.39%)	
Normal repeat EEG	4 (20%)	2 (10%)	0.0374
Abnormal repeat EEG	2 (10%)	12 (60%)	

Among infants with HIE, 10% had mild to moderate delay and 12.08% had severe delay. Among infants with hyperbilirubinaemia, 17.64% had mild to moderate delay and 11.76% had severe delay. Among preterm infants, 9.76% had mild to moderate delay and 4.78% had severe delay.

Among infants with sepsis, 7.69% had mild to moderate delay and 15.38% had severe delay. Among infants with MAS, 4.76% had mild to moderate delay and 9.53% had severe delay. Among infants with hypoglycemia, 20% had mild to moderate delay and 26.67% had severe delay.

59 infants with abnormal initial BAER underwent repeat BAER. 43 infants with abnormal initial CUS underwent repeat CUS. Initially 113 infants underwent EEG and it was repeated in 20 infants, who had abnormal results.

All the 35 infants with developmental delay underwent MRI brain. Abnormality was found in 25 (71.42%) cases. In first BAER, mild, moderate and severe abnormalities were found in 15.49%, 18.7% and 3.87% cases, whereas, in repeat BAER, the incidences were 1.3%, 5.16% and 3.87%.

Table-7: Showing the sensitivity, specificity, positive (PPV) and negative predictive values (NPV) of initial and repeat BAER, CUS and EEG.

Investigation	Sensitivity	Specificity	PPV	NPV
Initial BAER	88.5%	76.67%	52.54%	95.83%
Repeat BAER	92.30%	58.69%	38.70%	96.42%
Initial CUS	54.29%	80%	44.18%	85.71%
Repeat CUS	52.63%	91.66%	83.33%	70.96%
Initial EEG	40%	92.31%	70%	77.42%
Repeat EEG	85.71%	66.67%	85.71%	66.67%

Ophthalmological examination- Among 111 preterm infants, 6 (14.63%) had ROP. 3 infants had Zone1 stage 1 disease. Among them one had Plus sign and hence needed cryotherapy under general anaesthesia.

Zone 2 stage 1, zone 2 stage 2 and zone 3 stage 2 diseases were seen in one infant each, which resolved on further follow-up. 2 babies of birth asphyxia and 1 baby of sepsis with meningitis developed optic atrophy by 6 months of age.

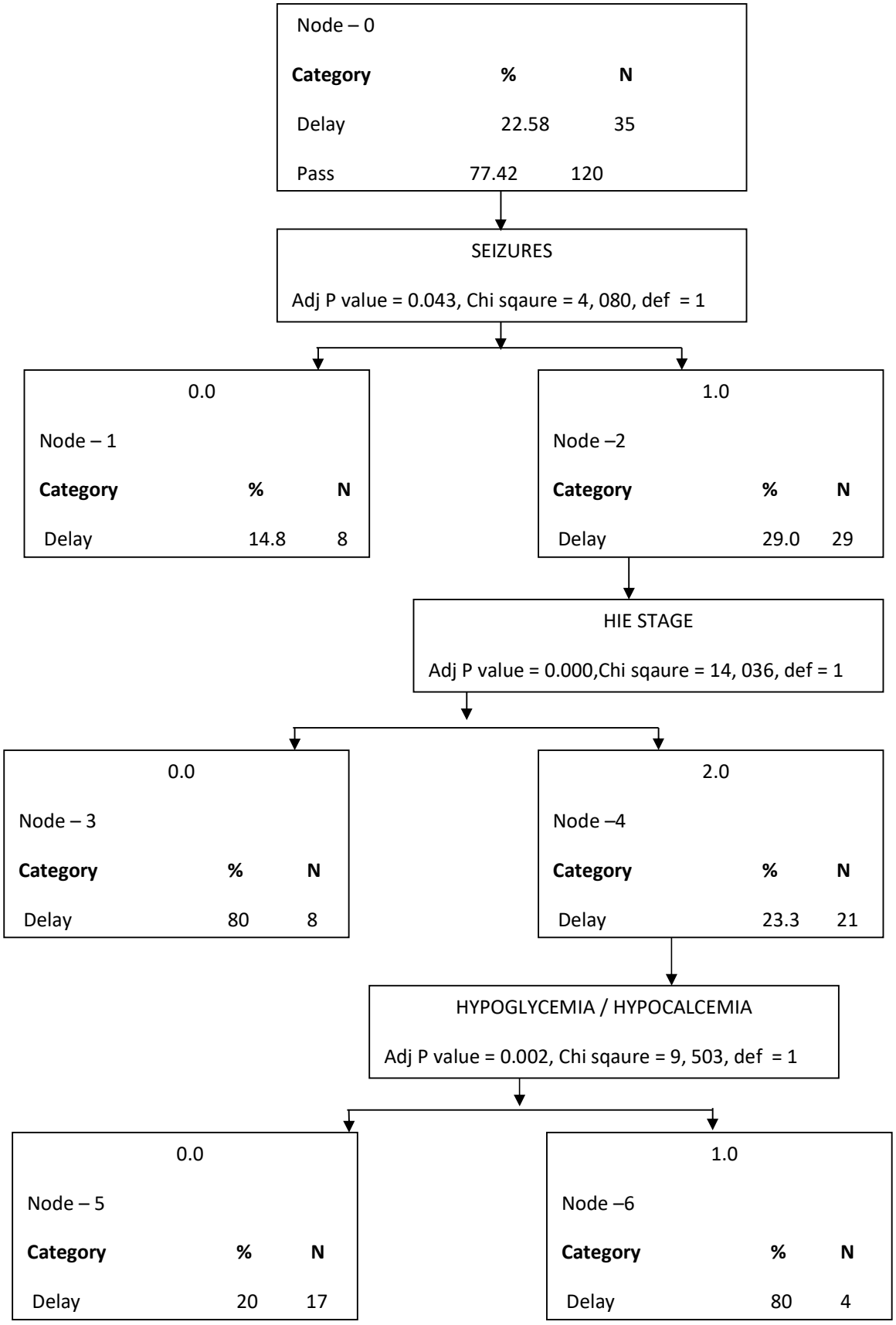
They had no wave formations in VEP. Hence, the incidence of visual loss was 1.9%.

Ongoing morbidities and readmissions during one year follow up- Recurrent lower respiratory tract infections was the most common cause of repeat hospitalisations affecting 23 (14.38%) of the infants. Readmission for blood transfusion was required in 2 preterm infants (anemia of prematurity) and 1 term infant (nutritional anemia).

39 infants were discharged on phenobarbitone as they had seizures during NICU stay and had abnormal neurological examination at discharge. In 24 infants, the drug was stopped since the neurological examination and EEG normalised during follow-up. Rest 15 (9.6%) developed seizure disorder, 3 needing multiple anticonvulsants (2 were follow-up cases of birth asphyxia and 1 had bilirubin encephalopathy).

1 patient with prematurity and intracranial bleed and 1 patient with meningitis needed ventriculo-peritoneal shunt for obstructive hydrocephalus. 12 out of 35 (34.29%) infants with developmental delay and 5 out of 120 (4.17%) normal infants had been readmitted, the difference being statistically significant (p=0.0000005).

Many of the neonates had suffered from multiple problems during NICU stay. An exhaustive CHAID analysis shown below was done with DDST as the dependent variable to identify the most important risk factor for developmental delay.


Node – 0
Category % N
Delay 22.58 35
Pass 77.42 120
SEIZURES
Adj P value = 0.043, Chi sqaure = 4, 080, def = 1
0.0
Node – 1
Category % N
Delay 14.8 8
1.0
Node –2
Category % N
Delay 29.0 29
HIE STAGE
Adj P value = 0.000,Chi sqaure = 14, 036, def = 1
0.0
Node – 3
Category % N
Delay 80 8
2.0
Node –4
Category % N
Delay 23.3 21
HYPOGLYCEMIA / HYPOCALCEMIA
Adj P value = 0.002, Chi sqaure = 9, 503, def = 1
0.0
Node – 5
Category % N
Delay 20 17
1.0
Node –6
Category % N
Delay 80 4

Discussion

The drop-out rate was 9.6% in our study whereas it was 7.7% in the study of Chandhari [11]. Budden [12] described that infants with normal weight and development often have high attrition rate from follow-up programmes. Other cause for drop out was residence in far-off cities and lower parental education.

Assessment of growth at 1 year of age revealed that failure to gain adequate weight, height and length was significantly higher among infants with developmental delay because of the associated feeding problems (oromotor dyssynergia) and increased incidence of intercurrent illness among these infants. Although the incidence of growth failure were higher among preterm and SGA infants, the difference was not statistically significant. Among the preterm infants, 44.44% AGA infants and 42.85% SGA infants had normal growth in our study. In the study of Maribel [13], 42.1% of AGA infants and 18.6% of SGA infants maintained adequate growth. However, Newman [14] described that 63% of SGA infants at 4 months of age had catch-up growth above the third percentile. In our study, 13 (81.25%) out of 16 infants with birth weight<1.5 kg had weight <3rd percentile. Yau [15] described that body weight, length and head circumference of SGA infants were less than those of AGA infants and this pattern of growth and the changes in body composition had been persistently observed in SGA infants of different gestational-age groups, different clinical status and different body proportionality. Differences between postnatal enteral nutrition and placental nutrition, or different energy utilization, in SGA infants were hypothesized to account for this observation.

Our study revealed high prevalence of tone abnormality (37.42%) among NICU graduates, whereas Chaudhari [11] reported as 35.2%.There was no statistically significant difference in the prevalence of transient tone abnormality between term and preterm infants (33.04% versus 48.78%) and between AGA and SGA infants (38.05% versus 35%), the results being similar to the study of Chaudhari [11], where prevalence of transient tone abnormality among term, preterm, AGA and SGA infants were 30.8%, 35.9%, 37.8%, 36.4% respectively. Similarly, no difference in the incidence of tone abnormality was found between term and preterm babies in the study of Baburaj (18% versus 27% at 8 months) [7].

In DASII test, 22% of the infants were confirmed to have developmental delay. The incidence of developmental disability in NICU survivor was described to be 10-20% by Budden [11], 15% by Paul [5], 15.6% by Sukumaran [6] and 46% by Galbriath [10]. There was no statistically significant difference in the incidence of developmental delay among term and preterm infants, and SGA and AGA infants. Among 35 infants with developmental delay, 2 were diagnosed at 2 months of age, 16 were diagnosed between 3-4 months age, 15 were diagnosed at 6 months of age and rest 2 were diagnosed at 9 months of age. The age of diagnosis of developmental delay was related to its severity since out of 18 infants diagnosed below 6 months of age, 12 (66.67%) had DQ<50% at 1 year. Thus, we find that there is a highly consistent correlation between developmental assessments at 6 and 12 months of age, hence it is possible that the long-term outcome is foreseen effectively according to the early developmental evaluation. Luo [8] also found that there is a highly consistent correlation among developmental findings at 6 months, one year, and 6-7 years of age. Godbole [16] also found out easily elicitable items at three and six months of age (inability to achieve social smile at three months and absence of pulling to sit position, transfer of objects and voluntary reach at six months) that predicted adverse neurodevelopmental outcome at one year in high risk babies. This suggests that the results of early developmental assessment are good predictors of long-term outcomes, i.e., the predictive value of the infant developmental scales tests are significant.

In the CHAID analysis, seizures followed by HIE stage and hypoglycaemia were found to be the most important decisive factors of adverse outcome. In this study, only 9.6% of the infants suffered from hypoglycemia, but 46.67% of them had developmental delay. In Luo's [8] study 6.5% had hypoglycemia, but 85.7% of them had mental retardation. Luo [8] described hypoglycaemia, preterm labour, low-birth weight, severe anaemia, polycythemia and hyperbilirubinemia as the risk factors in descending order of importance, associated with lower mental developmental delay. In our study, birth weight was not found to be a significant factor influencing outcome because of smaller number of ELBW infants. In our study, there was no statistically significant difference in the incidence of developmental delay among those babies with single problem versus with those with multiple problems (p=0.4229). However, in Luo's [8] study; there was statistically significant difference in WISC-R scores between children who were exposed to single high-risk factor and children to multiple high-risk factors.

Table-8: Comparison of incidence of developmental delay between our study and other studies:

	Index study	Other studies
HIE-II/III	Moderate delay-10.99% Severe delay-12.08%	6-20% 5-16% (Begum H) [17] 20% (Padayachee) [18]
Hyperbilirubinemia	29%	27% (Mukhopadhay) [19]
Prematurity	14%	8% (Bhakoo) [20], 4% (Kulkarni) [21]
VLBW	18%	15% (Budden) [12], 30% (Modi) [22]
Sepsis	23%	15-30% (Berry) [23]
MAS	14.28%	14% (Beligere) [24]

The mean motor and mental DQ was 87.98±67.79 and 85.28±68.00, compared to 78-80% in the study by Procianoy [25] and 77.2 (motor DQ) and 80.2 (mental DQ) in the study by Mukhopadhay [26], both of them conducting studies on VLBW infants. In the study by Baburaj [7], the mean DQ in low birth weight and normal weight infants were 92.12±8.25 and 93.55±14.23 respectively.

Initial BAER abnormality was found in 38.06% infants in our study and 30% and 16% in the studies by Saunders [27] and Maqbool [28] respectively. Incidence of mild, moderate and severe hearing loss in initial BAER was 15.49%, 18.7%, 3.87% in our study (11%, 10.7%, 3.3% in the study of Hossain [29]). BAER abnormality was significantly higher among infants with neurodevelopmental delay ($p<0.0000001$), which was also described Mukhopadhay [19]. In 77.97% cases, BAER abnormalities reverted to normal (44.4% and 50% cases as described by Mishra [30] and Sharma [31] respectively.

Persistent BAER abnormality was significantly associated with developmental delay ($p=0.001147$). Agarwal [32] also described that 100% patients with persistent BAER abnormality had developmental delay. For the composite high risk cohort, initial CUS had sensitivity, specificity, PPV and NPV of 54.29%, 80%, 44.18%, 85.71% and 52.63%, 91.66%, 83.33%, 70.96% when repeated. Shah [33] described the positive predictive value of USG was 60% and the negative predictive was 76%, when neurodevelopmental outcome of survivors of hypoxic ischemic encephalopathy was considered at 3 months. Sauve [34] reported that the sensitivity of cranial ultrasound examinations as predictors of later neurodevelopmental abnormalities in preterm babies increased from 16% at one and two weeks after birth, to 53% at six weeks and 58% at term-corrected age and the specificity was 99% to 100% in all age groups. Amess [35] described that for early prediction of neurological outcome in preterm babies, sensitivity and specificity of cranial ultrasound was 83% and 87%.

A single EEG study during the acute phase of the disease may suggest a more omnious outcome, but serial EEG better predicted the outcome. Out of 20 infants with initial abnormal EEG, 6 had normal EEG later (all had normal outcome); while 14 infants had persistent abnormality (12 among them had developmental delay). Zeinstra [36] clearly demonstrated that the distinct progression seen in serial EEGs is highly prognostic for a normal outcome and had even more prognostic value than one single severely abnormal EEG. 9.6% of the infants developed seizure disorder in our study compared to 3.9% and 2.2% in the studies by Chaudhri [4] and Sukumaran [6].

ROP was found in 6 (14.63%) preterm infants. Hossain [37] described the incidence of ROP to be 21.3%. 2.44% of our patient needed laser treatment of ROP and the value was 2.6% in the study by Bhakoo [20]. The incidence of visual loss was 1.9% in our study, compared to 0.3% and 1.1% in the studies by Chaudhri [4] and Sukumaran [6]. Readmission rates were significantly higher among infants with developmental delay; lower respiratory tract infection being the most common cause.

Respiratory illnesses comprise one of the major reasons for admission to hospital in the first few years after discharge home in both preterm and term children [38].Understanding the limitations of the available data on neurodevelopmental outcome in newborns in resource-limited settings provides clear direction for research and efforts to improve long-term outcome of high-risk newborns in these settings [2].

This study showed that there was no association between birth weight and gestational age among high risk newborns in respect to presence of disability and developmental delay. Hence, all high risk infants need to be followed up periodically irrespective of their weight and gestation. This is the first study from India which deals with the complete longitudinal follow-up of high risk cohort including anthropometric measurements, neurological examination, developmental assessment and calculating the developmental quotients and electrophysiological tests to identify hearing and visual loss. Thus, the study fulfils all the suggested minimum data set for research purposes by Doyle [38] that could be compared directly with other studies.

Moreover, the study also identifies the prominent risk factors and predictors of long-term outcome, which was one of the aims of the study by Doyle [38]. Such follow-up programme is helpful to identify growth failure and neurodisabilities, paving the way to form the best captive population for early intervention, thereby ensuring that high risk children maximise their potential and become productive and valued members of society. More studies on the outcomes of high risk subjects would facilitate the pooling of data, and the ability to bench-mark outcomes between centres and regions.

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Perission from IRB: Yes

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