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Profile and early prediction of neuromotor outcome of very low birth weight infants

Saugata Chaudhuri[1], Suchandra Mukherjee[2], Tanmoy Kumar Bose[3], Turna Roy Chowdhury[4], Kaushik Jana[5], Debarshi Jana[6]

[1]Assistant Professor, Department of Paediatrics, Dr B.C.Roy Post Graduate Institute of Paediatric Sciences, Kolkata, West Bengal, India, [2]Professor and Head, Department of Neonatology, IPGME&R, Kolkata, West Bengal, India, [3]Master of Physiotherapy, B.M.C.P, IPGME& R, Kolkata, West Bengal, India, [4]Rehabilitation Psychologist, Psychologist, DEIC, Nodal Centre, RBSK IPGME & R, Kolkata, West Bengal, India, [5]Statistician, PhD, Assistant Professor, School of Arts and Sciences, Ahmedabad University, India, [6]Statistician, PhD, Young Scientist, Department of Obstetrics & Gynaecology, IPGME&R, Kolkata, West Bengal, India

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ABSTRACT

Background: Very low birth weight infants are at increased risk of developmental disorder. Early identification is necessary for planning and implementation of early intervention. **Aims and Objective:** To test the association of neurological examination at 40 weeks and 3 months with neuro motor outcome of VLBW infants at 24 months and to identify the perinatal and neonatal risk factors for atypical neurological outcome. **Materials and Methods:** It is a prospective cohort study. Consecutive 120 VLBW infants were enrolled in a single centre level III neonatal unit of a teaching hospital. Neuro motor assessment was done by Dubowitz neurological examination at 40 weeks and by Hammersmith infant neurological examination (HINE) at 3 months and 12 months at neurodevelopmental clinic. Motor assessment were performed by Alberta Infant Motor Scale (AIMS) at 6 and 12 months and by Bayley Scale of Infant & Toddler scale, (BSID) 3rd edition at 6,12 and 24 months respectively. All assessment ages were corrected for prematurity. **Results:** At 12 months 4.5% infants developed abnormal tone and 5.6% had motor delay. Four infants developed cerebral palsy at 24 months. Shock in neonatal period had significant association with suboptimal motor outcome at 12 months. Suboptimal HINE score at 12 months was rightly predicted at 3 months by HINE. **Conclusion:** Early anticipation and early identification of abnormal neuro motor outcome of VLBW infants can be used as simple and cost-effective measures for preventing long term neuro motor morbidity at resource limited countries.

Key words: Neuromotor Outcome; Very Low birth Weight Infants; Shock

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INTRODUCTION

Worldwide 11.1% of total deliveries occur less than 37 weeks of gestational age. In lower- and middle-income countries 12% babies are born preterm compared to 9% in high income group countries. Prematurity is the leading cause of neonatal death and second leading cause of death in children less than 5 years. In addition to its significant contribution to mortality the complications associated with preterm birth may persist throughout life in some survivors.[1]

Very low birth weight infants (VLBW, <1500gram) remain vulnerable subgroup among preterm infants, having enhanced risk of developmental impairment, cerebral palsy, visual disorder, motor coordination disorder and difficulty in learning, behaviour and social interaction. The frequency and severity of adverse outcome seems to be related to birth weight, gestational age and structural brain changes.[2]

A systematic review in 2012 on long-term neurodevelopmental outcomes after intrauterine and neonatal insults assessed 6558 preterm infants from 47 studies, of them 31% had long term sequelae, 60% infants suffered from cognitive, general developmental delay, learning difficulties and 27% preterm infants ended up with cerebral palsy.[3]

Address for Correspondence:
Dr. Saugata Chaudhuri, Assistant Professor, Department of Paediatrics, Dr B.C.Roy Post Graduate Institute of Paediatric Sciences, Kolkata, West Bengal, India. **Mobile:** +91-9477036563. **E-mail:** saugata.dr@gmail.com

In India, very-low-birth-weight (VLBW) babies (birth weight <1500 g) constitute one-third (29.7%) of the neonatal deaths.[4]

In the present study, we have reviewed some perinatal factors and neurological examination in early infancy as predictors of abnormal neuro motor outcome of VLBW infants at 24 months at neuro developmental clinic of a teaching hospital in eastern India.

AIMS AND OBJECTIVES

1. Prognostic value of neurologic optimal score at 40 weeks and 3 months of corrected gestational age in predicting neurological outcome with neuro motor at 12 months and 24 months of corrected gestational age.
2. To identify the perinatal and neonatal risk factors for atypical neurological outcome of the very low birth weight babies.

MATERIALS AND METHODS

This is a prospective observational cohort study involving VLBW infants admitted in a level III NICU during the period of May to September 2016. All the infants discharged from NICU who were less than 1500 gram at birth were eligible for the study. The infants with chromosomal anomaly, major malformations and those who failed to attend for complete follow up were excluded. Informed consent was obtained from the parents of VLBW infants eligible for the study. The study was pre-approved by the institutional ethics committee.

The gestational age was determined by either the first trimester ultrasound or expected date of confinement and new Ballard Scoring. Birth weight was taken using electronic weighing within first 12 hours of delivery. The antenatal and perinatal data were recorded. The clinical management of babies were done as per standard protocol. Dubowitz neurological examination was done at 40 weeks at follow up clinic or in NICU as applicable. Hammersmith Infant Neurological Examination (HINE) was done at 3 months and 12 months of corrected age. At 6 and 12 months motor assessment was performed by Alberta Infant Motor Scale (AIMS) and motor subscale of Bayley's Scale of Infant and toddler development 3rd edition (BSIDIII). Motor assessment by BSIDIII was repeated at 24 months of corrected age. All the assessments were done by one to two domain specific trained and certified professional Physiotherapist and Psychologist. The assessors were unaware of case records and follow up.

Instrument and procedures

Dubowitz neurological assessment of the preterm and full-term infant: The examination includes assessment of behavioral states, tone, and primitive reflexes and also motility and some aspects of behavior. The development of optimal score allow quantification of the deviant scores and use in different settings. The examination has been validated in full term and preterm infants.

Hammersmith Infant Neurological Examination: This is a simple and scorable method for assessing infants between 2 and 24 months of age, including items for cranial nerve, posture, movements, tone and reflexes. It can be scored with the use of an optimality score, defining as optimal all the scores found in at least 90% of the normal population. The overall score ranges from a minimum of 0 to a maximum of 78.

Alberta Infant Motor Scale (AIMS): AIMS is a norm referenced developmental assessment that examines gross motor development in infants aged 0 to 18 months. The assessment emphasizes the attainment of gross motor skills, postural alignment, and weight bearing of the body and antigravity movements of the limbs in prone, supine, sitting and standing positions. Each infant's total raw score was converted to a standardized score (Z) according to the Canadian norm. Borderline and significant delays were defined as a score <-1 and <-2 respectively.

Bayley Scale of Infant and Toddler Development 3rd edition: This scale is widely used to measure the current level of functioning of typically developing and high-risk infants and toddlers and young children aged between 1 and 42 months. It provides coverage of 5 domains. Cognitive, language, motor, adaptive and social emotional development.

Data analysis

Linear correlation among two variables was calculated using Pearson correlation and then fit linear regression model to predict the response variables for a given covariate. Chi-square test of association was used to test significance of association between two categorical variables. Statistical software R was used here (Tables 1-3).

Data had been summarised as mean and standard deviation for numerical variables and count and percentages for categorical variables and analysed by SPSS software version 24.0. Unpaired proportions were compared by Chi-square test or Fisher's exact test as appropriate. Odds ratio was calculated for relative risk with 95% confidence interval value ≤0.05 was considered statistically significant (Table 4).

Table 1: Neuromotor outcome at 6 months and 12 months

Motor Development	Abnormal Tone Pattern	AIMS Score		
		Delay (<10th Percentile)	At Risk (10-25thPercentile)	Normal (>25th percentile)
6 months	7 (8.86%)	11 (13.92%)	26 (32.91%)	35 (44.30%)
12 months	4 (4.49%)	5 (5.62%)	4 (4.49%)	76 (85.39%)

Alberta infant motor development scale at 6 month and 1 year of corrected age {Abnormal tone (<10th percentile), At risk (10th-25th percentile), Normal (>25th percentile) (Table 1).

Table 2: Neurological score (HINE) at 40 weeks, 3 months and 12 months

Time of follow up	Optimal	Suboptimal	Mean	95% CI
40 weeks	92 (89.3%)	11 (10.7%)		
3 months	79 (83.2%)	16 (16.8%)	62.63	60.77-64.50
12 months	84 (95.5%)	4 (4.5%)	77.15	77.28-78.03

Table 3: Developmental outcome at 12 and 24 months

	Subscale	Composite Score(<70)	Composite Score (70-85)	Composite Score (>85)	Mean Score	95% CI
12 months	Motor	2 (2.25%)	12 (13.48%)	75 (84.27%)	89.29	88.16-90.40
Bayley III	Cognition	2 (2.25%)	24 (26.97%)	63 ((70.79%)	89.18	87.86-90.50
24 months	Motor	1 (1.16%)	3 (4.7%)	60 (93.8%)	92.82	91.32-94.31
Bayley III	Cognition	3 (4.7%)	5 (7.8%)	56 (87.5%)	90.78	88.93-92.64

Table 4: Predictors of neuromotor outcome

Corrected age	40 weeks			3 months			12 months		
	St.coeff β	P value	95%CI	St.coeff β	P value	95%CI	St.coeff β	P value	95%CI
Gestational age	.086	0.42	-.015,-.035	-.047	.687	-.038,.025	-.035	.781	-.022,.017
Birth weight	-.021	0.84	-.000.-.000	-.228	.044	-.001,.000	-.119	.322	.000,.000
Delivery room resuscitation	.126	0.22	-.019,-.079	-.038	.731	-.073,.051	-.152	.198	-.064,.014
Perinatal Asphyxia	.068	0.48	-.102,-.212	.147	.156	-.057,.350	.188	.087	-.016,.230
Shock	.321	0.001	.238,.908	.216	.028	.052,.872	.235	.027	.031,.508
IVH	.255	0.009	.201,1.407	.241	.020	.142,1.622			
Corrected age	**AIMS 12 months**			**BSID III motor 12 months**			**BSID III Cognition 12 months**		
	St.coeff β	P value	95%CI	St.coeff β	P value	95%CI	St.coeff β	P value	95%CI
Gestational age	-.078	.532	-.093,.048	-.032	.805	-.047,.037	-.213	.108	-.090,.009
Birth weight	.107	.365	.000,.001	0.223	.072	.000,.001	.189	.129	.000,.001
Delivery room resuscitation	.111	.334	-.071,.207	-.017	.889	-.089,.077	-.073	.550	-.127,.068
Perinatal Asphyxia	-.347	.001	-1.170,.291	-.043	.698	-.314,.211	-.099	.375	-.446,.170
Shock	-.135	.185	-1.431,.280	-.186	.083	-.962,.061	-.107	.319	-.902,.297

RESULT

Overall study was conducted in the following way (Figure 1).

Profiles of the babies and their relation with outcome is summarised in the Table 5.

Four infants (4.54%) were detected as having increased tone at 12 months; at 24 months, two were clinically classified as spastic diplegia, and one each as spastic quadriparesis and spastic hemiparesis respectively. One infant had expired before 12 months of follow up and showed increased tone in all the 4 limbs at 6 months follow up. All of them had suboptimal HINE scores at 3 months. The prediction of neurological impairment at 24 months and its severity was evident as early as early as 3 months by low HINE Score. (Table 2) While using AIMS at 12 months, nine infants (10%) scored subnormal (<25th centile) including five who scored less than 10th centile and considered as motor delay.

Alberta infant motor development scale at 6 month and 1 year of corrected age {Abnormal tone (<10th percentile), At risk (10th-25th percentile), Normal (>25th percentile) (Table 1).

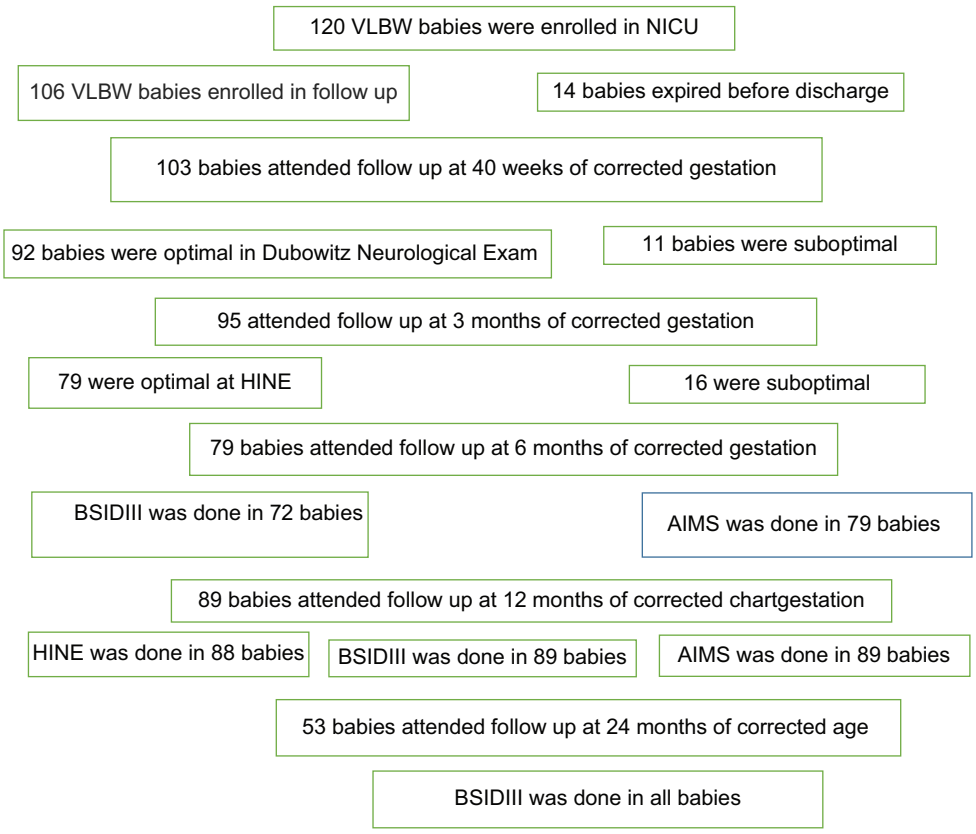

Figure 1: Study Flow Chart

At the end of 24 months of corrected gestation (1.6%) baby had motor delay, 3 babies (4.7%) had cognition delay and 5 babies (7.8%) had language delay. (Table 3)

In univariate analysis IVH was significantly associated with neurological examination at 40weeks (p value=.009), and at 3-month HINE Score (p value =.020). Perinatal asphyxia was observed as significant risk predictor of gross motor assessment (p=.001) by AIMS at 12 months. But in multivariate analysis only shock was found to have significant risk association with neurological examination at 40 weeks (p value=.001), and the association with low HINE score was found to persist at 3 months (p value=.028) and 12 months. (p value=-.027). Bayley scale composite score of motor and cognition did not show any significant correlation with shock, IVH, and perinatal asphyxia (Table 4).

Correlation of neurological examination (HINE) scores

The use of Chi-square test of independence of neurological examination at 40 weeks with 3months and 12 months HINE score both have p value <0.001.

The correlation between scores of HINE at 3 months and 12 months is 0.73. The test of linear correlation between these two variables produces p-value.0004 (Figure 2).

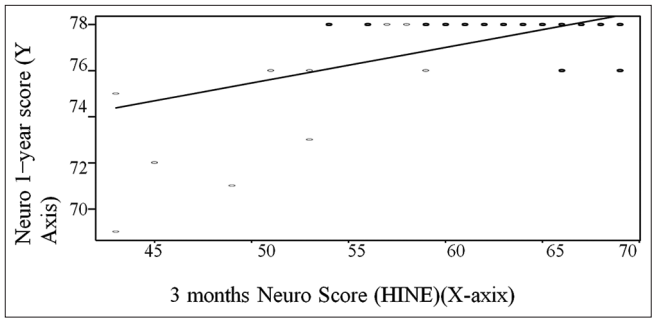

Figure 2: Correlation between HINE 3- and 12-months corrected age

Hence, the HINE at 40 weeks and at 3 months would be a good predictor of Motor Subscale of BSIDIII at 12 months. This actually helps to initiate and planning of early intervention therapy.

Correlation among neurological examination score (HINE) and bayley's motor score

Correlation between Motor Subscale 12 months and Neuro score 3 months and 12 month was 0.52 and 0.63 respectively (Figure 3) and between Motor subscale 12 months and Neuro 12 months 0.75. Test of significance in all the cases <0.0001 (Highly Significant) (Figure 4).

Table 5: Overall characteristics of VLBW babies and their association with outcome

Characteristics	N=120	Correlation with Mortality p-value	Correlation with HINE Score at 12 months p-value	Correlation with AIMS Score at 12 months p-value	Correlation with BSIDIII Motor Subscale at 12 months p-value
Birth weight (500gm to 1500gm)	Mean 1169.975g (SD 244.3135)	0.0003	0.1540	0.1888	0.0741
Gestation (25 weeks to 40 weeks)	Mean 32.2 weeks (SD2.85)	0.0273	0.0001	0.0025	0.1859
Antenatal steroid	Nil (40.8%), Partial (33.3%), Full Course (25.8%)	0.2650	0.6911	0.9716	0.5153
Pregnancy induced hypertension. Other antenatal risk factors are negligible	32 i.e (26.6%)	0.12154	0.26622	0.5876	0.7321
Small for date	65 i.e (54%)	0.16782	0.4524	0.1227	0.3099
Mode of delivery	NVD (51.6%), LSCS (48.3%)				
Place of delivery	Inborn (75.8%), Outborn (24.1%)				
Delivery room resuscitation	Routine care (.083%), Initial steps (51.6%), Bag and Mask (10%), Bag &Tube (15%),Unknown (22.5%)	<0.0001	0.2019	0.5298	0.6877
Perinatal asphyxia	No (75%), Yes (25%)	<0.0001	0.0563	0.0052	0.3978
Shock	No (86.7%), Yes (13.3%)	<0.0001	0.0149	0.1029	0.0010
Hypoglycaemia	No (89.2%), Yes (10.8%)	0.165243	1.173	0.0184	0.0813
IVH	No (97.5%), (2.5%)	0.00265	0.025	0.015	0.045
BPD	No (74.1),Yes (25.8%)	0.29359	0.2961	0.6964	0.6998
Anaemia requiring blood transfusion	No ((91%), Yes (9%)	0.2956	0.5174	0.6740	0.0704
PDA	No (98.3%), Yes (9.7%)	0.1689	0.3183	0.1326	0.8818
Culture positive sepsis	No (98.3%), Yes (9.7%)	0.1532	0.2572	0.3747	0.1220

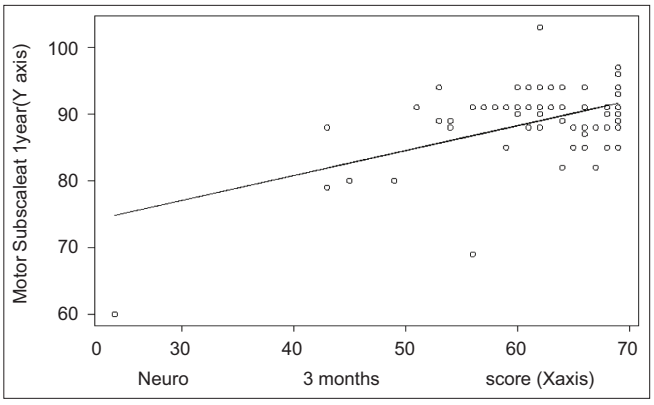

Figure 3: Correlation between BSIDIII Motor subscale 12 months and Neuro 3 months

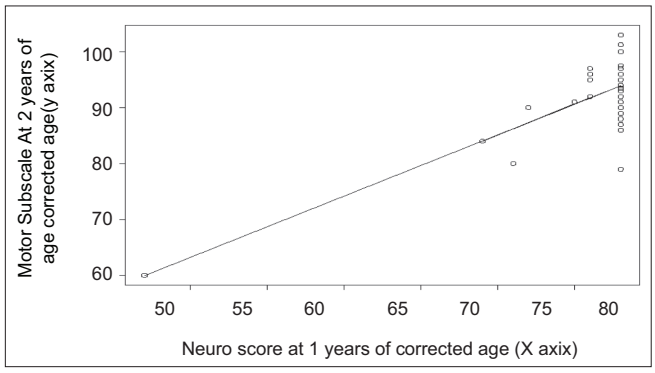

Figure 4: Correlation between BSID III Subscale 24 months and Neuro 12 months

DISCUSSION

The VLBW infants contribute 3.4% of total preterm population in India.[4] In the context of 3.5 million preterm deliveries per year the total number of surviving VLBW infants is of considerable magnitude. The improved survival of VLBW infants in the level II neonatal unit of the district hospitals has increased the potential risk of adverse

neuro -developmental outcome among preterm survivors. The long-term follow-up data from resource limited settings are particularly important due to the prevalence of high preterm birth rate, wide variation in neonatal care and very limited accesses to high risk follow up.

The current study reviewed two years neuro motor follow up of VLBW infants and early prediction of neuromotor delay by testing the association of some perinatal factors and neurological examination at initial few weeks of life.

In our study neonatal shock had significant and consistent association with neurological outcome at term equivalent age, 3 months and 12 months corrected age. The correlation was demonstrated as suboptimal HINE score and delay in gross motor development. In a study on hypotension in preterm neonates and neurodevelopmental outcome reported that low regional cerebral oxygenation (rSO_2 50% for 10% of time) determined by using near infrared spectroscopy was associated with lower neurodevelopmental outcome (median score 99vs 104 p=0.02) assessed by Griffith Mental Developmental Scale or Bayley Scale at 18 months. The effect of low organ perfusion in perinatal period may have affected the normal growth and maturation of corticospinal system that has manifested later by abnormal pattern of tone. [5] In our study the association was not reflected in Bayley score at 12 months. Shock was diagnosed clinically; low cerebral perfusion and duration and severity of hypotension may have been better marker for suboptimal neurological outcome. Jane E Brazye et al., reported significant correlation of poor neurodevelopmental outcome in all the subscales at 24 months with the duration of hypotension and perinatal asphyxia.[5]

In South Africa, neuro developmental outcome was studied in preterm infants with mean birth weight and mean gestational age of 1182 gram (SD: 197.78) and 30.81 weeks (SD: 2.67). The BSIDIII was done at median age of 16.48 months. Out of 106 babies, nine (8.5%) were <70 in cognitive subscale, 10 babies (9.4%) had composite score <70 in language and eight babies (7.6%) scored <70 in motor subscale. One third infants were at risk (score 70-85) in each subscale. Cerebral palsy was diagnosed in 4 (3.7%) babies.[6]

In our study population, the mean birth weight (Range 500-1500gm) and mean gestational age were 1169.975 grams (SD: 244.3135) and 32.2 weeks (SD: 2.85) respectively. Four infants developed Cerebral Palsy at 2 years. In contrary to the South African study, one infant was < 70 in motor and three infants were <70 in cognitive score. The "at risk" (score 70-85) were found in three and five infants in motor and cognition respectively. Regarding the motor development at 12 months by AIMS four infants had delay and five were under at-risk group.

The lesser number of infants with suboptimal score may be due to presence of more IUGR infants with higher gestational age in study cohort and relatively lesser number of infants assessed at 24 months due to higher drop outs. Another reason may be the early initiation of intervention immediately following the assessment.

Around five percent infants who were under at-risk category of motor and cognitive development may need special attention as they can have difficulties at school or in adult life.

The role of neurological examination in high-risk follow-up clinic along with developmental assessment has been found to be an effective measure for early identification of abnormal tone pattern. In the present study all four infants with Cerebral Palsy had suboptimal HINE score at 3 and 12 months of corrected age. So, HINE score at 3 months could successfully predict motor impairment at 12 to 24 months. The suboptimal neurological examination at 40 weeks had also shown good correlation with abnormal motor outcome. Further studies on HINE in the settings of district hospitals will be more informative for early prediction of abnormal outcome. Romeo et al assessed 1541 infants discharged from NICU using HINE at 3,6,9 and 12 and 24 months. Global score <56 at 3 months showed 90% sensitivity and specificity for the development of CP. Score<40 infants developed severe CP.[7,8]

I.C.van Hasster et al., assessed total 800 infants between 1 -18 months by using AIMS and corrected for degree of prematurity. Preterm infants scored significantly lower age level even with full correction for degree of prematurity.[9] In our study cohort at 12 months of corrected age 10.1% had abnormal gross motor development. Out of them 4.49% had abnormal tone, while assessed by AIMS, 5.6% had delay in gross motor development (<10^{th} percentile) and 4.5% were at risk (10-25^{th} Percentile).

Limitations of the study

Four infants with abnormal tone were not assessed by Bayley scale due to severity of lesion. Finally, the cognitive development should have been assessed at relatively older age to find out the association.

Though there was good compliance up to 12 months of follow up, at 24 months of follow up lost to follow up was 50%.

CONCLUSION

Risk of neurodevelopmental sequels can be identified as early as 40 weeks (by Dubowitz neuro score) 3 months

by HINE, 6 months of corrected gestation by AIMS and BSIDIII.

Shock, Perinatal asphyxia, Delivery Room Resuscitation, IVH, Birth weight, gestational age has significant association with mortality in the neonatal period. After Multivariate linear regression analysis only shock and perinatal asphyxia got significant correlation with poor neurodevelopmental outcome at 24 months of corrected age.

List of abbreviations

VLBW: Very Low Birth weight
NICU-Neonatal Intensive Care Unit
BSID-III- Bayley Scales of Infant and Toddler Development (version III)
HINE-Hammersmith Infant Neurological Examination
AIMS-Alberta Infant Motor Scale
IVH-Intra Ventricular Haemorrhage
PIH-Pregnancy Induced Hypertension
PDA-Patent Ductus Arteriosus
BPD-Broncho Pulmonary Dysplasia

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Author's Contribution:
SC-Concept and design of the Study, Collected the antenatal histories, did the whole study prospectively, reviewed literature and manuscript preparation, interpreted the results. **SM-** Guide of SC in preparation of concept and design of study and also manuscript preparation; **TKB-**Assessed the babies by Alberta's Scale and provided early stimulation; **TRC-** Assessed the babies by BSID Scale; **KJ-**Statistical analysis of outcome by various neuromotor scales and their correlation by R software; **DJ-**Statistical analysis among the various profiles of the study populations and their influences in neuromotor outcome and their comparison by SPSS software version 24.0.

Work attributed to:
IPGME& R, SSKM Hospital, Kolkata -700020, West Bengal, India.

Orcid ID:
Dr Saugata Chaudhuri- https://orcid.org/0000-0003-2565-9250
Dr Suchandra Mukherjee- https://orcid.org/0000-0002-7906-3738
Mr Tanmay Kumar Bose- https://orcid.org/0000-0002-8981-921X
Mrs Turna Roy Chowdhury- https://orcid.org/0000-0002-4714-7742
Mr Kaushik Jana- https://orcid.org/0000-0003-4832-1375
Dr Debarshi Jana- https://orcid.org/0000-0002-6399-1337

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