Original Article

Neurodevelopmental Status of Moderate to Late Preterm Infants at 6 Months Corrected Age

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Abstract

Background: *Moderate Preterm (MP) and Late Preterm (LP) infants together comprise more than 80% of all prematurely born infants. Since last decade, there has been growing concern about Neurodevelopmental Abnormality (NDA) in these infants. This study was aimed to assess neurodevelopmental status of moderate to late preterm born neonates and to determine factors associated with adverse neurodevelopmental outcome in a tertiary hospital in Bangladesh.*

Materials and methods: *In this prospective observational study 215 preterm (32 to <37 completed weeks gestation at birth) infants (107 MP and 108 LP) were enrolled from the Special Care Neonatal Unit (SCANU) Chittagong Medical College Hospital from June 2018 to May 2019. Neurodevelopmental assessment was done by Rapid Neurodevelopmental Assessment (RNDA) at 1, 3 and 6 months of Corrected Age (CA).*

Results: *Of the 215 enrolled children, 63 (29.3%) attended all the 3 follow-up, 123 (57.2%) had incomplete follow-up or lost and 29 (13.5%) died. At final follow-up out of 63 infants 43 (68.3%) had no abnormality in all 8 domains of RNDA. Seven infants (11.1%) had abnormality in one domain and 13 (20.6%) had abnormality in more than one domain. Gross motor abnormality was most common abnormality (28.6%), followed by cognition (14.3%), vision (12.7%) and behavior (12.7%). Small for gestational age and lower birth weight were found to be independent predictive factors for NDA in moderate to late preterm infants.*

Conclusion: *Study has shown that NDA persist till 6 months of CA in moderate to late preterm infants. It is important to closely monitor the neurodevelopmental status and provide early intervention in referred cases.*

Key words: Neurodevelopmental assessment; Neurodevelopmental abnormality; Preterm.

INTRODUCTION

Preterm birth is a live birth before 37 completed weeks of gestation, with subcategories of extremely preterm (<28 weeks), very preterm (<32 weeks) and moderate to late preterm (32-37 weeks)[1]. Approximately 15 million babies are born preterm annually worldwide, indicating a global preterm birth rate of about 11%. The burden of preterm birth is particularly high in Low- and Middle-Income Countries (LMICs) especially those in Southeast Asia and sub-Saharan Africa[2]. Bangladesh is one of the 10 countries with the greatest number of preterm births in the world[3].

Advances in perinatal care and establishment of improved neonatal services have increased the survival rates of preterm infants all over the world including Bangladesh. However, the gains in survival have concomitantly raised the question of long-term outcomes for these infants. Premature infants are at high risk of injury,

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particularly to the immature brain, which may be critical for their development with possible adverse effects lasting into adulthood[4]. Consequently, neurodevelopmental impairments, including cognitive, language, motor and neurosensory impairments as well as behavioural disorders, occur more frequently in this vulnerable group[5]. Despite accumulating evidence in the literature, data from Bangladesh and other LMICs are limited due to a lack of follow-up programs for high-risk infants in general and for preterm infants in particular[6].

Information on neurological outcomes is crucial for both policy making and future planning for healthcare, social and educational services and for counseling caregivers about expected outcomes following preterm birth[7]. Therefore, we examined neurodevelopmental outcomes in a hospital-based cohort of moderate to late preterm infants discharged from a Neonatal Intensive Care Unit (NICU) using the Rapid Neurodevelopmental Assessment (RNDA) tool at 1, 3 and 6-months Corrected Age (CA)[8]. We also estimated the prevalence of abnormal neurological examination and attempted to assess risk factors for poor outcome.

MATERIALS AND METHODS

This prospective observational study was conducted at the SCANU at Chittagong Medical College Hospital, in Chattogram city, one of the largest tertiary centers responsible for critical care of newborns in southeastern Bangladesh. The SCANU has 30 beds and 1200 admissions annually, of which the vast majority are transferred from healthcare facilities providing obstetric care and the others are admitted from home via the emergency room. The study was approved by the Ethical Review Committee of Chittagong Medical College and written parental consent was obtained for each study participant.

All preterm newborns of 32 to <37 completed weeks gestation admitted into SCANU from June 2018 to May 2019 were eligible for enrolment except those with perinatal asphyxia, meningitis, culture positive sepsis, hyperbilirubinemia > 20mg/dl or requirement of exchange transfusion, major morbidities such as intraventricular hemorrhage, major congenital malformation, congenital hypothyroidism.

Demographic data were obtained at enrollment including living place, maternal factors (Age, educational level and occupation) and monthly family income.Antenatal, perinatal, neonatal and relevant postnatal information including Comorbid maternal condition during pregnancy, Neonatal condition, Parity, Gestational age, Antenatal care, Mode of delivery, Place of delivery, Birth weight, Gestational weight, Length of stay in hospital and Multiple pregnancy were recorded.

At the time of discharge parents or guardians were advised to come for follow-up at one, three and six months of CA[9]. Periodic reminders was sent to parents through telephonic calls to improve follow-up. Neurodevelopmental assessment was done at each follow-up by RNDA tool. RNDA tool previously was shown to have acceptable reliability and validity in Bangladeshi children[8]. All tests were conducted by the principal investigator at hospital in a quiet room, and the results were recorded on standard assessment forms. Standard treatment was provided to the babies and appropriately intervened in the follow-up whenever required.

Data were analyzed with the help of computer software package (SPSS, version 23). Summary statistics are presented as mean (SD) or median (IQR) for continuous variables, and in absolute counts and percentages for categorical variables. To compare the continuous data between two group Independent sample t test or Mann-Whitney U test and among three groups ANOVA test or Kruskal Wallis Test was as appropriate. Chi-square test was used for group comparisons of categorical variables. Risk factors for adverse neurodevelopmental outcome were analyzed by logistic regression analysis. Results were shown by ORs with 95% CIs. Statistical significance was defined as P≤0.05.

RESULTS

In the study 215 moderate to late preterm infants were enrolled. During the follow-up period, 13.5% (29 of 215) infants died, 37.7% (81 of 215) were lost to follow-up, and 48.8% (105 of 215) survived and came for at least one follow up. Of the infants who came for follow-up, 40 came only for 1 assessment, 2 came for 2 assessment and 63 came for all the three assessment. Two infants died after 1st follow up, 2 died after 2nd follow up.

Sociodemographic, antenatal, perinatal, neonatal and other variables were compared across those who completed Follow-Up (F/U) till 6 months, those who didn't complete F/U or were lost to follow-up, and those who died (Table I). Significant differences were found in mothers' vocational status (Higher proportion of mother work outside among those who completed follow-up) family income (Which was lowest among those who died), residential location (Higher proportion lived in rural area among those who died) gestational age (Was lowest among those who died), birth weight (Was lowest among those who died) RDS (higher proportion among those who died), length of hospital stay (Which was higher among those who completed follow-up) .

Table I : Characteristics of preterm infants according to their study retention

Characteristics	Complete F/U (n=63)	Incomplete F/U or Lost (n=123)	Died (n=29)	p value
Maternal age (Years)	25 (23-27)	23 (21-26)	23 (20-27)	0.085‡
Maternal education[a]	10 (9-14)	10 (9-12)	9 (8-12)	0.060‡
Mother work outside	10 (15.9)	5 (4.1)	0 (0)	0.005*
MFI [b] (1000 BDT)	30 (15-50)	20 (15-30)	15 (9-27)	<0.001‡

Resides in Rural area	34 (54.0)	86 (69.9)	24 (82.8)	0.015*
Maternal HTN/PET/Eclampsia	9 (14.3)	11 (8.9)	3 (10.3)	0.518*
Parity	2 (1-2)	2 (1-3)	1 (1-3)	0.361‡
Had ANC	62 (98.4)	123 (100.0)	26 (89.6)	0.115*
Home delivery	4 (6.3)	6 (4.9)	3 (10.3)	0.510*
Delivered by CS	23 (36.5)	54 (43.9)	12 (41.4)	0.605*
Male infant	38 (60.3)	70 (56.9)	21 (72.4)	0.308*
Gestational age (Weeks)	33 (33-35)	34 (32-35)	32 (32-34)	0.038‡
Birth weight (kg)	1.73±0.36	1.67±0.29	1.47±0.18	<0.001†
SGA	23 (36.5)	49 (39.8)	15 (51.7)	0.375*
Neonatal sepsis	33 (52.4)	52 (42.3)	13 (44.8)	0.423*
RDS	16 (25.4)	12 (9.8)	14 (48.3)	0.011*
LOS	14 (9-20)	10 (7-14)	12 (9-16)	0.008‡

Data are expressed either as frequency (Percentage), Median (IQR: Interquartile Range) or Mean (±SD) as appropriate, p values were derived from *Chi-square test or †from ANOVA test or ‡: Kruskal Wallis Test as appropriate, [a]: Years of schooling, [b]: Monthly family income, FU: Follow-Up, ANC: Antenatal Care, CS: Cesarean Section, SGA: Small for Gestational Age, RDS: Respiratory Distress Syndrome, LOS: Length of Stay in hospital.

Out of 215 included infants only 63 had complete follow-up at 6 months of CA. Among them at 1 month of CA number of infants with abnormal domain were gross motor-18 (28.6%) fine motor-1(1.6%) vision-10 (15.9%) hearing-5 (7.9%) speech-4 (6.3%) cognition-15 (23.8%) and behavior- 12 (19%). At 6 months of CA number of infants with abnormal domain were gross motor-18 (28.6%) fine motor-3(4.8%) vision-8 (12.7%), hearing-3(4.8%) speech-5 (7.9%) cognition-9 (14.3%) and behavior- 8 (12.7%).

Table II : Frequency distribution of disability grade in different domains of RNDA at 1, 3 and 6 month of corrected age (CA) in moderate to late preterm infants

Domain	Status	Disability grade	Age at assessment		
			At 1 month CA	At 3 month CA	At 6 month CA
Gross motor	Normal		45 (71.4)	41 (65.1)	45 (71.4)
		Mild	9 (14.3)	6 (9.5)	4 (6.3)
	Abnormal	Moderate	5 (7.9)	8 (12.7)	7 (11.1)
		Severe	4 (6.3)	8 (12.7)	7 (11.1)
Fine motor	Normal		62 (98.4)	61 (96.8)	60 (95.2)
		Mild	1 (1.6)	2 (3.2)	2 (3.2)
	Abnormal	Moderate	0 (0)	0 (0)	0 (0)
		Severe	0 (0)	0 (0)	1 (1.6)
Vision	Normal		53 (84.1)	54 (85.7)	55 (87.3)
		Mild	1 (1.6)	3 (4.8)	2 (3.2)
	Abnormal	Moderate	6 (9.5)	2 (3.2)	1 (1.6)
		Severe	3 (4.8)	4 (6.3)	5 (7.9)
Hearing	Normal		58 (92.1)	58 (92.1)	60 (95.2)
		Mild	3 (4.8)	1 (1.6)	0 (0)
	Abnormal	Moderate	1 (1.6)	4 (6.3)	2 (3.2)
		Severe	1 (1.6)	0 (0)	1 (1.6)
Speech	Normal		59 (93.7)	58 (92.1)	58 (92.1)
	Abnormal	Mild	4 (6.3)	3 (4.8)	1 (1.6)
		Moderate	0 (0)	2 (3.2)	3 (4.8)
		Severe	0 (0)	0 (0)	1 (1.6)
Cognition	Normal		48 (76.2)	50 (79.4)	54 (85.7)
		Mild	6 (9.5)	6 (9.5)	2 (3.2)
	Abnormal	Moderate	7 (11.1)	3 (4.8)	1 (1.6)
		Severe	2 (3.2)	4 (6.3)	6 (9.5)
Behavior	Normal		51 (81.0)	53 (84.1)	55 (87.3)
		Mild	6 (9.5)	4 (6.3)	2 (3.2)
	Abnormal	Moderate	4 (6.3)	2 (3.2)	1 (1.6)
		Severe	2 (3.2)	4 (6.3)	5 (7.9)
Seizure	Normal		63 (100.0)	63 (100.0)	63 (100.0)

Data were expressed as frequency (Percentage).

At final follow-up (6 months of CA) out of 63 infants 43 (68.3%) had no abnormality in all 8 domains of RNDA tool. Seven infants (11.1%) had abnormality in one domain and 13 (20.6%) had abnormality in more than one domain (Figure 1).
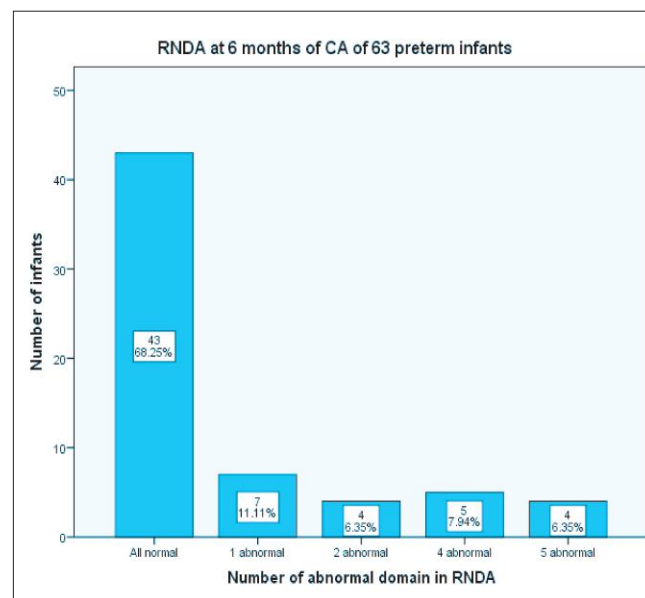

Figure 1: Clustering of abnormal domain in RNDA at 6 months of CA (n=63)

Association of developmental disability with socio-demographic, antenatal, perinatal, neonatal and other relevant characteristics are presented in Table III. Mode of delivery, birth weight, SGA and not exclusively breast fed had significant association with developmental disability at 6 months CA. Significantly higher number of infants with developmental disability had history of SGA (p= 0.001), less birth weight (p=0.016) and not exclusively breast fed (p= 0.049) compared to the infant with normal development. And significantly higher number of infants with normal development was delivery by CS (p= 0.016).

Table III : Association between socio-demographic, antenatal, perinatal, neonatal and other characteristics with developmental disability at 6 months corrected age (CA) of the 63 infants

Characteristics(unit)	RNDA assessment at 6 month CA		p value
	Normal (n=43)	Abnormal (n=20)	
Maternal age (Years)	24 (23-27)	25 (22-27)	0.783‡
Maternal education[a]	10 (8-14)	12 (9-14)	0.381‡
Mother work outside	6 (14.0%)	4 (20.0%)	0.541*
MFI [b] (1000 BDT)	25 (15-50)	30 (20-50)	0.328‡
Resides in rural area	24 (55.8%)	10 (50.0%)	0.633*
Maternal HTN/PET/Eclampsia	9 (20.9%)	7 (35.0%)	0.350*
Had ANC	43 (100%)	19 (95.0%)	0.139*
Home delivery	1 (2.3%)	3 (15.0%)	0.055*
Delivery by CS	20 (46.5%)	3 (15.0%)	0.016*
Male infant	27 (62.8%)	11 (55.0%)	0.566*
Gestational age (Weeks)	34 (32-35)	33 (33-34)	0.140‡
Birth weight (kg)	1.81 (±0.38)	1.57 (±0.27)	0.016†
SGA	10 (23.3%)	13 (65.0%)	0.001*
Neonatal sepsis	23 (53.5%)	10 (50.0%)	0.795*
RDS	9 (20.9%)	7 (35.0%)	0.350*
LOS (days)	14 (8-22)	14 (11-15)	0.882‡
Not exclusively breast fed	9 (20.9%)	9 (45.0%)	0.049*

Data are expressed either as frequency (Percentage) Median (IQR: Interquartile Range) or Mean (±SD) as appropriate, p values are derived from *Chi-square test or † from Independent sample t test or ‡: Mann-Whiteny U test as appropriate, [a]: Years of schooling, [b]: Monthly family income, ANC: Antenatal Care, CS: Cesarean section, SGA: Small for Gestational Age, RDS: Respiratory Distress Syndrome, LOS: Length of Stay in hospital.

To determine the independent effect on NDA, the variables which had p value of <0.1 were subsequently entered into a logistic regression model. Small for gestational age and birth weight were found to be as independent factor. Infant having SGA were 11.76 times more likely to have NDA than the infant with Appropriate for Gestational Age (AGA) and as the birth weight increased chance of NDA were decreased (p=0.016).

Table IV : Independent predictor of developmental abnormality by RNDA in 63 infants who came for follow up at 6 months corrected age

Variables (unit)	Odds ratio	(95% CI for OR)		p value
		Lower	Upper	
Delivery by CS	0.28	0.04	1.94	0.102
Home delivery	3.73	0.291	47.78	0.312
Small for gestational age	11.76	1.11	16.22	0.012
Birth weight, kg	0.117	0.026	0.673	0.016
Not exclusively breast fed	1.76	0.416	7.47	0.442

CI: Confidence Interval.

DISCUSSION

Our study reports neurodevelopmental outcomes for Bangladeshi moderate to late preterm infants at 6 months CA and contributes to the evidence of adverse outcomes for preterm infants in LMICs[10]. We found that certain number of moderate to late preterm infants had abnormal neurodevelopment in one or more of the seven domains (Gross motor, fine motor, vision, hearing, speech, cognition, behavior). All of the infants had normal development in seizure domain. Among neurodevelopmental abnormality most prevalent was in gross motor domain followed by cognition, vision and behavior.

One in 8 infants died during the course of the study and an additional 38% was lost to follow-up. Family income was lowest among those who died and highest among those who completed follow-up and mothers' literacy levels were highest among those who completed follow-up. All these factors, that is, rural residence, family income, gestational age, birth weight have emerged as important determinants of infant and child mortality in Bangladesh and its neighboring countries[11,12].

Out of 63 infants with completed 3 follow-ups till 6 months of CA, at 1 month of CA most frequently observed abnormal domain was gross motor (28.6%) followed by cognition (23.8%) behavior (19%) and vision domain (15.9%). At 6 months of CA abnormality in gross motor, cognition, vision and behavior were observed respectively in 28.6%, 14.3%, 12.7% and 12.7% respectively. In a previous study from Bangladesh where RNDA tool was used among preterm infants it was observed that, more than one domain affected in 34.9% infants and the single largest category of NDA was gross motor abnormality which is greater at 3 months of age than previously in the neonatal period. In contrast, other abnormal domains have come down to lower level[13].

LIMITATION

The prospective design is one of the strengths of our study and the considerable size of the initial cohort. Further, the assessment tool RNDA that we used had been previously adapted and validated for Bangladeshi infants. On the other hand, we acknowledge several limitations including the bias inherent in a single-centre study. The study lacked a full-term peer control group and included only NICU graduates. These issues may limit the generalization of our findings to the broader population of children born prematurely across the country. Furthermore, nearly 38% of the infants were lost to follow-up, potentially resulting in bias. Finally, the follow-up period was short.

CONCLUSION

In conclusion, about one third moderate to late preterm infants had abnormality in one or more domain of neurodevelopment assessed at 6 months CA. Lower birth weight and small for gestational age were found to have independent association

with abnormal neurodevelopment. This study demonstrated that a significant proportion of preterm newborn infants in this low-resource, LMICs setting are at risk for a range of neurodevelopmental abnormality, which called attention to the importance of surveillance of the neurobehavioral development of preterm children. Currently, this burden of morbidity is largely undetected and unaddressed throughout the developing world. Our study suggests consideration of long-term neonatal follow-up programmes in Bangladesh that could assist in ensuring this vulnerable group of children fulfills their potential.

DISCLOSURE

All the authors declared no competing interest.

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