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Neurodevelopmental Outcome of Very Low Birth Weight Indian infants with Periventricular Leucomalacia- A Prospective Cohort Study

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Abstract

There is a paucity of data on the neurodevelopmental (ND) outcomes associated with periventricular leucomalacia (PVL) in preterm VLBW babies from developing countries such as India. We prospectively evaluated the survivors of very low birth weight (VLBW) babies who had been screened for PVL in the neonatal period with ultrasonography for adverse ND outcomes at one year of corrected age as per standard protocol. Out of the 80 neonates from the original cohort who survived till discharge, 28 (35%) had PVL. A total of seven infants died in the follow-up period and 11 infants were lost to follow-up. Incidence of major ND disability was significantly higher in infants with PVL irrespective of the grade (5/24; 20.8%) than those without PVL (1/38; 2.6%) (RR: 7.92; 95% CI: 0.98 - 63.7; P = 0.03) The incidence of cerebral palsy was also higher in the PVL group irrespective of the grade (16.6 vs. 2.6%; RR: 6.33; 0.75 - 53.34; P = 0.07). Any evidence of Periventricular leucomalacia on ultrasonography detected in the new born period irrespective of the grade is a strong risk factor for adverse neurodevelopmental outcome at one year of corrected age.

Keywords: *Periventricular Leukomalacia; Cerebral Palsy; Neonate; Neurodevelopmental Outcomes*

Abbreviations

PVL: Periventricular Leukomalacia; VLBW: Very Low Birth Weight

Introduction

Major landmark advances in neonatal perinatal medicine over the last two decades have achieved 70 - 85% survival among very low birth weight (VLBW) population [1]. However, the downside is that about 5 - 15% of this population exhibit major neuromotor deficits and an additional 25 - 50% of them exhibit difficulties in learning and school performance at later age [2,3]. Several follow up studies-from developed countries have reported the association of adverse neuro-developmental (ND) outcome with presence of cystic periventricular leucomalacia (PVL) in neonatal period [4-8]. Till date, no studies from resource limited countries are available on this subject.

We therefore embarked on the present study with an objective to compare neurodevelopmental (ND) outcome among a cohort of VLBW neonates with and without PVL at one year of corrected age. We have previously published the natural history and incidence of periventricular leukomalacia among the same cohort of very low birth weight babies [9]. Such data would be useful not only in prognosticating parents on the possible ND outcomes of their children on follow up and to start timely early intervention as soon as the diagnosis of PVL confirmed, but also would provide the rationale for planning of long term follow up studies.

Materials and Methods

Participants

Enrolled participants were survivors from a cohort of 97 VLBW neonates born between April 2001 and May 2002 who had been screened for PVL with serial weekly cranial ultrasounds in their neonatal period [9]. All the infants discharged from the hospital were eligible for enrolment and were followed up at the weekly held high-risk clinic. Infants who developed PVL served as cases, while those who did not as controls for this follow up study.

Inclusion criteria: All the VLBW neonates born between April 2001 and May 2002 discharged were enrolled in the study. The neonates with PVL were actual cases. The neonates without PVL were included for controls.

Exclusion criteria: The neonates who did not survive before the discharge and after the discharge were excluded. The neonates other than the VLBW were excluded.

Participants were called for scheduled visits as per the high risk follow up program of the unit: fortnightly until the infant reaches 2 kg, monthly till 3 months corrected age (CA), and then every three months until one year of CA. Follow-up care consisted of an integrated comprehensive medical care including immunization and a detailed neurological, developmental, hearing and visual assessment as well as an investigative work up for any medical illness as and when required. Methods to maximize follow up included: fixing prior appointments, periodic reminders on phone, and clustering of follow-up care. Two contact addresses (local and permanent) and phone numbers were maintained and periodically checked and updated when necessary. For those not returning on follow-up, genuine effort was made to know the cause of being lost to follow up by communicating through telephone, letters (courier or mail) or directly by-passing messages through neighbours.

Neurodevelopmental assessment

Neurological Assessment

Neurological assessment on follow-up was done by the principal investigator based on Amiel Tison's method of tone assessment of infants was done up to one year of age [10]. Findings were confirmed by a senior neonatologist and graded as normal, suspect or abnormal. Suspect case was defined as one with variable abnormalities of tone or deep tendon reflexes with borderline delay in motor milestones. Abnormal tone was defined as one with definite abnormalities of tone (hyper or hypotonia) with brisk reflexes or consistent asymmetrical signs or persistent abnormal postures or dyskinetic movements in combination with delayed motor milestones.

Developmental assessment

Infants were also subjected to a developmental assessment using Developmental Assessment Scales for Indian Infants (Phatak, 1977) administered by the child psychologist. This method evaluates simultaneously but independently both motor development and mental functioning. Motor scale assesses control of gross and fine motor muscle groups. Mental scale assesses cognitive, personal and social skills development. The composite developmental quotient (DQ) is derived as an average of DMoQ (motor development quotient) and DMeQ (mental development quotient). A social quotient (SQ) was also derived using Malin (1973) adaptation of Vineland Social Maturity Scale (VSMS). This scale emphasizes on assessment of self -help and self- care activities though it includes items from all four domains namely gross motor, fine motor, language, and personal social adaptive and hence is closest in assessing functional limitations of the child at one year of corrected age.

Visual Assessment

Visual assessment was done binocularly using Teller acuity charts [11]. The procedure combines the high-quality grating stimuli used in forced preferential looking (FPL) testing with the observer's subjective judgment concerning qualitative aspects of the child's response to those stimuli. The procedure is easy requiring only uncomplicated equipment. A label of cortical visual impairment (cortical blindness)

was given if corrected vision was less than 20/200 or there was no perception or visual following of light despite intact pupillary reflexes. An attempt was made to confirm the diagnosis of cortical blindness by visual evoked responses. Blindness due to retinopathy of prematurity was not included as a marker of major Neurodevelopmental impairment.

Hearing Assessment

Hearing assessment was based on both subjective (clinical clues based on either reliable history or routine office examination) and objective assessment (brainstem auditory evoked responses, BAER). Cases were classified as normal or abnormal according to the locally generated normative data from our institution. A diagnosis of gross hearing impairment was made in those infants with failed BAER screening and later confirmed by a diagnostic BAER examination.

Seizures, other than febrile, were noted as a marker of major neurodevelopmental disability. The seizures must have appeared in the neonatal period (with metabolic causes such as hypoglycemia and hypocalcemia and/or dyselectrolytemia must have been excluded as primary causes of seizure) and persisted beyond, requiring single or multiple antiepileptic drugs for control. Type, frequency of occurrence of seizures and degree of control were noted.

Growth Assessment

Growth assessment was done in terms of weight and head circumference for age measured at the follow-up visit at 12 months corrected age. Growth (weight) was assessed using Centre for Disease Control (CDC) growth reference standards [12]. Infants whose weight fell below 80% of the reference standard were categorized into four grades of malnutrition according to Indian Academy of Pediatrics classification [13].

Post Discharge Mortality

In case of death of an infant, an attempt was made to establish possible cause, age and place of death (home/hospital).

Demographic data of parents:

A record of mother and father's educational status, profession and family income was made to evaluate socio economic status of the family using Kuppuswamy Scale [14].

Outcome variables

Primary outcome

The primary outcome variable was major neurodevelopmental impairment as defined by presence of abnormal tone either hypertone or hypotone with delayed motor milestones or Developmental Delay with DQ < 70 or cortical visual impairment (cortical blindness) or deafness requiring hearing aids or persistent seizures.

Secondary outcome

Secondary outcome variables included head circumference and growth status at 1 year of corrected age and post-discharge mortality.

Statistical methods

The difference in incidence of adverse neuro-developmental outcomes between PVL and non-PVL groups was compared using contingency chi square test with Yates correction; the relative risk (RR) with 95% confidence interval was also estimated. Student 't' test was used for continuous variables like head circumference and DQ scores. The size of the study was essentially determined by the number of infants in the original cohort.

Results

Of 80 VLBW infants enrolled for follow up, 28 (35%) had PVL. Two infants in PVL group and nine in non-PVL group were lost to follow up at one year of corrected age, giving a follow up rate of 92.8% and 82.6% respectively (cumulative follow up rate of 86.2%). Out of the

two losses in the PVL group, one neonate had localized frontal cystic PVL and the other had persistent flare on ultrasound. In the non PVL group, while seven were completely lost to follow up, two infants had one follow up visit each at 3 months corrected age. Both these babies had been normal at their last visit. Figure 1 shows the study flow chart.

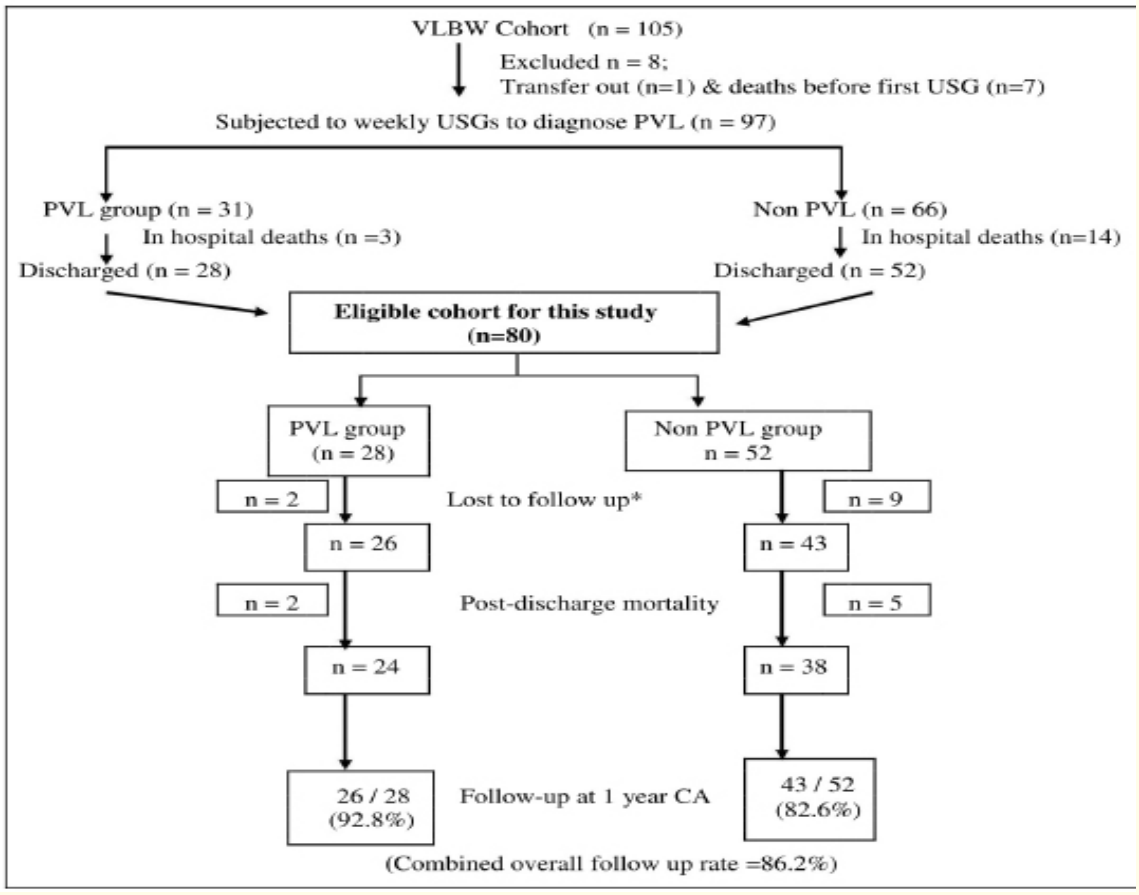

Figure 1: *Study Flow chart.*

Baseline characteristics

Birth weight, gestation and other demographic characteristics were comparable between the two groups (Table 1). However, the proportion of infants born at < 28 weeks gestation and mean duration of stay in NICU were significantly higher in the PVL group; also, less number of mothers of infants in this group received antenatal steroids.

Characteristics	PVL group (n = 24)	Non-PVL group (n = 38)	P value
Birth weight (g)	1243.6 ± 211.0	1220.0 ± 211.6	0.67
Birth weight < 1000 g	9 (37.5)	16 (42.1)	0.73
Gestation (weeks)	32.3 ± 1.9	32.3 ± 2.7	0.97
Gestation < 28 wks	13 (54.1)	4 (10.5)	0.001
Follow up age (months)	12.0 ± 1.9	12.6 ± 2.6	0.25

NICU stay (days)	39.3 ± 7.8	24.5 ± 8.4	0.001
Antenatal steroids	19 (79.1)	37 (97.3)	0.03
Multiple ANS	4 (16.6)	5 (13.1)	1.00
Gestational hypertension	9 (37.5)	26 (68.4)	0.02
Birth asphyxia	5(20.8)	5 (13.1)	0.44
RDS	5(20.8)	12 (31.5)	0.37
PDA	1 (4.1)	2 (5.2)	0.89
Sepsis	1(4.1)	2 (5.2)	0.89
Meningitis	1 (4.1)	0	0.39
Apnea	5(20.8)	13 (34.2)	0.27
Socio-economic status < Class III	5 (20.8)	7 (18.4)	0.99

Table 1: *Baseline characteristics of the study population.*

** Values are mean ± SD or number (%)*

NICU: Neonatal Intensive Care Unit; ANS: Antenatal Steroids; RDS: Respiratory Distress Syndrome; PDA: Patent Ductus Arteriosus

Major neurodevelopmental disability

Five infants in the PVL group (20.8%) were found to have major disability as compared to one (2.6%) in the control group (RR: 7.92; 0.98 - 63.7; P = 0.03; Table 2). Out of these five infants, four had abnormal tone while one infant had developmental delay without any tone abnormalities. Cortical visual impairment and deafness were present in two (8.3%) and one (4.2%) infants respectively in the PVL group; the corresponding rate in non-PVL group was 0 and 1/38(2.6%) respectively. Seizures were present in two infants, both belonging to PVL group. Thus, there were multiple disabilities per affected child. There were 13 disabilities among 5 children with PVL and 3 among the only child with abnormal tone from non PVL group.

Characteristic	PVL group (n = 24)	Non PVL group (n = 38)	RR (95% CI) p value	P
Infants with major disability	5 (20.8)	1 (2.6)	7.92 (0.98, 63.7)	0.03
Major disabilities:				
• Cerebral palsy	4 (16.6)	1 (2.6)	6.33 (0.75, 53.3)	0.07
• DQ < 70	5 (20.8)	1 (2.6)	7.92 (0.98, 63.7)	0.03
• Blindness	2 (8.3)	0 (0.0)	-	-
• Deafness	1 (4.2)	1 (2.6)	1.58 (0.1, 24.1)	1.00
• Seizures	2 (8.3)	0 (0.0)	-	-

Table 2: *Major neuro-developmental disability in VLBW infants with and without PVL.*

Data presented as number (%) (PVL: Periventricular Leucomalacia; DQ: Developmental Quotient; RR: Relative Risk; CI: Confidence Interval)

Outcome of different grades of PVL

The distribution of different grades of PVL among the 24 PVL babies, followed up to one-year corrected age was as follows: 13 with grade I PVL, 9 with grade II PVL and 2 with grade III PVL. Of those with Grade I PVL (persistent flares), 9/13 (69.2%) were normal at one year. In contrast, only 22.2% with grade II and none with grade III PVL had normal outcomes at one year of age. Thus, there was a linear trend of an increasing abnormal neurodevelopmental outcome with higher grades of PVL: the trend was highly significant (value of trend

chi-square being 16.79; $p < 0.001$). These differences in neurodevelopmental outcomes between different grades of PVL were also tested using a contingency chi-square and the association was found to be highly significant (value of chi-square with 6 degrees of freedom was 35.43; $p < 0.001$) (Table 3).

Outcome	No PVL (n = 38)	Grade I PVL (n = 13)	Grade II PVL (n = 9)	Grade III PVL (n = 2)
Normal	32 (84.2)	9 (69.2)	2 (22.2)	0
Moderate disability	5 (13.1)	2 (15.4)	6 (66.7)	0
Major disability	1 (2.6)	2 (15.4)	1 (11.1)	2 (100)

Table 3: *Neuro-developmental outcome of different grades of PVL.*

Data presented as number (%)

Note: Value of chi-square with 6 degrees of freedom is 35.43 (P value < 0.001)

Value of chi-square for trend is 16.79 (P value < 0.001)

Post discharge mortality

Post discharge mortality rate was 8.8% being not significantly different between PVL and non PVL group (7.1% vs. 9.6% respectively; RR: 0.63; 95% CI: 0.13-3.0).

Head circumference

Head circumference of < 5th centile was present in 15/24 (62.5%) of PVL and 20/38 (52.6%) of non PVL groups; the difference between the groups was not statistically significant.

Growth status

Overall, more than half (35/62; 56.4%) of the followed up infants were malnourished. The proportion of infants with PEM was not different between the two groups – 13 (54.2%) in the PVL group and 22 (57.8%) in the non-PVL Group (P = 0.98). The incidence of severe PEM (grade III or more) was slightly higher in the PVL group - 4 (16.6%) vs. 2 (5.2%), but the difference was not significant (P = 0.19).

Discussion

This study was designed to report neuro-developmental follow-up outcomes at one year of corrected age among a cohort of very low birth weight babies with and without periventricular leucomalacia. Though the optimal age for labeling a diagnosis of cerebral palsy has been suggested to be 18 - 24 months [7,15], at least a few studies have documented the utility of neuro-developmental status and ultrasound evaluation at one year of age which has been found to be a good predictor of outcome at 8 years including cognitive development and school performance [16,17]. We considered 'corrected age of one year' as the earliest optimal time to report major neurodevelopmental disability, so that timely intervention program could be initiated. Understanding the limitation of having long term follow up in developing countries, and the fact that we were only looking at major neurodevelopmental disability (Abnormal tone with delayed motor milestones, Cortical visual impairment, deafness, DQ < 70). Outcome parameters such as DQ and weight or head circumference measurements are corrected for age and hence are really age independent as far as making categorization into normal or abnormal is concerned. Hence, even a single follow up between 12 - 18 months of corrected age was considered satisfactory for this study purpose.

This study is the first from developing countries that describes the natural history of PVL linking it to neurodevelopmental outcome in a cohort of VLBW infants. The prevalence of all types of neurodevelopmental disability was found to be more frequent in the PVL group than those in the non-PVL group. Four out of the 5 babies with tone abnormality in the study had PVL. The only case of tone abnormality among the non PVL group developed it after an episode of meningitis at postnatal age of 4 months. The more extensive the damage the more severe tone abnormality. Parietal involvement led to motor dysfunction (2 in cystic PVL group). A severe cortical visual impairment

was found in those with occipital lesions 2 (8.3%) in PVL group while it is same in other study where 3 (11%) had blindness where damage was seen in optic radiations [18].

Studies from the developed countries have reported outcomes of children diagnosed to have PVL in the neonatal period. Though the initial follow-up studies had studied those with PVL irrespective of site, type, and extent of lesions [17]. (Cooke, 1987), subsequent studies have focused mainly on cystic PVL [19,20]. The data of most of these studies was analyzed by Holling and Leviton [21]. Just as they found the prevalence of cerebral palsy to be 35% in infants with small cystic lesions, the present study also confirmed that major neurodevelopmental abnormalities may occur in as many as 31% of those with persistent flares (grade 1 PVL). It is possible that small cysts 1 - 2 mm in diameter might have been missed on ultrasound and persistent flares most likely represent permanent microscopic changes resulting in neurodevelopmental abnormalities [22]. Hence those with persistent flares need to be followed up since they represent a group that could manifest both major abnormalities such as CP or develop minor developmental and learning problems later in school life.

Post discharge mortality was 8.8% in our cohort. Differences in mortality between PVL and non-PVL groups were not statistically significant. The most important cause of deaths was infections similar to other Indian studies on follow-up of high-risk infants [23]. Most deaths occurred within first three months of life and all these participants had no follow up visit to high-risk clinic until death.

Head circumference as a marker of brain growth has been correlated with neurodevelopmental status at different ages. Earlier studies reported that mean head circumference for low birth weight and very low birth weight appropriate-for-gestational age infants remained at 50^{th} centile and followed normal velocity curve after term date [23-26]. Hoskins reported 16% of their VLBW infants at 18 months had their head circumference < 10^{th} centile [26]. We found a slightly higher incidence of microcephaly among those with PVL as compared to those without PVL; moreover, all infants with major neurodevelopmental disability had an abnormal head size. Persistent seizures were noted as a major neurodevelopmental outcome in our study. The strength of our study is that it is the first study from Indian subcontinent which has prospectively evaluated the early neurodevelopmental outcome of VLBW babies with PVL with a good follow up rate.

Recent study in 2013 neurodevelopmental outcome with periventricular leukomalacia graded based on MRI findings was done. This study revealed the similar type of findings to our study where 60 - 70% of babies with PVL grade I had normal neurodevelopmental outcome, PVL II and III had 90 - 100% major neurodevelopmental outcome. The babies with Intra ventricular hemorrhage associated with PVL had severe neurodevelopmental outcome like our study [27].

However, our study has several limitations, the most notable being the small sample size. The sample size for this study is not enough to give precise estimates of primary outcome i.e. neurodevelopmental disability. This was due to the fact that this was only a follow up study of the original cohort designed to estimate the incidence of PVL. The small number also precluded us from carrying out a multivariate analysis to evaluate the independent effect of PVL on neurodevelopmental outcomes.

Conclusion

We conclude that preterm infants with evidence of PVL in the neonatal period are at increased risk of having adverse neurodevelopmental outcomes at one year of corrected age when compared to those without PVL. Major neurodevelopmental disability was seen with both cystic PVL as well as persistent flares. Therefore, those with persistent flares need to be followed up since they represent a group that could manifest both major abnormalities such as tone abnormalities or develop minor developmental and learning problems later in school life.

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Conflict of Interest

The authors have no conflict of interests relevant to this article to disclose.

Ethical Approval

Study has been done after taking ethical approval from the institution.

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