RESEARCH PAPER

Preterm White Matter Injury: A Prospective Cohort Study

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Objective: To determine the incidence and risk factors of preterm white matter injury [WMI; periventricular-intraventricular hemorrhage (PIVH) and/or periventricular leukomalacia (PVL)].

Design: Prospective cohort study.

Setting: Level-3 neonatal intensive care unit.

Patients: Inborn preterm neonates (*n*=140) delivered at <32 weeks gestation or birthweight <1500 g.

Methods: Serial cranial ultrasounds were performed at postnatal ages of 3 days (±12 hour), 7 (±1) days, 21 (±3) days and 40 (±1) weeks postmenstrual age (PMA). PIVH and PVL were graded as per Volpe and De-Vries criteria, respectively. Univariate followed by multivariate analysis was done to evaluate risk factors for PIVH and PVL.

Outcome measures: The primary outcome was the incidence of preterm WMI. The secondary outcomes were evaluation of risk factors and natural course of WMI.

Results: The mean (range) gestation and birth weight of enrolled neonates were 29.7 (24-36) weeks and 1143 (440-1887) g, respectively. PIVH occurred in 25 (17.8%) neonates. PVL occurred in 34 (24.3%) neonates. None of them were grade III or IV PVL. Preterm WMI (any grade PIVH and/or PVL) occurred in 52 (37.1%) neonates. Severe PIVH (grade III) and cystic PVL occurred in 7 (5%) and 5 (3.6%) neonates, respectively. On multivariate analysis, none of the presumed risk factors were associated with PIVH. However, hemodynamically significant patent ductus arteriosus, and apnea of prematurity were significantly associated with increased risk of PVL.

Conclusions: Significant WMI occurred only in one-third of the cohort, which is comparable to that described in literature from the developed countries.

Keywords: *Outcome, Periventricular- intraventricular hemorrhage, Periventricular leukomalacia, Risk factors*.

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Survival of very low birthweight (VLBW) neonates has improved over the last decade; survival rates being more than 90% in most centers [1]. This is largely due to improved obstetric and neonatal care practices, in particular, use of antenatal steroids and gentler non-invasive modes of ventilation [2]. Preterm white matter injury (WMI) and its associated neurological sequelae are of important concern to the neonatologist.

Periventricular-intraventricular hemorrhage (PIVH) and periventricular leukomalacia (PVL) are the two major forms of preterm WMI. PIVH originates in a highly active zone of cell proliferation in the preterm brain called as subependymal zone or germinal matrix, and later spreads into the ventricular cavity. PVL is characterized by foci of necrosis in periventricular white matter (focal component) and more diffuse glial response in the form of reactive gliosis and microglial activation in the surrounding white matter (diffuse component). Cranial ultrasound (CUS) is the screening procedure of choice for preterm WMI, especially PIVH [3].

Initial studies done in the 1980s showed a high incidence of PIVH (up to 40-50%) [4-6]. This has decreased to about 20-25% in developed countries in the last two decades [7,8]. In a study from our own center in 2004, the incidence of preterm WMI was about 32% [9]. No recent data is available from low-middle income countries like India. Hence, we planned this prospective cohort study to determine the incidence of WMI and its associated risk factors in VLBW neonates. The primary objective of this study was to determine the incidence of PIVH and PVL (i.e., preterm WMI) in neonates born at less than 32 weeks gestation or birth weight <1500 g. The secondary objectives were to evaluate the risk factors and natural history of PIVH and PVL till discharge from Neonatal intensive care unit (NICU) or 40 weeks postmenstrual age (PMA) using serial CUS.

METHODS

This prospective cohort study was conducted at a level-3 NICU, All India Institute of Medical Sciences, New Delhi from March, 2018 to June, 2019. Inborn preterm neonates born at <32 weeks gestation or birth weight <1500g were enrolled. Neonates with major CNS malformations (antenatally diagnosed or diagnosed at birth) or dying before the first cranial ultrasound were excluded. The

neonates were followed until 40 weeks PMA or discharge from NICU, whichever was later (**Fig. 1**).

The study was approved by the institutional ethics committee. Before enrolment an informed consent was obtained from parents.

Protocol for cranial ultrasound: Serial cranial ultrasounds (CUS) were performed on: Day 3±12 hours; Day 7±1 day; three weeks ± 3 days and 40 weeks/at discharge. If any CUS other than the last one was abnormal, clinical team decided frequency of next ultrasound. All initial CUS (within the first week) were performed bedside using Philips CX-50 (Philips). Subsequent CUS were done bedside wherever feasible (neonate in level 3 unit) or in the Radiology department (for neonates admitted in step down unit after stabilization) using Supersonic imagine (Aixplorer) or Antaris (Siemens).

Using a small footprint curvilinear probe with 2-5 MHz or higher frequency, CUS was performed using anterior fontanelle as an acoustic window. Standard views were obtained in the coronal and sagittal planes. Ventricular index (VI) was measured in coronal plane as the distance between falx and lateral end of anterior horn of lateral ventricle [10]. Thalamo-occiptal distance (TOD) was measured in oblique parasagittal view as distance between the outermost point of thalamus at its junction with choroid plexus and outermost extent of occipital horn [10].

An experienced pediatric radiologist performed the cranial ultrasound (CUS) in first 40 cases. Subsequently, CUS were done by the first author with a simultaneous review of all images done by the pediatric radiologist. There was < 10% discrepancy in the reported findings and in all such cases, report of the radiologist was considered final. PIVH was graded as per Volpe classification and PVL as per De Vries criteria [11,12]. Transient periventricular flare was defined as periventricular echogenicity not lasting for more than 7 days. The reference values of VI and TOD, were from the study by Brouwer, et al. [10].

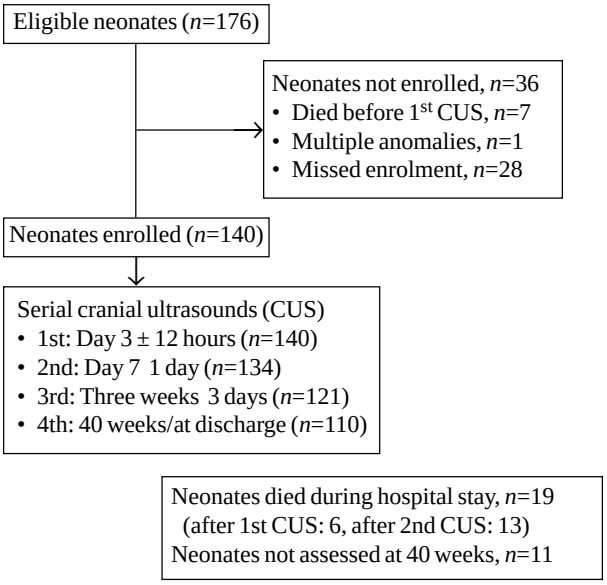

Fig. 1 Study flow chart.

Gestational age was assessed from the last menstrual period or first trimester ultrasound scan. If both were not available or a discrepancy of 1 week or greater was noted between the two, expanded New Ballard score was used [13]. Steroid coverage was considered 'complete', if the mother received 4 doses of dexamethasone 12 hours apart or 2 doses of betamethasone 24 hours apart, with last dose given at least 24 hours before delivery. Small for gestational age (SGA) was defined as birth weight less than 10th percentile on Lubchenco charts 14]. Birth asphyxia was defined as 5 minute Apgar score ≤5. Respiratory distress syndrome (RDS), sepsis, hemodynamically significant PDA (hs-PDA), shock, preterm premature rupture of membranes (PPROM) and prolonged rupture of membranes (PROM) were defined as per standard definitions [15]. Arterial blood gases (ABG) done by the NICU team for clinical monitoring were checked for PaCO2 values in first 72 hours of birth. Hypocapnia was defined as $PaCO_2$ <35 mmHg and hypercarbia as PaCO2 >45 mmHg. Hypotension was defined as BP < 5th centile [16].

The antenatal details like demographic data, obstetric history and current pregnancy details including antenatal steroid status, gestational age, cause of preterm delivery, duration of rupture of membranes, etc. were collected by principal investigator from mother's hospital records after the baby was enrolled. The details of delivery room resuscitation and NICU course like sepsis, hypotension, shock, hypocapnia, hypercarbia and acidosis in first 72 hours, were recorded in a predesigned proforma.

Based on the available literature, we assumed the prevalence of preterm WMI as 20%. With 95% confidence limit and an absolute precision of 7%, the sample size was calculated to be 126. Anticipating a loss to follow up at 40 weeks PMA, we decided to enroll 140 neonates.

Statistical analysis: A database was created in Microsoft Access 2016 (Microsoft) for recording the variables. Data analysis was done using STATA 15.1 version (Stata Corp). The incidence of PIVH and PVL along with 95% confidence intervals (95% CI) were calculated. For risk factors, we did univariate analysis followed by multivariate logistic regression with PIVH or PVL as dependent variable and identified risk factors as independent variables. Data analysis was done separately for PIVH and PVL.

RESULTS

During the study period, 176 eligible neonates were born, of which 140 were enrolled (**Fig. 1**). The mean (range) gestation and birthweight of enrolled neonates were 29.7 (24-36) week and 1143 (440-1887) g, respectively. The baseline characteristics of enrolled neonates are summarized in **Table I**.

Table I Baseline Characteristics and Hospital Course of Preterm Neonates Enrolled in the Study (*N*=140)

Characteristics	*N (%)*
Maternal characteristics	
Hypertension	30 (21.4)
Diabetes	30 (21.4)
PPROM	52 (37.1)
Antenatal steroids	130 (92.8)
Complete course	89 (63.6)
Vaginal delivery	24 (17.1)
Delivery room details	
5-min Apgar score ≤5	26 (18.6)
Delivery room CPAP	101 (72.1)
Delivery room intubation	36 (25.7)
Chest compressions	3 (2.14)
Neonatal characteristics	
Male gender	79 (56.4)
Small for date	50 (35.7)
Gestational age[a]	29.7 (24-36)
< 28 wks	26 (18.6)
28-31 wks	79 (56.4)
≥ 32 wks	35 (25)
Birthweight (g)[a]	1143 (440-1887)
<500	2 (1.4)
500-749	15 (10.7)
750-999	36 (25.7)
1000-1499	70 (50)
≥1500	17 (12.1)
RDS requiring surfactant	40 (28.6)
CPAP in NICU	121 (86.4)
IMV in NICU	49 (35)
Hypocapnia within 72 h[b]	9 (6.4)
Hypercarbia within 72 h[b]	15(10.7)
Acidosis within 72 h[b]	19(13.6)
Shock within 72 h[b]	8 (5.7)
Shock at any time	22 (15.7)
hsPDA	28 (20)
Sepsis	51 (36.4)
Meningitis	6 (4.3)
Necrotizing enterocolitis	4 (2.9)

Data presented as no. (%) or [a]mean (range). [b]Hours of life. PPROM: Preterm premature rupture of membranes; CPAP: Continuous positive airway pressure; RDS: Respiratory distress syndrome; IMV: Invasive mechanical ventilation; hsPDA: Hemodynamically significant patent ductus arteriosus; NICU: neonatal intensive care unit.

PIVH occurred in 25 (17.8%; 95% CI 12.3–25.2%) neonates-grade I, II, III, and IV in 17 (12.1%), 1 (0.7%), 6 (4.3%), and 1 (0.7%) neonates, respectively. Severe PIVH (grade III) occurred in 7 (5%) neonates. PIVH was bilateral in 15 neonates. PVL occurred in 34 (24.3%; 95% CI 17.8–32.2%) neonates-grade I and II in 29 (20.7%) and 5 (3.6%) neonates, respectively. Transient periventricular flares occurred in 7 neonates. We did not detect any grade III or IV PVL. Cystic PVL occurred in 5 (3.6%) neonates. PVL was bilateral in all our neonates. Preterm white matter injury (any grade PIVH and/or PVL) occurred in 52 (37.1%; 95% CI 29.5-45.5%) neonates (**Table II**).

PIVH was detected in first three days of life in 22 (88%) neonates and in all cases by day 7. Progressive ventricular dilation occurred in one-third of patients with grade III PIVH. Periventricular white matter echogeni-cities appeared in 33 (97%) cases within the first 7 days of life. Periventricular cysts were detected in 5 cases of cystic PVL by 3 weeks of age. Additional three neonates had ventricular dilation in CUS done at term gestation with no abnormality detected in previous scans, indicating likely periventricular white matter loss.

On univariate analysis, female gender, vaginal delivery, hypercarbia, acidosis and shock in first 72 hours of life were associated with increased risk of PIVH. However, on multivariate analysis none of these factors were significant. Similarly, delivery room endotracheal intubation, hypocapnia in first 72 hours of life, apnea, anemia requiring transfusion, hsPDA, sepsis, meningitis and BPD were associated with PVL on univariate analysis. However, on multivariate analysis, only hsPDA (OR 3.09; 95% CI 1.02–9.39; *P*=0.04) and apnea (OR 2.81; 95% CI 1.04-

Table II Profile of Preterm White Matter Injury Among the Study Cohort (*N*=140)

Characteristic	*No. (%) [95% CI]*
Peri-intraventricular hemorrhage	
Any grade	25 (17.8) [12.3-25.2]
Worst grade	
I	17 (12.1)
II	1 (0.7)
III	6 (4.3)
IV (PVHI)	1 (0.7)
Periventricular leukomalacia (PVL)	
Any grade	34 (24.3) [17.8-32.2]
Worst grade	
I	29 (20.7)
II	5 (3.6)
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Cystic PVL	5 (3.6)
Preterm white matter injury[a]	52 (37.1) [29.4-45.5]

7.56; P=0.04) were found to be significantly associated with increased risk of PVL (**Table III**).

DISCUSSION

In this cohort of 140 neonates, PIVH occurred in 25 (17.8%) neonates. Severe PIVH occurred in 7 (5%) neonates. PVL occurred in 34 (24.3%) and cystic PVL occurred in 5 (3.6%) neonates. Preterm WMI (any grade PIVH and/or PVL) occurred in 52 (37.1%) neonates. However, most neonates had low-grade lesions (grade I PIVH/PVL). Severe PIVH and cystic PVL occurred in less than 5% of neonates which is comparable to what is described in literature from developed countries.

Comparing our findings to a previous study done from our own center 17 years back by Maria et.al [9], the incidence of any grade PVL and cystic PVL decreased from 36.2% and 12.4% to 24.3% and 3.6%, respectively. The incidence of cystic PVL in our cohort is similar to that reported in data from developed world [17-18]. Studies from 1980s reported the incidence of PIVH in premature neonates up to 40-50% [4-7]. The incidence decreased to 20-25% in studies done in late 1980s and 1990s [8,19]. The incidence of PIVH has remained almost the same in the last decade i.e., 20-25% in VLBW and up to 40% in neonates born at d" 28 weeks gestation [17,20]. However, there has been an increase in the survival of ELBW neonates who are at even higher risk of PIVH, which may mask a true decline in incidence of PIVH.

Multiple studies have implicated the role of pressure passive cerebral circulation of preterm neonates in causation of PIVH; [18] the classic setting being severe RDS requiring mechanical ventilation [21-22]. Hypercarbia also increases the risk of PIVH [23]. However, in our study, none of these risk factors were associated with PIVH. In our cohort, vaginal delivery was not associated with increased risk of PIVH. Earlier studies had shown that VLBW neonates born vaginally were at higher risk of PIVH [24]. However, more recent studies have contrary results [25]. In a study on periventricular hemorrhagic infarction (PVHI) by Bassan, et al. [26], fetal distress, need for emergency cesarean section, low Apgar scores, and need for respiratory resuscitation were strongly associated with PVHI. Another interesting study in which 95 VLBW infants underwent amplitude- integrated EEG monitoring for first 72 hours of life found high incidence (48%) of seizures which increased the risk for IVH and white matter injury [27]. Our study failed to show any association of delivery room resuscitation or birth asphyxia with PIVH. In this study, hsPDA and apnea were associated with increased risk of PVL. We, however, did not find any significant association of PVL with low APGAR scores, RDS, hypocapnia, acidosis, PPROM or meningitis, contrary to what is described in literature [28-31].

In our study, PIVH was detected in first three days of life in 22 (88%) cases and in all 25 (100%) cases by day 7. Most cases of PIVH were clinically silent. Approximately 90% of cases of IVH occur within the first 72 hours of life, with 50% occurring in first 6 hours [5,32,33]. The lesion progresses in about 10-20% cases over 3-5 days [34].

We had 3 neonates with apparently normal first 3 CUS scans, but showed ventriculomegaly in CUS done at term equivalent age. Data suggests that presence of persistent echo-densities for >7 days is significant and may actually represent non-cystic PVL [35,36]. In a study by Inder et.al, on 96 VLBW neonates, 10 neonates who had either normal CUS or transient echodensity had subsequent evidence of WMI on MRI at term. Further, 22 neonates with overtly abnormal CUS as persistent echo-density had normal MRI

Table III Risk Factors of Periventricular Leukomalacia (PVL) Among the Study Cohort (*N*=140)

	PVL (n=34)	*No PVL (n=106)*	*Adjusted OR(95% CI)*	*P value*
Male gender	19 (55.9)	60 (56.6)	1.07 (0.47-2.48)	0.86
Small for gestational age	16 (47)	34 (32.1)	2.48 (0.94-6.54)	0.06
Prolonged rupture of membranes	4 (1.2)	19 (17.9)	0.32 (0.07-1.47)	0.15
Preterm premature rupture of membranes	14 (41.2)	38 (35.8)	2.69 (0.79-9.14)	0.11
Antenatal steroids	20 (58.8)	69 (65.1)	1.31 (0.50-3.39)	0.58
Vaginal delivery	8 (23.5)	16 (15.1)	0.72 (0.17-3.05)	0.65
5-min Apgar score <5	8 (23.5)	18 (6.9)	1.57 (0.50-4.94)	0.43
Respiratory distress syndrome	10 (29.4)	30 (28.3)	0.47 (0.13-1.47)	0.18
Apnea	23 (67.6)	39 (36.8)	2.81 (1.04-7.56)	0.04
Shock requiring inotropes	8 (23.5)	14 (13.2)	1.01 (0.29-3.57)	0.73
Hemodynamically significant patent ductus arteriosus	12 (35.3)	16 (15.1)	3.09 (1.02-9.39)	0.04
Meningitis	4 (11.8)	2 (1.9)	2.05 (0.24-17.4)	0.50

WHAT IS ALREADY KNOWN?

- The incidence of preterm white matter injury (any grade) and severe peri-intraventricular hemorrhage (PIVH) /cystic periventricular leucomalacia (PVL) is 20-25% and below 5%, respectively in the developed countries.
- Incidence of any grade PVL and cystic PVL in India 15 years ago was 36.2% and 12.4%, respectively.

WHAT THIS STUDY ADDS?

- Severe PIVH and cystic PVL occurred in less than 5% of neonates.

at term gestation. Therefore, the sensitivity and specificity of transient and persistent echodensity on CUS for predicting abnormal MRI findings at term may not be good [35]. Therefore, while periventricular cysts are sensitive and specific for abnormal MRI correlates and poor neurodevelopmental outcomes, transient and persistent echodensities/flares are variably predictive of WMI on MRI at term gestation. We decided to follow PVL using CUS only because of the ease of doing bedside CUS and the risks involved in doing MRI under anesthesia.

The strengths of this study are its prospective cohort design and meticulous follow up of VLBW neonates till term gestation. About 80% of enrolled neonates underwent at least four CUS. All CUS images were reviewed by an expert pediatric radiologist. Data analysis was done separately for PIVH and PVL.

Our study has some limitations too. The study was not powered to evaluate the risk factors of WMI. We chose a relatively larger margin of precision (7%) primarily due to feasibility considerations. In addition, MRI brain would have been a better modality for characterization of PVL. However, literature does suggest acceptable agreement between serial CUS and MRI done at 40 weeks' gestation [37]. We also could not assess the impact of the CUS abnormalities on subsequent neuromotor development.

In conclusion, most VLBW neonates in our cohort had low-grades of preterm WMI (grade I PIVH and PVL). The incidence of severe PIVH and cystic PVL in our setting is low and is comparable to data from developed countries. We also noticed a decrease in the incidence of preterm WMI over the last 15 years in our setting.

Note: Additional material related to this study is available with the online version at *www.indianpediatrics.net*

Ethics clearance: Institutional ethics committee, All India Institute of Medical Sciences, New Delhi; No. IECPG-457, dated November 29, 2017.

Contributors: MRM: principal investigator; reviewed literature; prepared the initial protocol and this manuscript; collected data; performed cranial ultrasounds of enrolled neonates with images reviewed by MJ; AKD: framed the idea and rationale of this study; reviewed the protocol; supervised this study throughout its course; critical revision and finalization of this manuscript; MJ: Framed the cranial ultrasound (CUS) protocol; performed CUS in first 40 cases and reviewed all CUS images; RA,JS,AS: helped in preparation of initial protocol and this manuscript; supervised the study and critical revision of this manuscript.

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