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Report

Periventricular Leukomalacia in Ulin General Hospital Banjarmasin: A Prevalence and Baseline Characteristics Study

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Abstract

Preterm neonates are at high risk of long-term neurodevelopmental morbidities. Periventricular leukomalacia (PVL) is the main form of brain injury and is mostly found in premature neonates. This study aims to discover the prevalence of PVL and provide baseline characteristics of PVL. The study included term and preterm neonates diagnosed with PVL, detected by head ultrasound, during hospitalization in the neonatal intensive care unit (NICU) or neonatology ward in Ulin General Hospital Banjarmasin from February 2021 to January 2023. Data were gathered from medical records. During the study, nineteen patients were enrolled, 18 preterm neonates (<37 weeks of gestation) and one full-term neonate. The mean gestational age was 32.3 $\pm$ 2.5 weeks. The overall prevalence rate of PVL in preterm neonates was 4.4% (18/409), and in extremely preterm neonates was 5.7% (7/122). Diffuse PVL is the most common form of PVL (78.9%). The risk factors revealed were sepsis and respiratory distress. Blood transfusion was found in nearly all of the neonates. The prevalence of extremely preterm neonates with PVL was lower than previously reported due to limited resources (absence of bedside ultrasound). Diffuse (non-cystic) PVL was the predominant ultrasound finding. Common neonatal risk factors such as sepsis, respiratory distress, and blood transfusion could be related to PVL.

Keywords

Brain Injury, Neonates, Neurodevelopmental, Periventricular Leukomalacia, Preterm

1. Introduction

Preterm birth accounts for approximately 15 million births every year worldwide. [1] Globally, the estimation of preterm birth rate in 2014 was 10.6%. Of this, according to gestational age, over 11.3% represents very preterm neonates (gestational age <32 weeks) and 4.1% extremely preterm neonates (gestational age <28 weeks). Indonesia was on the fifth position for number of preterm births with rate of 10.4%, equating about half a million neonates. [2] Preterm neonates, especially very preterm and extremely preterm neonates are at risk of long-term medical morbidity and neurodevelopmental impairment. [3, 4]

The immature brain in preterm neonates is susceptible to

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injury. [5] The most common, yet also the leading cause of poor long-term neurodevelopmental outcomes in preterm neonates is periventricular leukomalacia (PVL). [6, 7] Periventricular leukomalacia is an ischemic white matter injury, which characterized by focal necrotic lesion and diffuse gliosis around ventricles area. [8, 9] The two suggested main mechanisms that involved in pathogenesis of PVL are hypoxia-ischemia and inflammation/infection. [8, 10]

Prevalence of white matter injury in preterm neonates, based on a recent systematic review, was 39.6% for extremely preterm neonates and 27.4% for very preterm neonates, and 7.3 for moderately and late preterm neonates. [11] Decreasing gestational age of preterm neonates is associated with higher incidence of PVL. [11, 12] However, the true incidence of PVL remains unclear because of the spectrum of injury, neuroimaging modalities, and timing of imaging. [5, 8, 13] Liu J, et al. (2008) reported the incidence rate of PVL in preterm neonates in China was 29.4%. [14] In Indonesia, the prevalence of PVL is not known yet. The only published study regarding PVL from Indonesia is a single center study in 2003. This study found that prevalence of PVL in neonates with gestational age less than 32 weeks and more than 32 weeks were 6/21 and 13/30. [15] Therefore, we conducted this study to find out the prevalence of PVL and provide baseline characteristics of PVL.

2. Methods

This descriptive study enrolled all term or preterm neonates diagnosed with PVL that were admitted to the neonatal intensive care unit (NICU) or neonatology ward in Ulin General Hospital Banjarmasin from February 2021 to January 2023. The PVL diagnosis was made by head ultrasonography performed by radiologist at Ulin General Hospital, others were excluded. The data were collected from medical record. Informed consent was obtained prior. Incomplete medical record data were also excluded.

The data include gestational age, gender, birth weight, birth length, risk factors (chorioamnionitis, premature rupture of membrane, fetal distress, preeclampsia/ hypertension, diabetes, maternal age, etc), type of delivery, multiple pregnancy, age at diagnosis, PVL grade, maternal age, date of admission and discharge, length of hospital stay, other diagnosis (primary and secondary diagnosis), oxygenation, history of blood transfusion, and place of birth (in hospital birth or referral from other hospitals and health facilities). The PVL diagnosis was made by head ultrasound examinations that was done by our hospital radiologist.

2.1. Head Ultrasound Examination

The head ultrasound examinations were done during hospitalization, at 10 to 14 days of life if possible, or after the patients didn't require any oxygen supplementation. Findings of PVL from ultrasound were graded as following: (I) increased echogenicity in periventricular white matter with bilateral but asymmetric distribution (noncystic PVL); (II) localized small cysts that can be located around central grove or at frontal region (microcysts); (III) widespread cysts, extending to the fronto-parietal and occipital regions (cystic PVL); (IV) extensive cysts that located in subcortical white matter (subcortical PVL or multicystic encephalomalacia). [14, 16, 17]

2.2. Statistical Analysis

Data were collected as continuous and categorical variables. Descriptive analysis was done using IBM SPSS Statistics 23.0 (IBM Corp., Armonk, NY, USA). Continuous data were reported as median or mean and categorical data were reported as frequencies and proportions.

3. Results

Nineteen neonates were identified with confirmed PVL diagnosis, 15 neonates (78.9%) were grade I and other were grade II. Of 19 neonates, only 1 was born full-term, with gestational age 39 weeks. The preterm neonates, based on gestational age, 7/18 were very preterm, 7/18 were moderate preterm, and 4/18 were late preterm neonates. Twelve neonates were referral from other hospital or heath care facilities and the rest was born in our hospital. The baseline characteristics of periventricular leukomalacia are listed in Table 1.

The total preterm neonates during our study period were 409 neonates, in which 300 neonates were born at our hospital. The other 109 neonates were referred from regional hospitals to our hospital (tertiary hospital). There were 28 extremely preterm neonates, 94 very preterm neonates, 90 moderate preterm neonates, and 191 late preterm neonates. The overall prevalence rate of PVL in preterm neonates at our hospital was 4.4% (18/409). Prevalence of PVL in neonates below 32 weeks was 5.7% (7/122). In four neonates, diagnosis of PVL were made within 10-14 days of life and others were made after 2 weeks of life.

The median birthweight was 1700 gram, with the highest weight was 4400 gram and the lowest weight was 1140 gram. Our study consists of 7/19 very low birth weight neonates, 10/19 low birth weight neonates, one normal birth weight neonates and one macrosomia neonates. PVL risk factors were divided into prenatal period and neonatal period. Almost all of them had respiratory distress and sepsis. Four neonates experienced seizure. We also found 2 cases of hypoxic-ischemic encephalopathy (HIE), one with hydrocephalus, and one with subarachnoid hemorrhage (SAH). Only one neonate never got any blood transfusion during hospitalization. None of the neonates died during hospitalization. All of the neonates were discharge and sent to the outpatient clinic for long-term follow-up.

Table 1. Baseline characteristics of periventricular leukomalacia.

Parameter	Total (n = 19)
Gender (n, %)	
Male	10 (52.9)
Female	9 (47.4)
Gestational age (weeks) (mean ± SD)	32.3 ±2.5
Premature (n, %)	18 (94.7)
Birth weight (gram) (median, min-max)	1700 (1140-4400)
Birth length (cm) (mean ± SD)	40.89 ±4.38
Type of delivery (n, %)	
Vaginal delivery	4 (21.1)
Caesarean delivery	15 (78.9)
Multiple pregnancy (n, %)	7 (36.8)
Maternal age (years) (median, min-max)	26 (20-44)
Maternal factors (n, %)	
Preeclampsia	3 (15.8)
Antepartum hemorrhage	1 (5.26)
Prolonged rupture of membranes	4 (21.1)
Urinary tract infection	1 (5.3)
Maternal age ≥35 years	5 (26.3)
Neonatal factors (n, %)	
Respiratory distress	15 (78.9)
Sepsis	18 (94.7)
Necrotizing enterocolitis	3 (15.8)
Shock-vasopressor requirement	4 (21.1)
Hyperbilirubinemia	13 (68.4)
Acute kidney injury	3 (15.8)
Hypoglycemia	2 (10.5)
PVL grade (n, %)	
Grade I	15 (78.9)
Grade II	4 (21.1)
Age at diagnosis of PVL (days) (mean ± SD)	21 ±7.2
Oxygenation (n, %)	
NIV	13 (68.4)
Mechanical ventilation	2 (10.5)
Blood transfusion (n, %)	
PRC	17 (89.5)
FFP	12 (63.2)
TC	6 (31.6)
Length of hospital stay (days) (mean ± SD)	28.84 ±7.26

FFP: fresh frozen plasma; NIV: non-invasive ventilation; PRC: packed red cell; PVL: Periventricular leukomalacia; TC: thrombocyte concentrate

4. Discussion

The prevalence of PVL in our hospital was 4.4% which was lower than reported in a systematic review (7.3%). [11] This number was also lower than reported in China, Korea, and India. [14, 18, 19] Most of the premature neonates with PVL (66.7%) were born >32 weeks of gestation. There was no patient with gestational age <28 weeks in our study. Kurniati N et al. also reported similar results. [15] Conversely, previous studies reported increased incidence inversely related to gestational age. [14, 19, 20] Wang et al. showed that gestation age did not vary within the cystic PVL neonates. The cystic PVL prevalence rate increased from 3.5% to 10.8% with decreased gestational age, 30 weeks to 23 weeks. [21] This result might be due to the high mortality rate in neonates below 32 weeks, especially the ones below 28 weeks of gestation. While in our hospital, bedside head ultrasound by a radiologist wasn't available so neonates were sent to the radiology department for this examination.

We had one full-term neonate with PVL who presented with neonatal seizure, SAH, and HIE. Periventricular leukomalacia might affect term neonates under some circumstances. [5] Lasry O et al. reported 15-term neonates with PVL and cerebral palsy. It was suggested that timing of injury, such as early insults in the second to early third trimester during pregnancy, is comparable to "vulnerable period" in premature-born brain; or perinatal insults [22]. These suggest that hypoxic-ischemic events and infection/inflammation during the perinatal period could lead to the development of PVL in term neonates.

Periventricular leukomalacia is the most common form of cerebral white matter injury (WMI) in preterm neonates. [23] In the past decades, advances in perinatal care have improved the survival of preterm neonates. Of these neonates, preterm birth complications could result in disabilities and decreased quality of life [24]. Several evidences suggested the immature brain was more vulnerable before 32 weeks of gestation, particularly at 23-32 weeks of gestation. [24-27] This is the high-risk period, when critical and rapid developmental processes of human brain happen. [24] Throughout this period, cerebral white matter is predominated by preoligodendrocytes (pre-OL). Preoligodendrocytes are very susceptible to hypoxia-ischemia, infection, and inflammation. These insults cause degeneration of pre-OL which leads to arrest pre-OL maturation and abnormal myelination. Disturbance of myelination will result in diffuse WMI [10, 24-26]. Pre-OL is the main cell type that role in diffuse PVL (noncystic PVL),

whereas cystic PVL consists of degeneration of all cell types [17, 23].

Grade I PVL (diffuse PVL) accounted for 78.9% of neonates and grade II was 21.1%. Diffuse PVL is the most observed form in premature neonates nowadays. [14, 19, 25] The overall burden of cystic and microcystic PVL, as the major form of PVL in preterm neonates previously, has decreased significantly by less than 5% of PVL cases. [25] This marked decline was due to advances in neonatal intensive care and neuroimaging. [16]

Perinatal risk factors such as chorioamnionitis and premature rupture of membrane have been associated with neonatal white matter injury. [6, 28] However, in our study, we didn't find chorioamnionitis in our cases medical records. As for premature rupture of membrane, we found 4/19 (21.1%) neonates, which is lower than other studies by Liu J et al. (36.7%). [14]

Neonatal sepsis was significantly higher and considered as important risk factor for PVL according to studies. [6, 7, 14, 21] Study by Firman K et al. reported 17/19 neonates had respiratory distress. [15] In our study, neonatal sepsis and respiratory distress were found in almost of PVL neonates. Neonatal seizure occurred in 21% of all neonates in this study. It was lower than was reported in K. I. Al Tawil et al. study (35%) and Tsimis et al. (28.6%). [7, 29]

The rate of PVL with multiple pregnancy was 36.8%. It was quite similar to a study in China (31.4%). [14] Wang et al. reported the number of multiple births in cystic PVL patients was 20/93 (21.5%). [21] Tsimis et al. showed lower rate 14.3% (5/35). As for blood transfusion in PVL neonates, 18/19 had blood transfusion during hospitalization. A systematic review and meta-analysis by Wang P et al. concluded that restrictive transfusion in very low birth weight (VLBW) neonates was not related with increased incidences of PVL. [30] Otherwise, in another study, PVL rates were much lower in VLBW neonates receiving restrictive transfusion than neonates receiving liberal transfusion. [31]

Periventricular leukomalacia is the most common brain injury in preterm neonates. Nevertheless, full-term neonates might be affected under certain conditions. Advanced neuroimaging like magnetic resonance imaging (MRI) is considered as the gold standard to identify PVL. Still, head ultrasound is the preferred method for initial screening and follow-up studies of PVL. [16] In this study, we used head ultrasound to diagnose PVL. Although head ultrasound has been revealed to be sensitive in identifying PVL, serial examination should be done because it could miss noncystic PVL [14, 16]. There are several limitations in this study. This is a single-center, descriptive study that included small sample size. We only included PVL patients who were diagnosed during hospitalization. The timing of the diagnosis varied because a bedside head ultrasound was unavailable. Also, assuming a higher prevalence of PVL in preterm neonates than this study reported given the possibility that PVL in unstable extremely premature neonates was not detected due to limited hospital resources.

5. Conclusion

The prevalence of PVL in preterm neonates with gestational age below 32 weeks was lower than previously reported, probably because of the high mortality rate of this group in our hospital. Diffuse (noncystic) PVL was the predominant ultrasound finding in our study. Sepsis and respiratory distress were found in more than half of our patients and almost all neonates received blood transfusion. These neonatal risk factors could be associated with PVL. Further studies are needed to evaluate these possible risk factors for PVL.

Abbreviations

FFP	Fresh Frozen Plasma
HIE	Hypoxic-Ischemic Encephalopathy
MRI	Magnetic Resonance Imaging
NICU	Neonatal Intensive Care Unit
NIV	Non-Invasive Ventilation
PRC	Packed Red Cell
PVL	Periventricular Leukomalacia
SAH	Subarachnoid Hemorrhage
TC	Thrombocyte Concentrate
VLBW	Very Low Birth Weight
WMI	White Matter Injury

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Authors Contributions

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Data Availability Statement

The data supporting the outcome of this research work has been reported in this manuscript.

Conflicts of Interest

The authors declare no conflicts of interest.

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