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Original Article

Periventricular leucomalacia in premature infants in neonatal ward, Cipto Mangunkusumo Hospital: A preliminary study

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ABSTRACT

Introduction Periventricular leucomalacia (PVL) is a major cause of neurodevelopment delay in premature infants, so early detection of the preterm infant at high risk for the subsequent development of this lesion is critical.

Objectives To determine the prevalence of PVL in premature infants hospitalized in neonatal ward, Cipto Mangunkusumo Hospital using cranial ultrasound scans and define its characteristics

Methods Premature infants hospitalized in the neonatal ward from January to July 2003 were included in this study. Clinical features were retrieved from medical charts. Ultrasound scan was performed once, after the age of 7 days and interpretations were read separately by two consultants of the radiology division.

Results Fifty-one infants were included, 21 with ≤32-week gestation, 30 with >32-week gestation; birth weight range were 1000 to 2600 gram. Nineteen infants had cystic lesion and/or dilatation of the ventricle from the cranial ultrasound scan. The prevalence of PVL in gestational age (GA) of ≤32 weeks was 6/21 and that in GA of >32 weeks was 13/30. Risk factors found in infants with PVL were maternal infection, respiratory distress, sepsis and circulatory failure.

Conclusion The prevalence of PVL in preterm infants in Cipto Mangunkusumo neonatal ward was higher than that was reported in developed countries. Maternal infection, respiratory distress, sepsis, and circulatory failure which were commonly found in these infants were factors to be considered as risks for PVL **[Paediatr Indones 2004;44:117-122-126]**

Keyword: *premature infant, periventricular leucomalacia, prevalence, cranial ultrasound scan*

Advances in prenatal and neonatal care have significantly improved neonatal survival and decreased long-term morbidity, especially in infants born at <32-week gestation. These improvement are at least partly because of better understanding of neonatal diseases and improved care for extremely low birth weight infants (<1250 grams).[1,2] Extremely small newborn infants and those born too early are of special interest for medical, economical, social, and ethical reasons. In the United States premature birth accounted for 12% of all live birth.[1] In our hospital, preterm births were up to 19% of all live births, and the smallest infant survivor had birth weight of 900 gram.[3] Experts noticed that premature infants who survived have a higher possibility to have neurodevelopmental disability, especially cerebral palsy, visual or hearing disturbance, and learning difficulties.[4-6] Hemorrhage, white matter damage (periventricular leucomalacia or PVL), and brain atrophy are some of the causes.[7-11] Periventricular leucomalacia (PVL) is a decrease in brain parenchyma. It appears on cranial ultrasonography as echoluscent lesions i.e., cavities or cysts within periventricular white matter.[8,9] The pathophysiologic features of PVL are currently hypothesized to be multifactorial, including hypoxia/perfusion failure, genetic factors, and neurochemical-mediated injury to white matter (i.e., release of cytokines with infections or release of neurotransmitters e.g. glutamate with hypoxia).[9-20]

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Ultrasound has been used regularly to detect lesions in preterm brain, which can be done on very critical infants during their hospitalization.[21,22] Neonatal centers in developed countries regularly perform cranial ultrasound scan with time protocol based on birth weight.[17,23,24] American Academy of Neurology has outlined a protocol to evaluate preterm brain.[25] Our hospital had limited facilities for delivering high care to high-risk infants, including imaging facilities. Until this study was conducted, PVL had never been recorded from our preterm survivors, which motivated us to investigate and find out the incidence of PVL in premature births.

Methods

This study was a cross sectional study. Ethical approval to study the premature infants' brain using ultrasound scan was given by the Research Ethics Committee, Medical School, University of Indonesia and parental consent was obtained for each subject. The patients were identified from the medical records of the neonatal ward, Cipto Mangunkusumo Hospital for deliveries between January and July 2003 at gestational age of less than 37 weeks with first-week hospitalization in our neonatal ward. Gestational age (GA) was determined according to the New Ballard Score[26] and approved by the supervisor of the ward. Birth record was obtained from the medical chart of the infant. Infants who survived beyond the age of 7 days underwent cranial ultrasound studies, at least once (without a certain time protocol to follow).

Ultrasound studies

The ultrasound data collections were performed by 2 pediatric-radiologists who had kappa of 0.57 between them (moderately good). All sonographic studies were performed with a high-frequency transducer (Digital Gaia MT Sonoace 8800; 7.5 MHz) and preserved for further assessment by hard copy and computer data (JPEG file). The data at least contain 3 frames of coronal and/or sagittal views; all used the anterior fontanel as the sonographic window. There was neither any time-set protocol to do the ultrasound data collection nor a detailed scanning procedure. All lesions were described as cysts or ventriculomegaly.

Data retrieval

The medical charts of the infants were reviewed for the presence or absence of the following characteristics including prolonged rupture of the membranes (PROM, defined as rupture for $\geq$18 hours), pregnancy induced hypertension (defined as a systolic blood pressure of >140 mmHg and a diastolic blood pressure of >90 mmHg, plus proteinuria with or without edema), multiple pregnancy, maternal infection (defined as maternal fever of >38^{o}C, leukocytes of >15,000/ml, or signs of chorioamnionitis-like foul smelling discharge, uterine tenderness, and fever-), 1- and 5- minute Apgar scores, the need for delivery room resuscitation, birth weight, respiratory distress (defined as grunting, periodic apnea, retraction, hypoxia), the need for volume expanders with or without inotropic medications to support circulatory function in the neonatal period, evidence of sepsis, necrotizing enterocolitis (NEC), and patent ductus arteriosus (PDA) requiring either medical or surgical ligation.

A cystic lesion was defined either as echoluscent lesions observed in both coronal and sagittal views of periventricular area or ventricular dilatation with irregular lining. Echodense lesion was not included in this study because ultrasound examination was performed after 7 days of age.

Consensus reading

Each set of scan was read independently twice by two pediatric-radiologist consultant. Their interpretation was recorded separately. For final agreement individualized for each patient, the images were read together and final decision was made for each infant.

Results

Subjects' characteristics

Ninety-five infants were admitted to the neonatal ward with the diagnosis of prematurity. Gestational age was

reaffirmed by the supervisor of the ward. Nine of these infants were term but small-for-date. Fifteen infants died before 7 days of age and 17 were missed to enter the study because they were discharged before 7 days of age or transferred to other hospitals. Until the end of the study, 1 infant did not undergo ultrasound scan and 2 sets of infant data were lost. Finally, we had 51 infant data to consider.

Thirty infants were of >32-week gestation (59%) and 21 of ≤32-week gestation. Birth weight ranged from 1000 to 2600 grams with 53% (27/51 infants) had birth weight of >1500 grams. There were no data about maternal chorioamnionitis, although maternal infections were recorded in 27 infants (53%). PROM was only found in 10/51 mothers. Asphyxia on 5-minute Apgar score affected only 11/51 infants (22%).

Recorded postnatal complications were respiratory distress, circulatory failure, cyanosis, sepsis, and hyperbilirubinemia. From all studied infants, respiratory distress affected 90% of the infants, while circulatory failure affected 69% (35/51). Cyanosis was noted on 29% of them (15/51). Sepsis with positive blood culture was documented in 32/51 (63%) infants and hyperbilirubinemia affected almost 57% (29/51) of them.

Cranial ultrasound findings

Images were obtained in 51 infants, who , at the time of examination, had a median chronological age of 21 days (the earliest was 8 days, and the latest was 38 days). PVL lesions were observed in 19 (37%) infants. The prevalence of PVL in infants with ≤32 week-gestation was 6/21 while in those with>32 week-gestation was 13/30. It was noted that PVL was more frequent found in infants with GA of 35 weeks

Cystic lesions were noted in 15 infants, ventriculomegaly in 7 infants. Four infants had both ventriculomegaly and cystic lesions with irregular lining. Cystic lesions were recorded mostly in infants having ultrasound scan beyond the second week of life. Ventriculomegaly was seen as early as 8 days age. The size of the dilatation of the ventricle was not measured in this study. (Kappa's agreement between 2 reader after the study was 0.63, which was categorized as good)

Other findings were intraparenchymal echodense that suggested the possibility of hemorrhage which was in accordance with the clinical appearance of the infants. This finding was found in 3 subjects. Cranial ultrasound scan performed in 2 weeks apart showed decreased area of hyperdensity.

Clinical characteristics of infants with PVL

Among 19 infants with PVL lesion, PROM was only found in 5 of them although maternal infection was found in 9 infants (**Table 1**). Respiratory distress, circulatory failure, and sepsis were found almost in all of them.

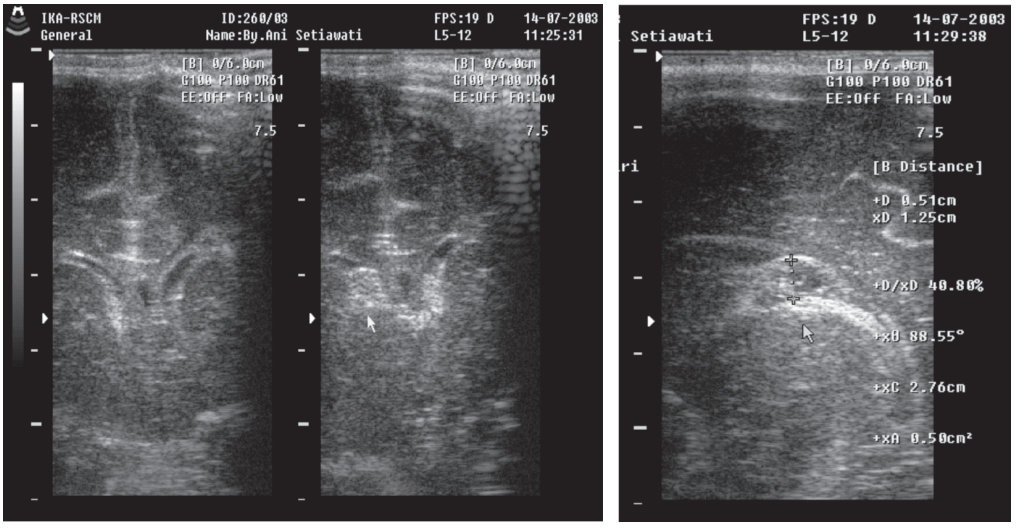

Figure 1. Cystic lesion in periventricular area

TABLE 1. CHARACTERISTICS OF 19 INFANTS WITH PVL

Clinical features	GA ≤32 wk (n=6)	GA >32 wk (n=13)
Birth weight (mean) (grams)	1437	1808
5-minute Apgar score ≤6	2	4
>6	4	9
Preeclampsia	3	4
PROM	1	4
Maternal infection	4	5
Respiratory distress	6	11
Circulatory failure	4	10
Sepsis	4	8
Hyperbilirubinemia	3	6
Time of US (mean) (day)	21	21
Image Cysts lesion	3	12
Ventriculomegaly	4	3

US=ultrasound

In 4 infants with both cyst lesion and ventricular dilatation, one had a quite extensive lesion and his early clinical appearance was seen as spasticity of the lower extremities and right side arm. **Figure 1** shows cystic lesions of this infant.

Two out of 19 infants died during hospitalization. Two infants showed spasticity of only lower extremities and 2 infants had feeding problem. Infants with PVL were sent to the outpatient clinic for long-term follow-up after hospital discharge.

Discussion

Only 54% of the premature infants who were hospitalized in our hospital underwent cranial ultrasound scan. More than half of premature infants with GA of <32 weeks died in our hospital. The most common cause of death was infection, similar to that mentioned by Barton.[5] Unfortunately chorioamnionitis was not recorded in the maternal medical chart, so that comparison could not be done with literature data. Perlman[16] stated that chorioamnionitis and/or PROM history were important risk factors for preterm birth and subsequent PVL.

Maternal infection in this study was recorded higher compared to that of other study (9/19); it was probably the main cause of premature birth. The same condition was found in PROM (20% of all infants compare to Perlman's[16] data of 6%). Based on these two conditions, the risk of infection in premature infants was high on our study.

Respiratory distress was found in 17 out of 19 infants and was managed without using mechanical ventilation because of lack of such facilities in our ward. This was higher than that reported by Fujimoto[15] (30.8%) or Perlman[16] (22%). Monitoring of distress or cyanosis in these infants was done by clinical observation indicating that mild ischemia was likely to be missed. According to Perlman observation and others working on the same problem, even such mild ischemia can be harmful to preterm brain.[10,11,16,18]

In this study, we found that the PVL prevalence for infant less than 32 week-gestation was

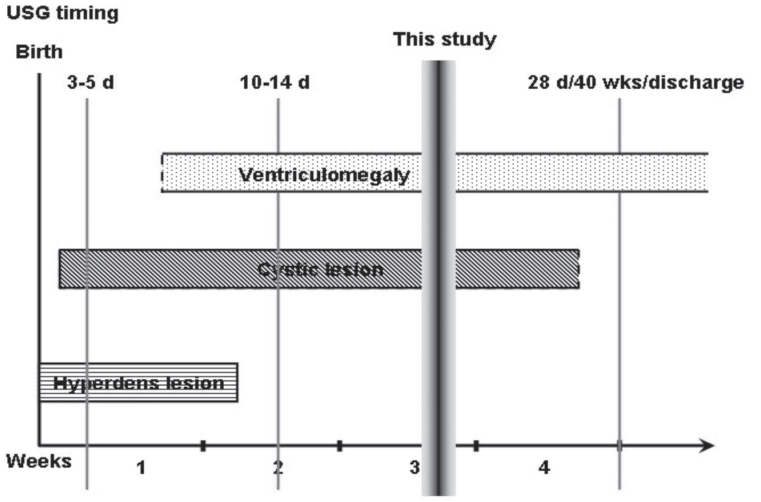

Figure 2. Timing of cranial ultrasound scans

6/21, higher than reported by Murphy *et al*[23] (6.8%) who worked on the same gestational age. It might be because the mortality was still high and infants who had chance to undergo cranial ultrasound scan were limited. The same condition was found in older infant. The occurence of PVL in preterm infants of >32-week gestation was 13/30. It was higher than that was reported by Graziani *et al*[14] (8.9%) or Fujimoto *et al*[15] (7.8%).

We did not expect to find hyperdense lesion such as mentioned by Volpe[9] because ultrasound scan was performed after the age of first week. Protocol to screen premature infant had not been developed in our hospital and infant must be transported to the radiology unit to have an ultrasound scan. Screening protocol for preterm brain is well developed in some countries and long-term management can be delivered to ensure adequate growth and development. **Figure 2** shows the comparisons of time protocol for performing cranial ultrasound scan in developed countries to that was used in this study.

We concluded that premature infants of less than 32-week gestation survived less than older preterm infants in our hospital. PVL as a consequence of brain insult was found higher than that was reported in literatures, both in infants of less than 32-week gestation and the older ones.

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