**Periventricular Leukomalacia with Late-Onset Circulatory Dysfunction of Premature Infants: Correlation with Severity of Magnetic Resonance Imaging Findings and Neurological Outcomes**

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KOBAYASHI, S., FUJIMOTO, S., FUKUDA, S., HATTORI, A., IWAKI, T., KOYAMA, N., TANAKA, T., KOKUBO, M., OKANISHI, T. and TOGARI, H. Periventricular Leukomalacia with Late-Onset Circulatory Dysfunction of Premature Infants: Correlation with Severity of Magnetic Resonance Imaging Findings and Neurological Outcomes. Tohoku J. Exp. Med., 2006, 210 (4), 333-339 — The incidence of late-onset circulatory dysfunction (LCD) of premature infants, which is characterized by sudden hypotension and oliguria, has recently increased in Japan. This condition suddenly occurs after several days of age without obvious causes in preterm infants with stable respiration and circulation. Intravenous steroids frequently improve the hypotension. The main problem with LCD is the subsequent and frequent onset of periventricular leukomalacia (PVL), and neurological development appears to be worse in PVL patients with LCD than those without LCD. The aim of this study was to determine whether the severity of magnetic resonance imaging (MRI) findings and neurological outcomes differ between infants who developed PVL after LCD and those who developed PVL without LCD. We retrospectively studied preterm infants who were delivered at less than 33 weeks of gestation between the years 2000 and 2003. During the study period, 10 and 26 infants developed PVL with and without LCD, respectively. The incidence of severe or moderate MRI findings was significantly higher in PVL patients with LCD (100%) than those without LCD (50%; p < 0.05). The incidence of severe cerebral palsy was 88% in PVL infants with LCD and 43% in PVL infants without LCD (p < 0.05). Moreover, the incidence of visual disorders was significantly higher in PVL infants with LCD (63%) than those without LCD (9%; p < 0.01). In conclusion,
Episodes of hypotension and oliguria that suddenly appear in preterm infants who are generally stable after the acute stage have been reported, mainly in Japan. This condition was originally recognized in Japan in 1996 (Suzuki et al. 1996). Thereafter, two reports were published in 2001 (Hamajima et al. 2001; Nagasaki et al. 2001) and the number of reports describing this type of hypotension has gradually increased since then. Such sudden hypotension episodes are referred to as late-onset circulatory dysfunction (LCD) of premature infants. Although the pathogenesis of LCD remains unclear and criteria have not been established, such hypotension and oliguria that suddenly occur in apparently stable preterm infants after several days of delivery are resistant to volume expanders and inotropic agents, whereas intravenous steroids (dexamethasone or hydrocortisone) are effective (Koyama et al. 2005; Nakanishi et al. 2005). Hyponatremia, hyperkalemia and excessive body weight gain are also frequently evident (Nakanishi et al. 2005). The key issue associated with such episodes is the subsequent and frequent onset of periventricular leukomalacia (PVL), which comprises lesions in the cerebral white matter of the immature brain that develop cysts about 2 weeks after events such as ischemia. PVL usually appears at 2 to 3 weeks of age. Despite advances in the intensive care of preterm infants, PVL remains the main cause of cerebral palsy (CP): spastic diplegia in mild cases, tetraplegia and extreme mental retardation in severe cases. Nakanishi et al. (2005) reported that this hypotension episode was significantly associated with the late development of PVL in 7 (10.9%) of 64 infants, and Koyama et al. (2005) reported that 6 (9.5%) of 63 LCD infants developed PVL. Iijima and Ohzeki (2005) described an infant with extremely low birth weight who developed cerebral infarction after sudden hypotension and oliguria 34 days after delivery. Patients who developed PVL with this type of hypotension appear to have worse neurological development than those with PVL that is not related to such episodes of hypotension. In this study, we compared the magnetic resonance imaging (MRI) findings and neurological development between infants who developed PVL with and without LCD.

**Patients and Methods**

**Patients**

We retrospectively studied preterm infants who were delivered at less than 33 weeks of gestation between the years 2000 and 2003 and who were followed up at six hospitals (Nagoya City University Hospital, Nagoya, Japan; Gifu Prefectural Tajimi Hospital, Tajimi, Japan; Toyohashi Municipal Hospital, Toyohashi, Japan; Nagoya Second Red Cross Hospital, Nagoya, Japan; Kainan Hospital, Yatomi, Japan; and Seirei-Mikatahara Hospital, Hamamatsu, Japan). Infants with chromosomal or any other major anomalies were excluded from the study. We classified infants who were diagnosed as PVL by ultrasonography or MRI into two groups depending upon whether or not PVL developed after LCD (PVL with LCD or PVL without LCD). We defined PVL with LCD as an episode of LCD in an infant with no head abnormalities according to ultrasonography at the time of LCD and in whom PVL developed over 10 days thereafter. We defined PVL without LCD as a confirmed diagnosis of PVL but without LCD episodes. This study was proceeded according to the ethics committee of Nagoya City University.

**Definition of LCD**

We defined LCD as the sudden development of hypotension or oliguria requiring treatment without obvious causes such as sepsis, patent ductus arteriosus (PDA), or intraventricular hemorrhage (IVH) in preterm infants with circulatory and respiratory conditions that had been stable for several days. Hypotension was defined as a
blood pressure below 80% of the mean value before the episode, and oliguria was defined as at least one of the following: (1) passed less than 50% of the urine volume before the episode over 8 hrs, (2) passed less than 1 ml/kg/hr of urine over the past 8 hrs, or (3) anuria during the past 4 hrs (Koyama et al. 2005). A blood examination including acute phase protein and culture was performed to exclude sepsis as a cause. We confirmed that C-reactive protein and blood cultures were all negative. Ultrasonography also excluded PDA and IVH as a cause of hypotension.

MRI findings and neurological outcomes

We compared gestational age, birth weight, gender and postnatal age at which a periventricular cyst was initially discovered among the infants diagnosed by ultrasonography. We also compared the grade of severity in head MRI findings between PVL with and without LCD in infants at over 10 months of age. Grades of MRI findings were as follows: mild, localized white matter damage without enlargement of the lateral ventricle; moderate, obvious white matter damage with mild enlargement of the lateral ventricle; severe, diffuse white matter damage with extreme enlargement of the lateral ventricle (Fig. 1). One of the authors (S.K.) evaluated all of the images.

We studied the occurrence of CP, epilepsy, visual disorders and auditory disorders as well as the severity of CP (severe or mild) in infants who were followed up for at least 2 years. Grades of CP were established as follows: infants who could not hold their heads up as having “severe CP” and those who could hold their heads with some movement dysfunction “mild CP” at over 2 years of age.

Statistical analysis

Statistical analyses were performed using SPSS for Windows (ver. 13.0). We compared continuous data using Mann-Whitney’s U-test and categorical data using the Fisher’s exact test. Multivariate logistic regression analysis was performed on factors which were found to be significant in univariate analysis. A probability value of $p < 0.05$ was considered statistically significant.

RESULTS

During the study period, 36 infants were diagnosed as PVL by ultrasonography or MRI. Of these, 10 infants (27.8%) developed PVL after LCD. The average day of LCD onset in PVL was $22.6 \pm 10.4$ days. Another 26 infants (72.2%) developed PVL without LCD.

Gestational age was significantly lower in PVL infants with LCD than those without LCD ($27.7 \pm 1.7$ vs $29.9 \pm 1.8$ weeks; $p < 0.01$) (Table 1). The birth weight was significantly lower in PVL infants with LCD than those without LCD ($1,077 \pm 364$ vs $1,300 \pm 326$ g; $p < 0.05$). The

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Fig. 1. Grade of MRI findings
A: Mild, localized white matter damage without enlarged lateral ventricle. B: moderate, white matter somewhat reduced with mildly enlarged lateral ventricle (arrows show irregular ventricular dilation that was most obvious posteriorly). C: severe, diffuse white matter is damaged with extreme enlargement of lateral ventricle (white matter adjacent to lesions from anterior horns [open arrows] to trigones [solid arrows] is lost).
day in which periventricular cysts were initially discovered by ultrasonography was significantly later in PVL patients with LCD than those without LCD (49.4 ± 17.5 vs 19.3 ± 9.3 days; \(p < 0.001\)) (Table 1).

Of the 36 infants with PVL, 3 died during infancy and follow-up of 2 infants was lost because the parents moved. We excluded these five patients and studied the neurological outcomes of PVL with \((n = 8)\) and without \((n = 23)\) LCD. The characteristics of these PVL infants with vs without LCD were as follows: gestational age, 27.6 ± 1.5 vs 29.8 ± 1.8 weeks, \(p < 0.01\); birth weight, 1,047 ± 285 vs 1,269 ± 333 g, \(p = 0.08\). Seven (88%) PVL patients with LCD and 22 (96%) without LCD developed CP (\(p = 0.46\)) (Table 2). The incidence of severe CP was much greater in PVL patients with LCD (7 infants, 88%) than those without LCD (10 infants, 43%; \(p < 0.05\)). The incidence of visual disorders was significantly higher in PVL with LCD (5 infants, 63%) than without LCD (2 infants, 9%; \(p < 0.01\)). The occurrence of epilepsy and auditory disorders did not significantly differ (Table 2).

Eighteen of the 36 infants (PVL with and without LCD, \(n = 6\) and \(n = 12\), respectively) were followed-up by MRI at over 10 months of age (Table 3). The characteristics of these PVL infants with vs without LCD were as follows: gestational age, 27.6 ± 1.7 vs 29.7 ± 1.8 weeks, \(p < 0.05\); birth weight, 1,053 ± 317 vs 1,255 ± 341 g, \(p = 0.19\). The MRI findings from PVL infants with LCD indicated 4 severe (67%) and 2 moderate cases (33%), whereas the MRI findings from those without LCD indicated 2 severe (17%), 4 moderate (33%) and 6 mild cases (50%). All six infants with LCD had severe or moderate MRI findings (100% vs 50% for PVL without LCD; \(p < 0.05\)) (Table 3). In multivariate logistic regression analysis, none of factors being significant in univariate analysis were independently significant. When the model was run with visual disorder as a single independent variable, it was significant (\(p < 0.01\)). With gestational age and birth weight added to this model, it remained significant (\(p < 0.05\)). When the severities of CP

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<th>Table 1. Characteristics of PVL infants with and without LCD.</th>
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<td>PVL with LCD ((n = 10))</td>
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<tr>
<td>Gestational age (wk)</td>
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<td>Birth weight (g)</td>
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<td>Day of first detection of periventricular cysts (d)</td>
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<td>Gender (male)</td>
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Statistical analyses were performed using Mann-Whitney’s U-test or Fisher’s exact test. \(*p < 0.05\) is considered statistically significant difference.

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<th>Table 2. Neurological outcomes of PVL infants with and without LCD.</th>
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<td>PVL with LCD ((n = 8))</td>
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<tr>
<td>CP</td>
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<td>Severe CP</td>
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CP, cerebral palsy.
Statistical analyses were performed using Fisher’s exact test. \(*p < 0.05\) is considered statistically significant difference.
or MRI findings were added to this model, it failed to achieve significance (data not shown).

**DISCUSSION**

In this study, PVL infants with LCD had more severe MRI findings and developed more severe CP than those without LCD. The pathogenesis of PVL development in patients with LCD is thought to be remarkable hypotension that might lead to a striking decrease in cerebral blood flow (CBF) to the white matter. Young et al. (1982) demonstrated that regional CBF to the periventricular and occipital white matter significantly decreases during severe hypotension in newborn dogs, whereas regional CBF to all gray matter structures is preserved. Matsuda et al. (1999) reported that 5 of 6 fetal sheep with hemorrhagic hypotension exhibited periventricular white matter injuries similar to clinical PVL and neither of the controls had any lesions. Postnatal hypotension was associated with an increased risk of echolucency or white matter damage (Miall-Allen et al. 1987; Watkins et al. 1989; Low et al. 1993). These reports support the notion that hypotension is associated with PVL, yet some others have reported that hypotension is not associated with PVL (Trounce et al. 1988; Perlman et al. 1996; Dammann et al. 2002; Resch et al. 2004). Recent studies of PVL pathogenesis have focused on maternal inflammation such as chorioamnionitis in which cytokine release is thought to play a role (Murphy et al. 1995; Perlman et al. 1996; Resch et al. 2000; Wu and Colford 2000). However, PVL actually developed in our infants 2 to 3 weeks after the onset of LCD. Therefore, we presume that hypotension during LCD is associated with the development of PVL. Moreover, volume expanders and inotropic agents are often clinically administered as first line strategies against hypotension and then intravenous steroids might be administered if the hypotension remains resistant. This time lag might be sufficient to cause longer ischemia in the cerebral white matter and be related to the development of severe PVL. However, the pathogenesis of LCD remains obscure although it is considered an adrenal dysfunction because volume expanders and inotropic agents are ineffective whereas intravenous steroids are significantly effective in most cases. Brain injury in cerebral ischemia is currently thought to consist of apoptosis, excitotoxicity (e.g., glutamate and aspartate) and inflammation (Harukuni and Bhardwaj 2006). Besides damage to the cerebral white matter as a direct consequence of remarkable hypotension, other unknown factors might cause severe PVL during LCD. Future studies are necessary to clarify the pathogenesis of LCD and the association between LCD and PVL.

We also found significant differences in visual disorders. The degree of visual acuity in patients with PVL was related to a reduction in the amount of peritrigonal white matter where optic radiations run (Uggetti et al. 1996). Thus, our findings might be attributable to the more severe grade of MRI findings in PVL with LCD.

Gestational age was significantly lower in PVL with LCD than those without LCD. We do not know whether this means that preterm infants of lower gestational age tend to develop LCD compared with those of higher gestational age, or that preterm infants of lower gestational age with LCD tend to develop PVL compared with those of higher gestational age. Volpe (2001) described that the vascular supply to the cerebral white matter consists of long and short penetrating
Limbic System Dysfunction- multiple institutions study-. Demonstrated that brain developmental stage is an important intrinsic factor in antenatal PVL induced by hemorrhagic hypotension in fetal sheep. These findings mean that vulnerable end zones exist in the cerebral white matter of preterm infants of lower gestational age. These anatomical characteristics might explain why preterm infants of lower gestational age who develop LCD might be at higher risk of developing PVL. The significant difference in gestational age between the groups in the present study might affect our findings. However, the severity of MRI findings with PVL was not associated with smallness of gestational age (Olsen et al. 1997). Ventriculomegaly and the reduction in white matter did not differ between PVL patients over and under 28 weeks of gestational age (Fujimoto et al. 1999). Thus, the present study supported the notion that MRI findings and neurological outcome significantly differ between PVL infants with and without LCD despite the different gestational ages of the two groups.

Periventricular cysts were initially detected far later in PVL with LCD than those without LCD. This difference results from our finding that the average age at which LCD developed was 22.6 ± 10.4 days. Therefore, the onset of LCD would be late. The latest time of LCD onset in our infants was 37 days of age and PVL was initially identified at 61 days of age in the patient described herein. Blood pressure might not be checked so frequently and urine volume might no longer be measured if the general condition of a preterm infant is stable at over one month of age. The onset of LCD must be considered and vital signs should be carefully checked during the management of preterm infants, especially those delivered between 24 and 28 weeks of gestational age. A delay in administering treatment might lead to the occurrence of PVL and the development of severe CP. Therefore, when a hypotension episode is suspected to be due to LCD, the immediate administration of steroids should be considered. If the duration from the onset of LCD to the beginning of steroid administration were shorter, this might help to prevent negative outcomes in the neurological development of infants with LCD.

The average day on which cystic PVL with LCD was diagnosed (49.4 ± 17.5 days) was over 3 weeks after the average day at which LCD occurred (22.6 ± 10.4 days) in our study. This might be attributed to a decrease in the frequency of ultrasonography at over one month of age in some patients.

We postulate that PVL with LCD leads to a worse neurological outcome than that without LCD. More studies are needed to establish the pathogenesis and treatment of LCD.

References


