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ORIGINAL ARTICLE

Neurodevelopmental Outcomes of Children with Periventricular Leukomalacia

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Key Words
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walking ability

Objectives: To examine the neurodevelopmental outcomes of children with periventricular leukomalacia (PVL).
Materials and methods: Twenty-five children diagnosed with grade 1, 2 or 3 PVL on the basis of magnetic resonance imaging (MRI) findings between January 2002 and December 2011 were enrolled and followed from 15 months to 10 years of age.
Results: Of the 25 children, one was a term and 24 were preterm-births. Nine (36%) had spastic diplegia and 12 (48%) had quadriplegia. Ten of the 25 (40%) were able to walk independently at 36 months utilizing short leg braces, whereas 13 children (52%) were unable to walk independently. MRI findings revealed grade 1 PVL in nine (36%), grade 2 in 12 (48%), and grade 3 in four (16%) of the 25 children. Eleven of the 16 children (69%) with grade 2 or 3 PVL had Papile III or IV intraventricular hemorrhage (IVH), and many of these children had severe neurologic motor abnormalities, severe psychomotor delay, and seizures. Five of the nine children (56%) with grade 1 PVL had normal psychomotor development. There were statistically significant differences in the motor impairment and walking ability between the children with grade 1 and those with grade 2 PVL ($p = 0.008$ and 0.005, respectively).
Conclusion: Most children with grade 2 or 3 PVL had severe neurodevelopmental delays, but attention should also be paid to the 56% of children with grade 1 PVL who presented with

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normal psychomotor development. Further studies of larger populations, including long-term follow-up, are necessary to evaluate the outcomes of children with PVL.

1. Introduction

Periventricular leukomalacia (PVL) is the predominant form of brain injury underlying neurologic morbidity and is the most common cause of cerebral palsy (CP) in premature infants.[1] In the United States, approximately 55,000 live newborns are born with very low birth weights (LBW) each year, with approximately 10% subsequently exhibiting CP.[2] PVL occurs in term, as well as preterm infants, as shown by neuroimaging studies.[3] However, there have been few long-term follow-up studies of PVL in children in Japan. The purpose of this study was to examine the neurodevelopmental outcomes of children with PVL from the neonatal period to childhood.

2. Materials and Methods

2.1. Definitions

The diagnosis of PVL was established on the basis of magnetic resonance imaging (MRI) findings,[4] and severity was graded as 1, 2, or 3 according to the following criteria: (1) PVL grade 1. An abnormally high signal intensity in the periventricular white matter on T2-weighted images and fluid-attenuated inversion recovery images, most commonly observed bilaterally in the trigone regions of the lateral ventricles (Figure 1A); (2) PVL grade 2. Loss of the periventricular white matter in the regions with abnormally high signal intensities, and ventricular enlargement adjacent to the regions of the lateral ventricles (Figure 1B); and (3) PVL grade 3. Focal and extensive cystic changes in the white matter (Figure 1C).

Gestational age (GA) was determined on the basis of the last maternal menstrual period, obstetric history, and examination and prenatal ultrasound findings. A term infant was defined as a neonate born at or after 37 weeks of gestation. Small for GA was defined as a BW under the 10th percentile for GA in accordance with the gender-specific growth charts of Kramer et al.[5] Intraventricular hemorrhage (IVH) was diagnosed by ultrasonography and graded in accordance with the definitions in Papile et al.[6] Retinopathy of prematurity was diagnosed by an ophthalmologist in our hospital and classified in accordance with an international classification of retinopathy of prematurity.[7]

2.2. Patients

Our study was conducted at Takeda General Hospital in Fukushima Prefecture, Japan. Takeda General Hospital is a general hospital located in the western part of Fukushima and equipped with 939 beds. One thousand two hundred and twenty infants were admitted to the neonatal intensive care unit (NICU) of Takeda General Hospital, from January 2002 to December 2011. Among them, 30 children were diagnosed with PVL. Five children were excluded from this study due to the absence of follow-up data. The remaining 25 children were completely followed from 15 months to 10 years of age and the findings analyzed.

All 25 children satisfied the definition of PVL based on MRI findings. On the basis of Volpe's study,[2] MRI was routinely performed on infants meeting the following criteria in our NICU: (1) a GA of $<$32 weeks or a BW of $<$1500 g with the infant under mechanical ventilation; (2) the presence of specific conditions, such as severe asphyxia, and neurological findings, including apnea, after the expected date of confinement; (3) abnormal cranial ultrasonographic findings, such as hyperechogenicity of the cranium higher than that of the choroid plexus or cystic changes in the periventricular white matter; and (4) the

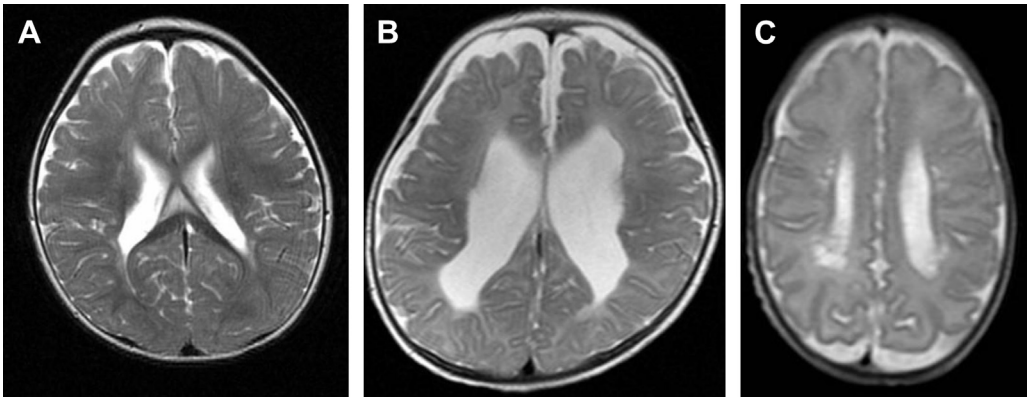

Figure 1 Periventricular leukomalacia (PVL) grades determined on the basis of magnetic resonance imaging (MRI) findings (T2-weighted imaging sequences in the transverse plane): (A) PVL grade 1; (B) PVL grade 2; (C) PVL grade 3.

presence of gait disturbance, such as toe-walking, at the toddler stage. Infants with myelodysplasias, neuromuscular diseases, or genetic or metabolic diseases were excluded from this study.

2.3. MRI

Sequential conventional MRI studies were performed under pharmacologic sedation on an Intera Achieva 1.5 Tesla MRI system (Philips Medical Systems, The Netherlands). We obtained conventional spin-echo magnetic resonance images consisting of axial T1-weighted image (TR = 400 ms, TE = 6 ms, FOV = 220 mm, slice thickness = 5 mm) and T2-weighted image (TR = 4000 ms, TE = 110 ms, FOV = 220 mm, slice thickness = 5 mm) sequences in both the transverse and sagittal planes. The first MRI session was performed prior to discharge from our hospital. Magnetic resonance images were reviewed by radiologists and pediatricians in our hospital.

2.4. Neurodevelopmental evaluation

Children were assessed at between 12 months and 72 months of age, to determine motor and cognitive outcomes. Motor impairment was determined on the basis of physical examination showing changes in tone, strength, reflexes, posture, and motor skills. Motor impairment subtype was determined on the basis of the following well-recognized classification profile at the most recent objective assessment[8]: (1) spastic diplegia (spasticity in the lower extremities, which may or may not be relatively asymmetric, far in excess of any discernible spasticity in the upper extremities); and (2) spastic quadriplegia (spasticity in all four limbs with equivalent or greater spasticity in the upper extremities). A standardized neurologic examination was performed and recorded by a pediatrician. Cognitive outcomes were assessed by a physical and occupational therapist in Takeda General Hospital using the Tsumori-Inage Scale (M. Tsumori and N. Inage 1961, printed by Dainippon Tosho Publishing Co., Ltd., Japan), the Japanese version of the Psychological Development Screening or Judgment Test. It provides for differences in age range (1 month to 12 months, 12 months to 36 months, 36 months to 84 months), is used to identify deficits in young children and includes items covering the motor domains, performance, social abilities, cognitive, and language. The developmental quotient (DQ) was categorized as within normal limits (>85), mild to moderate psychomotor delay (60–85), or severe psychomotor delay (<60). Children who were too disabled for cognitive testing were assigned a quotient of 50 for this study.

2.5. Data collection and statistical analysis

Data were collected from perinatal case records. A p value of 0.016 (0.05/3) or less obtained using Fisher's exact test with Bonferroni correlation was considered to be statistically significant. This study was approved by the ethics committee of the Takeda General Hospital.

3. Results

3.1. Clinical characteristics

Table 1 shows the perinatal characteristics for the 25 children. The 25 children consisted of 17 singletons and eight multiple births (twin and triplets). The median GA of these children was 29.6 weeks (range = 25–38 weeks). There were one term and 24 preterm birth children. The median BW of these children was 1276 g (range = 800–3572 g). The median Apgar scores at 1 minute and 5 minutes were 6 (range: 1–8) and 8 (range: 5–9), respectively. None of the mothers received prenatal steroid treatment.

3.2. Clinical courses

Table 2 shows the clinical courses of the 25 children. Eleven children (44%) required mechanical ventilation for either bronchopulmonary dysplasia (n = 9) or apnea (n = 2) for

Table 1 Perinatal characteristics for the 25 children.

Female sex	12 (48)
Fetus number	
Singleton	17 (68)
Multifetus	8 (32)
Gestational age	
<26 wk	3 (12)
26–28 wk	8 (32)
29–32 wk	8 (32)
33–36 wk	5 (20)
>36 wk	1 (4)
Median (range) wk	29.6 (25–38)
Birth weight	
<1000 g	9 (36)
1000–1499 g	11 (44)
1500–1999 g	2 (8)
2000–2500 g	0
>2500 g	3 (12)
Median (range) g	1276 (800–3572)
Mode of delivery	
Vaginal	5 (20)
Cesarean section	20 (80)
Birth place	
In born	17 (68)
Out born	8 (32)
Apgar score	
1 min, median (range)	6 (1–8)
5 min, median (range)	8 (5–9)
Small for gestational age	1 (4)
Antenatal corticoid	
Administered	0 (0)
Not administered	25 (100)

Data presented as n (%) unless otherwise indicated.

Table 2 Clinical courses of the 25 children.

Mechanical ventilation	
None	5 (20)
<1 wk	4 (16)
1–4 wk	5 (20)
5 wk–6 mo	8 (32)
>6 mo	3 (12)
IVH	
Grade I or II	11 (44)
Grade III or IV	14 (56)
Retinopathy of prematurity stage	9 (36)
1	0
2	5
3	1
4	0
5	3
Necrotizing enterocolitis	1 (4)
Length of hospitalization	
<1 mo	3 (12)
1–5 mo	17 (68)
6–12 mo	1 (4)
>12 mo	4 (16)
Grade of PVL	
1	9 (36)
2	12 (48)
3	4 (16)
Confirmed diagnosis of PVL	
<1 mo	7 (28)
1–5 mo	8 (32)
6–12 mo	1 (4)
>12 mo	9 (36)
Motor impairment	
Diplegia	9 (36)
Quadriplegia	12 (48)
Following	4 (16)
Walking	
1.5–2 y	3 (12)
2–3 y	4 (16)
>3 y	4 (16)
Following	1 (4)
Inability	13 (52)
Treatment for walking disorder	
Short leg brace	8 (32)
Wheel chair	6 (24)
Botulinum toxins	4 (16)
Achilles' tendon extension	1 (4)
No treatment	11 (44)
Epilepsy	8 (32)
West syndrome antiepileptic treatment	6 (24)
Clonazepam	6
Valproic acid	3
Zonisamide	3
Adrenocorticotropic hormone	2
Lamotrigine	2
Vitamin B6	2
Carbamazepine	1
Developmental quotient	
>85	5 (20)
60–85	1 (4)
<60	17 (68)
Not examined	2 (8)
Current age	
1–3 y	8 (32)
4–6 y	10 (40)
7–10 y	7 (28)

Data presented as *n* (%). IVH = intraventricular hemorrhage; PVL = periventricular leukomalacia.

>4 weeks, with three of the 11 (27%) children requiring it for >6 months, due to severe bronchopulmonary dysplasia. Eleven of the children (44%) had IVH Papile grade I or II and 14 (56%) children had Papile grade III or IV. Nine children (36%) had retinopathy of prematurity, with three of the nine (33%) children having no visual ability. Sixteen children (64%) were diagnosed with PVL at less than 12 months, and the remaining nine (36%) children were diagnosed with PVL, with walking abnormalities, after 12 months. Among the 25 children, nine (36%) had spastic diplegia and 12 (48%) had spastic quadriplegia. The remaining four children (16%) did not yet satisfy either definition of motor impairment type. Ten of the 25 children (40%) were able to walk independently at 36 months utilizing short leg braces. Botulinum toxin therapy was administered in four children (16%) with walking disorders. Thirteen of the children (52%) were unable to walk independently. Eight of the 25 children (32%) had epilepsy, and six of these eight children (75%) were diagnosed with West syndrome in their first year of life. None of these eight could walk independently, and all showed a DQ of <50. Seventeen children (68%) had severe psychomotor delay, such as a DQ of <60. Two children were unable to perform the developmental judgment test completely. Currently, eight (32%) of the 25 children are aged 1–3 years, 10 (40%) are aged 4–6 years, and seven (28%) are aged 7–10 years.

3.3. Different grades of PVL

Table 3 shows a comparison of the clinical courses according to the different grades of PVL. MRI revealed PVL grade 1 in nine (36%), PVL grade 2 in 12 (48%), and PVL grade 3 in four (16%) of the 25 children. Eleven of the 16 children (69%) with PVL grade 2 or 3 had IVH graded at Papile III or IV. There were no statistically significant differences in IVH grade and DQ or in the prevalence of epilepsy among children with different grades of PVL. Seven of the nine children (78%) with PVL grade 1 were able to walk independently, and five (56%) of them presented with a DQ of 85 and over. The remaining 3 (33%) children with PVL grade 1 showed a DQ of <85. There were statistically significant differences in the motor impairment and walking ability between children with PVL grade 1 and those with grade 2 ($p = 0.008$ and 0.005, respectively).

Table 3 Comparison of clinical courses by grade of periventricular leukomalacia.*,†

PVL grade	1	2	3	*p*		
n (%)	9 (36)	12 (48)	4 (16)	PVL 1 vs. 2	PVL 1 vs. 3	PVL 2 vs. 3
IVH						
I, II	6 (I 6, II 0)	4 (I 3, II 1)	1 (I 1, II 0)	0.198	0.245	1.000
III, IV	3 (III 1, IV 2)	8 (III 7, IV 1)	3 (III 2, IV 1)			
Motor impairment						
Diplegia	5	3	1	0.203	0.559	1.000
Quadriplegia	1	9	2	0.008	0.203	0.547
Following	3	0	1	0.063	1.000	0.250
Walking				0.005	0.236	0.245
Ability	7	2	2			
Inability	1	10	2			
Developmental quotient				0.018	0.182	1.000
≥85	5	1	0			
<85	3	11	3			
Epilepsy	1	6	1	0.159	1.000	0.585
West syndrome	0	5	1	0.045	0.308	1.000

IVH = intraventricular hemorrhage; PVL = periventricular leukomalacia.

* Some totals in columns do not add up to the number indicated in the top row due to missing data.

† Fisher's exact test was used to compare categorical factors. A value of $p < 0.016$ (0.05/3) after Bonferroni correlation was taken as significant.

4. Discussion

Few reports have addressed the neurodevelopmental outcome with PVL children graded on the basis of MRI findings in Japan. To the best of our knowledge, this is the first report in which PVL children were graded on the basis of MRI findings and 56% of children with grade 1 PVL presented with normal psychomotor development.

The neurodevelopmental outcome after fetal or neonatal brain injury likely reflects the severity of the brain injury detected by neuroimaging.[9] The most widely used imaging technique in NICU is cranial ultrasonography. This method is useful for the detection of IVH and cystic PVL; however, it has poor sensitivity for diffuse white matter abnormalities detected by MRI,[10] and the time to detection of the most severe abnormalities by ultrasonography varies. MRI studies have revealed that the majority of infants with PVL have white matter abnormalities, including signal abnormalities, loss of volume, cystic abnormalities, enlarged ventricles, thinning of the corpus callosum, and delayed myelination.[11]

Kusters et al reported that the presence of IVH grade III and IV increases the risk of cystic PVL.[12] Three of the 14 children (21%) with Papile grade III or IV IVH had cystic PVL in this study and had no ability to walk independently. Resic et al reported that the deep focal necrotic lesions associated with PVL grade 2 or 3 occur in areas that are considered arterial end zones.[13] The mechanisms underlying cortical reorganization seem to be related to abnormalities in the neural migration process, secondary to damage to the oligodendrocyte precursor, subplate zone, and biochemical alterations associated with PVL, which may be implicated not only in the acute phase of PVL pathogenesis, but also in long-lasting cortical and deep grey neuronal dysfunctions.[14–16] In this study, seventeen (68%) of the children with PVL with a DQ of <60 had motor abnormalities of such severity that it may be difficult for them to live independently in the future. However, it should be noted that 56% of children with PVL grade 1 had normal psychomotor development. Although these children may have minor motor problems, it is possible that they will not experience major functional impairments in the future.

There are differences in clinicopathologic entities, despite a common radiologic pattern, between preterm and term infants with PVL.[17] Lasry et al reported that neurologic subtype differed significantly between preterm and term-born children with respect to the frequency of spastic diplegia,[3] and the authors suggested that different gestational timings were responsible for the acquired injuries in these different clinicopathologic entities. It is difficult to discuss these differences, because there was only one term-born child in this study, and she was one of four children who did not yet satisfy either definition of motor impairment. The MRI classification of PVL has a prognostic value not only for neurodevelopmental outcome, specifically motor function, but also for epilepsy.[18,19] PVL in epileptic children is associated with multiple seizure types and medically refractory diseases such as West syndrome.[20] Eight of the 25 PVL children (32%) in this study had epilepsy, with six of the eight (75%) also having West syndrome. All children experienced difficulty with series of spasms under various antiepileptic treatments. The potential etiologic

factors for seizures in infants with PVL include the distribution and severity of white matter pathology, and focal and diffuse cortical injuries.[21]

This study includes a retrospective component, and has three major limitations. First, the routine MRI sessions were modified because the majority of children with PVL were preterm and demonstrated respiratory and circulatory disturbances during that period. Barkovich et al also reported different time courses regarding changes in MRI findings.[22] As the timing of brain injury associated with PVL is not necessarily the same in each child, children already demonstrating end-stage PVL at the first MRI session, at which age the brain normally demonstrates an adult pattern of myelination, were included in this study. Furthermore, 13 (52%) of the 25 children did not receive follow-up MRI, as consent to perform the second MRI session was not obtained from parents, or because of a too severe psychomotor delay. Thus, it is possible that the evaluation of MRI findings was affected. Second, nine (36%) of the 25 children were extremely low BW infants (ELBWIs), so that we could not examine the relationship between MRI findings and neurodevelopmental outcomes. As we have experienced some ELBWIs with psychomotor delays who had few abnormal signals, such as PVL on MRI, it is considered too difficult to clearly identify the causes of psychomotor delay in ELBWIs on the basis of MRI findings. Last, we did not evaluate CP children with clinical patterns known not to be associated with PVL; therefore, we may have missed a few cases with coincidental, but not clinically apparent, PVL.

We examined the neurodevelopment outcomes of children with PVL on the basis of MRI findings in this study. Children with PVL grade 2 or 3 showed severe neurodevelopmental delays, but attention should also be paid to the 56% of children with PVL grade 1 presenting with normal psychomotor development. It is possible that some PVL grade 1 children may have a normal to mildly impaired functional outcome or slight motor problems in the future. Further studies of larger populations, including long-term follow-up, are necessary to evaluate the outcomes of children with PVL.

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