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Evaluation index for asymmetric ventricular size on brain magnetic resonance images in very low birth weight infants

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Abstract

Objective: Asymmetric ventriculomegaly is often evident on brain magnetic resonance imaging (MRI) in very low birth weight infants (VLBWI) and is interpreted as white matter injury. However, no evaluation index for asymmetric left-right and anterior-posterior ventricular sizes has been established.

Methods: In this retrospective multicenter cohort study, brain T2-weighted MRI was performed at term-equivalent ages in 294 VLBWI born between 2009 and 2011. The value of a lateral ventricular index (LVI) to evaluate asymmetric ventricular size, as well as the relationship between the LVI value and walking at a corrected age of 18 months was investigated. At the level of the foramen of Monro in a horizontal slice, asymmetry between the left and right sides and between the anterior and posterior horns was identified by the corrected width and was detected by a low concordance rate and κ statistic value. An LVI representing the sum of the widths of the four horns of the lateral ventricle corrected for cerebral diameter was devised.

Results: Asymmetric left-right and anterior-posterior ventricular sizes were confirmed. The LVI value was significantly higher in the non-walking VLBWI group (n=39) than in the walking VLBWI group (n=255; 18.2 vs. 15.8, p=0.02). An LVI cut-off value of 21.5 was associated with non-walking. Multivariate analysis revealed that an LVI value > 21.5 was an independent predictor of walking disability at the corrected age of 18 months (odds ratio 2.56, p=0.008).

Conclusions: The LVI value calculated via MRI may predict walking disability at a corrected age of 18 months in VLBWI.

Key words: lateral ventricle, magnetic resonance imaging, motor development, very low birth weight infants, walking

Introduction

In Japan, the survival rate of very low birth weight infants (VLBWI; birth weight <1500 g) has improved since 2000 [1], such that the mortality rate of infants born at a gestational age of 24–31 weeks was only 5% in 2007 to 2010 [2]. However, cerebral palsy is identified in approximately 10% of surviving VLBWI [3].

The immature blood vessels and glia in the brains of VLBWI are susceptible to ischemia and inflammation [4], rendering these infants prone to diffuse white matter injury. Especially, periventricular leukomalacia (PVL) and intraventricular hemorrhage (IVH) cause decreases in white matter volume, resulting in enlargement of the lateral ventricles in VLBWI [5, 6].

Neuroimaging at term-equivalent ages has been studied in VLBWI to predict the neurodevelopmental outcome [7]. Ment et al. reported that ventricular size at term-equivalent age was an independent predictor of adverse cognitive and motor development at a corrected age of 4 years [8]. However, other studies have shown that ventricular size has a limited ability to predict the neurodevelopmental outcome in the absence of other pathologic lesions [9-11]. No conclusion has been reached regarding the association between ventricular size and neurodevelopmental outcome, possibly on account of the lack of a definitive method for evaluation of ventricular size in VLBWI; the lack of both symmetry and uniform enlargement of the ventricles in VLBWI may explain the absence [12, 13].

The aims of the present study were to devise an index for the evaluation of asymmetric left-right and anterior-posterior ventricular size in VLBWI using brain magnetic resonance imaging (MRI) at term-equivalent ages, as well as to study the relationship between this index and unaided walking at 18 months of corrected age.

Materials and methods

Study design and subjects

Of the VLBWI born in 2009–2011 and treated in the neonatal intensive care unit at Kobe Children's Hospital, Kobe University Hospital, Takatsuki General Hospital, Japanese Red Cross Society Himeji Hospital, Saiseikai Hyogo General Hospital, or Toyooka Hospital, 346 were enrolled in this retrospective multicenter cohort study. The study protocol was approved by the ethics committees at Kobe University Graduate School of Medicine and the participating hospitals. A number of the initial participants were later excluded from the study: 20 VLBWI who had other pathophysiologic abnormalities or died before a corrected gestational age of 37 weeks and 32 VLBWI whose MRI examinations were conducted at the wrong time, yielded inadequate sections, or were lost in follow-up. The final number of VLBWI for whom we were able assess the ability to walk unaided at 18 months of age thus totaled 294 (Fig. 1). A simple and clear marker of motor development, an "unaided walk" was defined as more than 5 steps without any support.

The following clinical data and findings were collected from the medical charts for analysis: gestational age, birth weight, sex, duration of artificial ventilation, retinopathy of prematurity requiring photocoagulation therapy, grade 3 or 4 IVH diagnosed on brain ultrasonography during the stay in the neonatal intensive care unit, cystic periventricular leukomalacia (cPVL) diagnosed by brain MRI before discharge, and confirmation of walking at a corrected age of 18 months.

Measurement of ventricular size via brain MRI

Brain T2-weighted MRI was performed at term-equivalent ages (corrected gestational age 36–43 weeks). The widths of the right anterior horn, left anterior horn, right posterior horn, and left posterior horn of the ventricles, cerebral anteroposterior diameter, and cerebral lateral diameter were measured on a horizontal slice at the level of the foramen of Monro (Fig. 2) [4].

As shown in Fig. 2, the anterior and posterior horn widths were measured at the maximum oblique distance and maximum lateral distance of the horn, respectively [4].

We used the uniform fit-ellipse method, which can be used to calculate an outline of the head from brain imaging sections, to obtain values for cerebral size [14]. The cerebral anteroposterior and the lateral diameters were measured, as the longitudinal and cross-sectional distances in the cerebrum, respectively. The measurements were performed by one neonatologist at each participating hospital and were used to devise a lateral ventricular index (LVI).

Study methods and statistical analyses

Inter-examiner reliability of measured width

The inter-examiner reliability of each horn width (mm) as measured by two examiners from the brain MRIs conducted for 58 VLBWI was analyzed and is shown as the intraclass correlation coefficient.

Confirmation of asymmetric ventricular size

Each horn width measurement was corrected for the cerebral diameter (corrected horn width = [100*measured width (mm)]/[cerebral anteroposterior diameter + lateral diameter (mm)]). To determine whether the size of the ventricles in the VLBWI brain was asymmetric, the median corrected horn widths were compared between the left and right sides of the anterior and posterior horns and between the anterior and posterior horns in the right and left ventricles using the Wilcoxon signed-rank test. The proportion of VLBWI with ventriculomegaly, defined as the horn widths being above the 90th percentile for the study population, was calculated and the concordance rate and κ statistic were compared between the horns.

Cut-off value for LVI associated with walking disability

A cut-off value for LVI associated with walking disability was determined using the maximum Youden index with more than 80% accuracy in the receiver-operating characteristic (ROC) curve. The Youden index is the point farthest from the boundary delineating the area under the curve (0.500 on the ROC curve), and represents the value of [sensitivity + specificity - 1] [15].

Clinical factors associated with walking disability

The 294 VLBWI were categorized according to whether they were confirmed to be walking unaided at a corrected age of 18 months. The aforementioned clinical factors associated with walking disability documented during their stay in the neonatal intensive care unit were analyzed using the Wilcoxon signed-rank test or Pearson's chi-square test and multiple logistic regression analyses. All statistical analyses were performed using JMP version 13 (SAS Institute Inc., Tokyo, Japan). A p-value < 0.05 was considered statistically significant.

Results

Inter-examiner reliability of width measurements

The intraclass correlation coefficients for the widths measured by two neonatologists were 0.95 for the left anterior horn, 0.98 for the right anterior horn, 0.99 for the left posterior horn, 0.98 for the right posterior horn, 0.99 for the cerebral anteroposterior diameter, and 0.99 for the cerebral lateral diameter.

Evidence of asymmetric ventricular size

The corrected width of each horn is shown in Table 1. There was a significant difference in width measurements between the left and right sides of the anterior and posterior horns; the widths on the left side were significantly larger than those on the right side in both horns ($p<0.0001$). Similarly, there was a significant difference in the widths of the anterior and

posterior horns in the right and left ventricles: the latter were significantly greater than the former in both the right and left ventricles ($p<0.0001$). The concordance rate and κ statistic values for the difference in width were less than 80% and 0.4 respectively, suggesting asymmetric left-right and anterior-posterior ventricular size in the brains of VLBWI.

Devised LVI

We devised an LVI that could be calculated using the following formula: [3*(a + b) + c + d]*[100/(e + f)], where a is the right anterior horn width, b is the left anterior horn width, c is the right posterior horn width, d is the left posterior horn width, e is the cerebral anteroposterior diameter, and f is the cerebral lateral diameter [4, 14]. Given our finding that the ventricles in VLBWI were not symmetric or uniform, the width of each horn was added. As the width of the posterior horn was approximately three times greater than that of the anterior horn, the latter was tripled to prevent the value from being underestimated. Furthermore, it was corrected by brain size using the cerebral anteroposterior and lateral diameters; the outline of the cerebrum at the level of the foramen of Monro can be outlined as an ellipse with an approximate circumference of 2π*(long radius + short radius) [14].

Clinical factors associated with walking disability

Of the 294 VLBWI, 255 (87%) were walking while 39 (13%) were not walking at a corrected age of 18 months (Fig. 1). An LVI cut-off value of 21.5 was associated with non-walking according to the Youden index from the ROC curve analysis (Table 2). The percentages of IVH and cPVL were significantly lower in the walking group than in the non-walking group ($p<0.001$, Table 3). The median LVI value was significantly higher in the non-walking group than in the walking group ($p=0.020$, Table 3). Multiple logistic regression analysis using gestational age, birth weight, and an LVI value > 21.5 was performed. IVH and cPVL were not included in the analysis because of their relationship with large ventricular size. An LVI

value > 21.5 was identified as being independently associated with non-walking (odds ratio 2.56, 95% confidence interval 1.02–6.41; p=0.008, Table 4).

Discussion

In this study, we confirmed that the ventricular size on a horizontal MRI slice at the level of the foramen of Monro in VLBWI is asymmetric in both the left-right and anterior-posterior directions. These results agree with previous reports of neonate ventricular size being larger on the left than on the right [16, 17]. We therefore developed an LVI to evaluate the degree of asymmetry in ventricular size; an LVI value > 21.5 at a term-equivalent age was an independent clinical predictor of non-walking at a corrected age of 18 months. Our LVI is simple, cost-free, and easy to perform in clinical practice. Further, this method of evaluation of lateral ventricular size features a good inter-examiner reliability, because it only requires the simple measurement of multiple sites on plain MRIs; in these respects our method differs from other MRI techniques that have been previously reported to predict neurodevelopment outcomes at term-equivalent ages in VLBWI, such as volumetric MRI, magnetic resonance spectroscopy, diffusion tensor imaging, diffusion MRI, and resting-state functional connectivity MRI [7].

Prior studies have employed MRI to establish a variety of indices of ventricular size for the prediction of neurodevelopment outcomes: Ment et al. assessed lateral ventricular body width [8], Maunu et al. determined ventricle-to-brain ratio (a ratio of the lateral ventricular body width to cerebral diameter) [10], and other researchers have used the width of a portion of the lateral ventricle [9, 11]. These indicators, however, may be insufficient; the asymmetry of lateral ventricular size on brain MRI in VLBWI extends in both the left-right and anterior-posterior dimensions. Fox et al. recorded detailed lateral ventricular size measurements using brain ultrasonography during 25–35 days of life in preterm neonates and

found that a large lateral ventricle was associated with delayed language development at 2 years of age [6]. We therefore devised an LVI to detect the ventricular size relative to the that of the cerebrum of VLBWI with asymmetric ventricular enlargements and investigated the association between the LVI value and ability of VLBWI to walk unaided at a corrected age of 18 months.

In this study, 13% of VLBWI could not walk unaided at a corrected age of 18 months, which is similar to the figure of 11% presented in a previous report [18]. It is well known that IVH and cPVL are related to motor development in VLBWI [19, 20]. Jeng et al. have also reported that gestational age, severe retinopathy of prematurity, and duration of artificial respiration or administration of oxygen were significantly associated with walking disability at a corrected age of 18 months [18]. A relationship between sex and cerebral palsy has also been reported [21]. Therefore, we analyzed these clinical factors, in addition to the LVI, for their ability to predict walking disability at a corrected age of 18 months; the only independent predictor identified, however, was an LVI value of > 21.5.

The limitations of this study were as follows. 1) IVH and cPVL were excluded in the multiple logistic regression analysis, because IVH and cPVL are associated with asymmetric ventricular enlargements; the results shown in Table 4 might be strongly associated with IVH and cPVL. We therefore performed an additional analysis that excluded infants with IVH or cPVL, leaving a total of 277 VLBWI. In this population, the multiple logistic regression analysis using gestational age, birth weight, and an LVI value > 22.0 (obtained from the Youden index) showed that an LVI value > 22.0 resulted in an odds ratio of 2.30 and a 95% confidence interval of 0.77 – 6.12; the results were not significant (p=0.130). As our study may have been limited by the low population of the non-walking group (n=26), further studies using a larger group of VLBWI are needed to discern the relationship between LVI and

unaided walk at 18 months of corrected age in VLBWI without major brain impairments, such as IVH and cPVL. 2) The only neurodevelopmental outcome evaluated was the ability to walk unaided at a corrected age of 18 months. Johnson et al. reported that 56% of infants with delayed walking ability were subsequently found to have a neurodevelopmental disorder [22]; therefore, evaluation of walking at a corrected age of 18 months is an important index. In addition to motor dysfunction, however, preterm infants with moderate-to-severe cerebral white matter injury are also at an increased risk of cognitive dysfunction and sensory impairment [23]. Therefore, the complete investigation of the effect of marked asymmetry in ventricular size on neurodevelopmental outcomes in VLBWI should include not only motor development, but also cognitive and audiovisual sensory functions.

In conclusion, we developed an LVI for detecting the size of the ventricles relative to that of the cerebrum in VLBWI with asymmetric ventricular enlargements. An LVI > 21.5 on brain MRI at term-equivalent age may be a clinical factor that predicts walking disability at a corrected age of 18 months.

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Conflict of interest

The authors have no financial or personal relations that could pose a conflict of interest in this study.

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Figure legends

Figure 1. Flow of subjects through the study.

MRI, magnetic resonance imaging; VLBWI, very low birth weight infants.

Figure 2. Measurement of lateral ventricular size in a horizontal slice at the level of the foramen of Monro on brain T2-weighted magnetic resonance images at term-equivalent ages. (a) Right anterior horn width, (b) left anterior horn width, (c) right posterior horn width, (d) left posterior horn width, (e) cerebral anteroposterior diameter, and (f) cerebral lateral diameter.

Table 1. Evidence of asymmetric ventricle size

	Corrected horn width	p-value	Ventriculomegaly*	
			Concordance rate	κ statistic
Anterior horn				
Right	1.2 (0.0–5.2)	<0.0001	74.8%	0.205
Left	1.3 (0.4–6.3)			
Posterior horn				
Right	3.8 (1.6–10.6)	<0.0001	78.9%	0.435
Left	4.6 (0.0–10.9)			
Right side				
Anterior	1.2 (0.0–5.2)	<0.0001	71.4%	0.083
Posterior	3.8 (1.6–10.6)			
Left side				
Anterior	1.3 (0.4–6.3)	<0.0001	76.9%	0.386
Posterior	4.6 (0.0–10.9)			

The data for corrected horn widths are shown as the median (range). *The width of each horn above the 90th percentile for this study population (see the Patients and Methods section in text).

Table 2. Cut-off values for the lateral ventricular index value associated with walking disability

	Sensitivity	Specificity	Accuracy	Youden index
15	0.692	0.416	0.452	0.108
15.5	0.692	0.478	0.507	0.171
16	0.667	0.549	0.565	0.216
16.5	0.641	0.588	0.595	0.229
17	0.590	0.608	0.605	0.198
17.5	0.590	0.635	0.629	0.225
18	0.513	0.694	0.670	0.207
18.5	0.436	0.722	0.684	0.157
19	0.410	0.753	0.707	0.163
19.5	0.410	0.788	0.738	0.198
20	0.333	0.820	0.755	0.153
20.5	0.333	0.835	0.769	0.169
21	0.308	0.851	0.779	0.159
21.5	**0.308**	**0.882**	**0.806**	**0.190**
22	0.256	0.902	**0.816**	0.158
22.5	0.179	0.906	**0.810**	0.085
23	0.179	0.922	**0.823**	0.101
23.5	0.179	0.925	**0.827**	0.105
24	0.128	0.933	**0.827**	0.062
24.5	0.128	0.941	**0.833**	0.069
25	0.128	0.949	**0.840**	0.077

Table 3. Univariate analysis

	Walking at 18 months of corrected age		
	Yes (n=255)	No (n=39)	p-value
Gestational age (weeks)	29.1 (22.6–36.4)	28.4 (23.1–33.0)	0.080
Birth weight (g)	1082 (412–1498)	1048 (477–1482)	0.106
Male sex	134 (52.5)	20 (51.3)	0.883
Duration of mechanical ventilation (days)	23.9 (0–94)	26.8 (0–76)	0.569
ROP	22 (8.6)	2 (5.1)	0.457
IVH*	3 (1.2)	6 (15.4)	<0.001
cPVL*	1 (0.4)	9 (23.1)	<0.001
Width of each horn (mm)			
Right-anterior	1.2 (0.0–3.5)	1.3 (0.5–5.2)	0.016
Left-anterior	1.3 (0.4–3.5)	1.4 (0.4–6.3)	0.122
Right-posterior	3.8 (1.6–7.3)	4.1 (1.9–10.6)	0.053
Left-posterior	4.6 (0.0–10.9)	5.0 (0.9–10.1)	0.067
LVI	15.8 (8.3–33.4)	18.2 (10.3–50.2)	0.020

The data are shown as the median (range) or number (%). * Two infants had both IVH and cPVL. cPVL, cystic periventricular leukomalacia; IVH, intraventricular hemorrhage, grade 3 or 4; LVI, lateral ventricular index; ROP, retinopathy of prematurity requiring photocoagulation therapy.

Table 4. Multivariate analysis

	OR (95% CI)	p-value
Gestational age (weeks)	0.91 (0.73–1.14)	0.371
Birth weight (g)	1.00 (1.00–1.00)	0.814
LVI >21.5	2.56 (1.02–6.41)	0.008

CI, confidence interval; LVI, lateral ventricular index; OR, odds ratio.