The relationship between enlargement of the lateral ventricle and periventricular leukomalacia in infants

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Running Title

PVL is predicted from ventriculomegaly

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Abstract

Aim: To examine if we could predict periventricular leukomalacia (PVL) from the area of the lateral ventricle (LV).

Methods: Six neonates in whom cystic PVL could be detected by magnetic resonance imaging (MRI) but not by ultrasound (US) were termed the “invisible group”. Six neonates in whom cystic PVL could be detected by MRI and US were termed the “visible group”. Eleven neonates in whom cystic PVL could not be detected by MRI or US were termed the “control group”. The ratio of LV to head circumference (HC) was calculated as the area of LV (cm^2)/HC (cm) × 100. Receiver operating characteristic (ROC) curve analysis was carried out to find the cutoff value.

Result: There were no significant differences among the three groups with respect to gestational age, birth-weight, post-natal age and HC. The ratio of LV to HC in the control group was a median value of 0.38, it was 0.79 in the invisible group, and 0.96 in the visible group. The ratio was significantly higher in the visible group ($p<0.001$) and in the invisible group ($p<0.05$) than in the control group. This ratio was low in the two infants who had PVL only in the collateral trigone. The ROC curve suggested a cutoff value of 0.6 (sensitivity 79.17%, specificity 100%) to suspect PVL.

Conclusion: We may need to suspect PVL in infants whose lateral ventricle is enlarged even if cystic PVL is not detected by ultrasound. PVL present only in the collateral trigone needs to be evaluated using cerebral MRI.

Key words: lateral ventricle, periventricular leukomalacia

Introduction

Neonatology has progressed to the extent that many low birth-weight infants can survive even though the developing brain can suffer injury from various ischemic, infective, inflammatory, and neurotoxic factors.[1] It is thought that periventricular leukomalacia (PVL) is the most important factor in neurological disorders, and that it can be detected by ultrasound in surviving infants. PVL in infants was detected by magnetic resonance imaging (MRI) in whom cystic PVL could not be detected by ultrasound.[2,3,4] The image acquisition of ultrasound is dependent upon the machine, probe and operator. It is limited by the size of the fontanelles and the angle of view. In addition, abnormal echogenicity is not lesion-specific, and the signal can be attenuated with distance. MRI is not available in many centers, and is very sensitive to movement artifact. Nevertheless, it provides high-resolution images and more detailed characterization of injury to white matter in PVL. Even though ultrasound has disadvantages compared with MRI, ultrasound is a very useful, safe and accessible bedside tool. PVL produces enlargement of the lateral ventricle. We therefore focused on neonates in whom cystic PVL could be detected by MRI but not by ultrasound. We also investigated if we could predict PVL from enlargement of the lateral ventricle.

Patients and Methods

This study was approved by the Local Ethical Committee of Imakiire General Hospital (Kagoshima, Japan). Written informed consent was obtained from each patient.

Twenty-three neonates who were admitted to the Perinatal Center in Imakiire General

Hospital from 28 December 1999 to 7 March 2005 were the study population. These neonates were divided into three groups. Cystic PVL could be detected by MRI but not by ultrasound in six neonates (gestational age 32.7 ± 1.1 W, birth-weight 1680 ± 328 g, Figure 1), and these subjects were termed the “invisible group”. The six neonates in whom cystic PVL could be detected by MRI and ultrasound (gestational age 31.9 ± 1.4 W, birth-weight 1707 ± 241 g, Figure 2) were termed the “visible group”. Eleven neonates in whom cystic PVL could not be detected by MRI or ultrasound (gestational age 32.8 ± 2.0W, birth-weight 1546 ± 352g, Figure 3) were termed the “control group”.

Ultrasound was carried out as soon as possible after hospital admission and every second week until hospital discharge. Ultrasound images were acquired with 5.0–6.0-MHz probes using a ultrasound machine (LOGIQ 500, GE Medical System, USA). Four coronal views (at the level of the orbits, Monro foramen, third and fourth ventricle, and bodies of the lateral ventricle) and five sagittal–parasagittal views (midline, ventricle, and paraventricular white matter) were obtained from the anterior fontanelle. In this study, we used ultrasound images in the coronal view to view the Monro foramens through the anterior fontanelle when MRI was done. MRI was planned for infants weighing >2000 g and was carried out within two weeks after planning The area of the lateral ventricle was measured by ImageJ (Research Services Branch, National Institute of Mental Health, Bethesda, MD, USA).

All sonographic measurements were studied by one examiner (A.K). The intra-rater and inter-rater reliability for the assessment of lateral ventricle volume was analyzed using the intraclass correlation coefficient. Intra-rater reliability was determined by carrying out five

examinations on eleven subjects, and the result was 0.984 (95% confidence intervals (CI) 0.963 to 0.995). To evaluate inter-observer reproducibility, sonographic measurements were done by another examiner (H.K). Inter-rater reliability was determined by carrying out five examinations on eleven subjects, and the result was 0.961 (95% CI 0.746 to 0.979).

The ratio of the lateral ventricle to head circumference was calculated as the area of lateral ventricle (cm^2) /head circumference (cm) × 100 (Figure 4). (This ratio is hereafter termed the “LV/HC ratio”.) Head circumference was measured each week, and this value was also evaluated when the ultrasound examination was done. PVL was defined as a parenchymal echolucent cavity around the lateral ventricle of size >3 mm. Diffuse PVL was not evaluated in the present study.

Neurological outcome was compared the number of the patients of cerebral palsy (CP) among three groups. All infants had been followed up at the Division to Neonatology, Perinatal Medical Center, Kagoshima City Hospital, but three neonates in the control group and two neonates in the invisible group were not followed up. Outcomes were classified as CP or normal development. CP was defined as a disorder of movement and posture due to non-progressive brain damage or brain defect that occurs up to four weeks after birth. [5]

Statistical analysis

Statistical analysis was done using Graph Pad Prism 4 for Windows (Graph Pad Software, Incorporated, San Diego, CA, USA) to compare the ratio of the lateral ventricle to head circumference on ultrasound between the three groups by one-way analysis of variance

(ANOVA) with pairwise multiple comparison procedures. Multiple comparisons were done using by the Bonferroni test. Perinatal variables were analyzed by one-way ANOVA with the Bonferroni test. Neurological outcome were analyzed by Fisher's exact test. $P<0.05$ was considered significant. Non-parametric receiver operation characteristic (ROC) curve analysis was carried out to find a cutoff point for the ratio of the lateral ventricle to head circumference. The area under the curve (AUC), 95% CI of the AUC, sensitivity and specificity were also calculated.

Results

There were no significant differences among the three groups with respect to gestational age, birth weight, postnatal age and head circumference (Table 1).

Neurological outcome

All infants who were diagnosed as having CP were classified as "spastic CP" (three infants in the invisible group and five infants in the visible group). All infants in the invisible group and four infants with CP in the visible group were diplegic. One infant in the visible group was quadriplegic. The number of CP patients was significantly higher in the invisible group (3 of 4 patients, $p<0.01$) and in the visible group (5 of 6 patients, $p<0.01$) compared with the control group (0 of 8 patients). There was no significant difference between the visible and invisible group with respect to the number of CP patients (Table 2).

Ultrasound examination

The LV/HC ratio in the invisible group (median 0.79 (range 0.09 to 0.97) $p < 0.05$) and in the visible group (median 0.96 (range 0.62 to 1.8) $p < 0.001$) was significantly higher than in the control group (median 0.38 (range 0.10 to 0.59)). However, the LV/HC ratio in the two infants who had PVL only in the collateral trigone was low (Figure 5). The ROC curve (AUC = 0.8466, 95% CI 0.7163 to 0.9769) suggested a cutoff value of 0.6 (sensitivity 79.17%, specificity 100%) to suspect PVL (Figure 6).

Discussion

It has been recognized that PVL is the most important factor of neurological damage in the preterm infant. Banker et al. reported necrosis around the lateral ventricle and suggested a relationship with CP.[6] After 1980, PVL was detected in surviving infants by ultrasound examination of the head. Recently it has become clear that some cases of PVL cannot be detected by ultrasound. Fujimoto et al. found that the prevalence of PVL in a group of surviving preterm infants of gestational age <33 weeks was 4.8–4.9% if detected on ultrasound and 7.7–7.9% on MRI and/or CT.[2] Debillon et al. found that ultrasound could detect PVL on MRI in 68% of cases.[4] Inder et al. tried to detect PVL from the echolucency on ultrasound examination of the cranium; it had a sensitivity of 75% and a specificity of 100% for cystic changes on MRI.[3] Usually, the characteristics of PVL on ultrasound examination are high echodensity of the periventricular area, cyst formation, enlargement of the lateral ventricle, and irregularity of the lateral ventricle wall. Elias et al. showed that the severity of impairment of the motor or cognitive area in children with PVL correlated with increased mean lateral ventricular volumes.[7] In the present study, we focused on

enlargement of the lateral ventricle to detect PVL. Enlargement of the lateral ventricle induced by PVL was found as brain atrophy. Brain atrophy is usually observed as enlarged subarachnoid spaces, widened inter-hemispheric fissure, and reduction in complex gryal folding by ultrasound.[8] Detecting abnormal enlargement of the lateral ventricle is easy if all of these characteristics of brain atrophy are found, but finding these characteristics is usually difficult. We therefore thought that we initially needed to find an objective marker to evaluate enlargement of the lateral ventricle. We used the length of the head circumference and the lateral ventricle area, and there are three reasons to use it. First, the length of the head circumference may be a good predictor of the neurological prognosis in the fetus.[9] Second, it was clear that there is an important relationship between the lateral ventricular area and head circumference.[10, 11] Third, it was clear that PVL was associated with a different ratio of the lateral ventricle to head circumference.[12] Enlargement of the lateral ventricle can be observed not only due to loss of white matter volume, but also due to post-hemorrhagic hydrocephalus, so we excluded infants with the latter disorder.

The reason why PVL could not be detected by ultrasound but could be detected by MRI may be due to tissue characterization. Usually, PVL was diagnosed by ultrasound examination if the size of the cyst was >3 mm. If the cyst was too small, it is possible that PVL could not be detected by ultrasound, in which the resolution is 5–7 MHz. Using a 10-MHz transducer for ultrasound has been suggested in several studies,[13, 14] and would improve the sensitivity to detect smaller cysts, but evaluating deep lesions (e.g., in the collateral trigone) may be difficult.

Evaluating the subdual space at the level of corona radiata by ultrasound is also difficult.

The LV/HC ratio of the lateral ventricle at the level of corona radiata was not significantly different among the three groups (0.07 ± 0.01, control group and 0.09 ± 0.02, invisible group and 0.11 ± 0.05, visible group, data not shown). It may be that ultrasound could not evaluate the subdural space around the occipital lobe, and the subdural space around the occipital lobe may be an important factor in evaluation of brain atrophy at the level of the corona radiata. Couchard et al. also used the coronal view at the Monroe foramen level to evaluate enlargement of the lateral ventricle.[15] Martin et al. reported on the pattern of white matter loss: posterior only is most common, but the next most common is posterior and middle only.[16] These reports suggested that it is favorable to evaluate brain atrophy from the middle part of the lateral ventricle. If brain damage occurred only in the posterior part, this method would not be useful to detect it. Nevertheless, brain damage must be suspected if the lateral ventricle is enlarged even if cystic PVL cannot be detected by ultrasound.

Neurological outcome was not significantly different between the invisible group and visible group. PVL location was important for CP. If PVL was too small and could not be detected by ultrasound and MRI, detecting PVL from cyst formation is difficult. Recently, it was shown that some PVL could not be detected even with MRI.[17] These cases of PVL were thought to be white-matter injuries, and many researchers tried to detect it using by other methods.[18, 19] It may be worthwhile to use the LV/HC ratio if enlargement of the lateral ventricle is observed.

In conclusion, we may need to suspect PVL in infants whose lateral ventricle is enlarged even if cystic PVL is not detected by ultrasound examination. PVL present only in the collateral trigone needs to be evaluated using cerebral MRI.

References

1. Kuban KC, Leviton A. Cerebral palsy. *N Engl J Med.* 1994 Jan 20;330(3):188-95.
2. Fujimoto S, et al. National survey of periventricular leukomalacia in Japan. *Acta Paediatr Jpn* 1998; 40: 239-243.
3. Inder TE, Anderson NJ, Spencer C, Wells S, Volpe JJ. White matter injury in the preterm infant: a comparison between serial cranial sonographic and MR findings at term. *Am J Neuroradiol* 2003; 24: 805-809.
4. Debillon T, N'Guyen S, Muet A, Quere MP, Moussaly F, Roze JC. Limitations of ultrasonography for diagnosing white matter damage in preterm infants. *Arch Dis Child Fetal Neonatal Ed* 2003 Jul; 88(4): F275-9.
5. Fukuyama Y. Definition of cerebral palsy (in Japanese). *Shoni No Seishin To Shinkei* (Tokyo) 1961;1:103-111
6. Banker BQ, Larroche JC.Periventricular leukomalacia of infancy. *Arch Neurol* 1962; 7 : 386-410.
7. Melhem ER, Hoon AH Jr, Ferrucci JT Jr, et al. Periventricular leukomalacia: relationship between lateral ventricular volume on brain MR images and severity of cognitive and motor impairment. *Radiology* 2000 Jan; 214(1): 199-204.
8. Sandra H, Carsten N, Annett F, Claudia R. Ultrasound diagnosis of brain atrophy is related to neurodevelopmentntal outcome in preterm infants. *Acta Paediatri* 2005; 94: 1815-1821.
9. Blair E, Stanley F. Intrauterine growth and spastic cerebral palsy II. The association with morphology at birth. *Early Hum Dev.* 1992 Feb; 28(2): 91-103.

10. Elie Saliba, Philippe Bertrand, Francis Gold, Marie C Vaillant, Jean Laugier. Area of lateral ventricles measured on cranial ultrasonography in preterm infants. *Arch Dis Child* 1990; 65: 1029-1032.

11. Dittrich M, Dinkel E, Peters H. Sonographische Diagnostik und Verlaufsbeureilung der Himblutung bei Risikoneugeborenen. In: Haller U, Wille L *Diagnostik intrakranieller Blutungen beim Neugeboren,* Springer, Berlin Heidelberg New York; S.95-104.

12. Elie Saliba, Philippe Bertrand, Francis Gold, Sophie Marchand, Jean Laugier Area of lateral ventricles measured on cranial ultrasonography in preterm infants: association with outcome. *Arch Dis Child* 1990; 65: 1033-1037.

13. Sie LTL, van der Knaap MS, van Wezel-Meijler G, et al. Early MR features of hypoxic-ischemic brain injury in neonates with periventricular densities on sonograms. *ANJR Am J Neuroradiol* 2000; 21: 852–61.

14. Pierrat V, Duquennoy C, van Haastert IC, et al. Ultrasound diagnosis and neurodevelopmental outcome of localised and extensive cystic periventricular leucomalacia. *Arch Dis Child Fetal Neonatal Ed* 2001; 84: F151–6.

15. Couchard M, de Bethmann O, Sciot C, Dubois B, Relier JP. Measurement of the lateral ventricles by cerebral echography in the newborn infant. *Ann Radiol (Paris).* 1984 Jan; 27(1): 37-41.

16. Bax M, Tydeman C, Flodmark O. Clinical and MRI correlates of cerebral palsy: the European Cerebral Palsy Study. *JAMA* 2006 Oct 4; 296(13): 1602-8.

17. Volpe JJ. Cerebral white matter injury of the premature infant-more comom on than you think. *Pediatrics* 2003; 112: 176-180.

18. Kato T, Okumura A, Hayakawa F, Kuno K, Watanabe K. The evolutionaly change of flash visuals evoked potentials in preterm infants with periventricular leukomakacia. *Clin Neurophysiol* 2005; 116: 690-695.

19. Hayakawa F, Okumura A, Kato T, et al. Determination of timing of brain injury in preterm infants with periventricular leukomalacia with serial neonatal electroencephalography. *Pediatrics* 1999; 104: 1077-1081.

Table 1 Baseline characteristics of patients

	Control	Invisible	Visible	P value
Gestational age (weeks)	32.8 ±2.0	32.7± 1.1	31.9± 1.4	0.4899
birth weight (g)	1546±352	1680±328	1707±241	0.5502
Post-natal age when US was done (days)	43.6±21.6	39.7±18.1	45.7±17.9	0.8676
Gestational age when US was done (weeks)	39.1 ±3.1	37.7 ±3.0	38.5 ±1.3	0.6222
Body weight when US was done (g)	2266 ±365	2367 ±540	2482 ±88	0.5330
Head circumference when US was done (cm)	33.0 ±1.8	32.7 ±2.5	33.0 ±1.0	0.8724

Values are mean ± SD. P: versus control by one-way ANOVA with Bonferroni test.

US: ultrasound

Control: neonates in whom cystic PVL cannot be detected by MRI or ultrasound.

Invisible: neonates in whom cystic PVL can be detected by MRI but not by ultrasound.

Visible: neonates in whom cystic PVL can be detected by MRI and ultrasound.

Table 2 Neurodevelopmental outcome

	Control	Invisible	Visible
Not CP	8	1	1
CP	0	3	5
P value		0.0047	0.0013

P: versus control by Fisher's exact test

Control: neonates in whom cystic PVL cannot be detected by MRI or ultrasound.

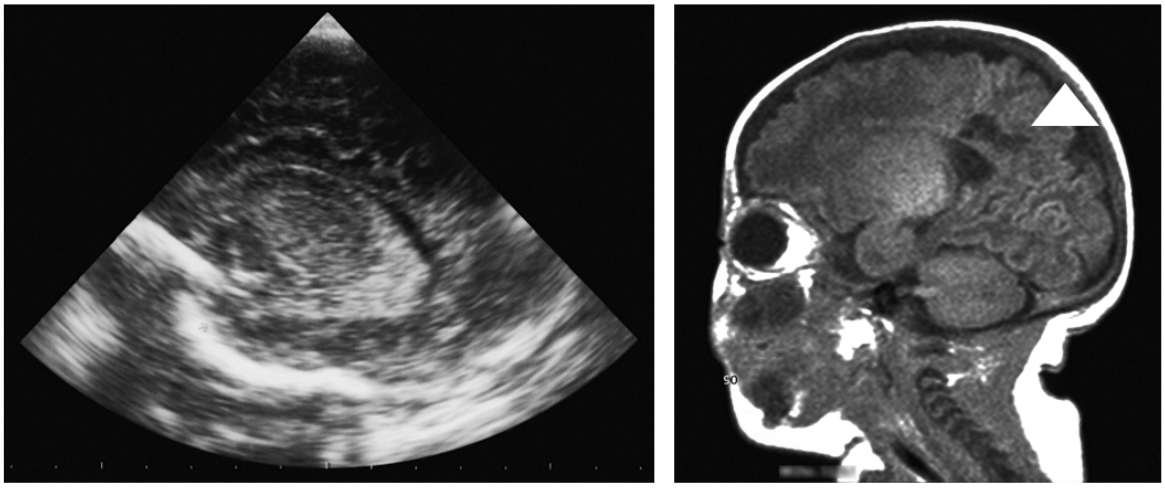
Invisible: neonates in whom cystic PVL can be detected by MRI but not by ultrasound. Visible: neonates in whom cystic PVL can be detected by MRI and ultrasound.

CP: cerebral palsy.

PVL: periventricular leukomalacia.

MRI: magnetic resonance imaging.

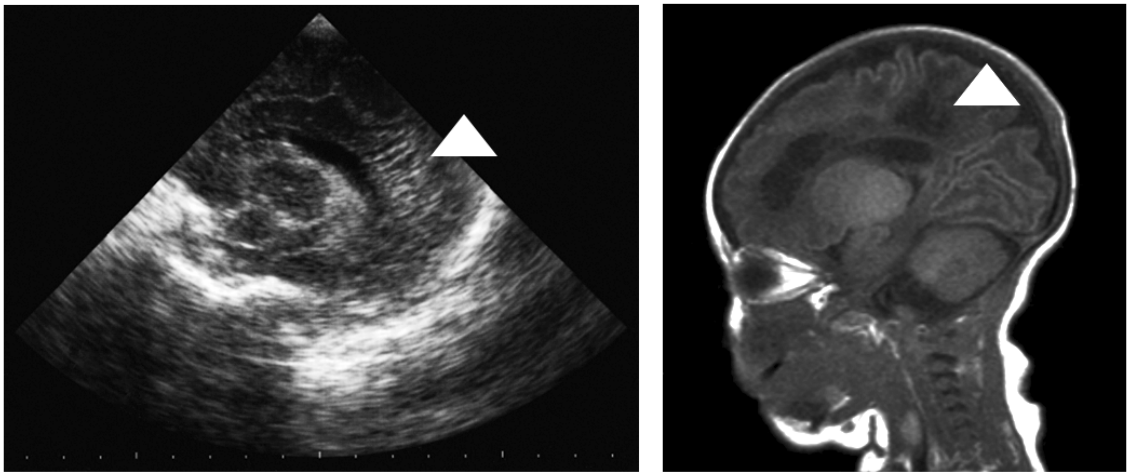
Figure1



Invisible group (n=6)

All neonates were classified into “invisible”, “visible” and “control” groups. The invisible group was defined as neonates in whom cystic PVL can be detected by MRI but not by ultrasound. The white triangle denotes PVL.

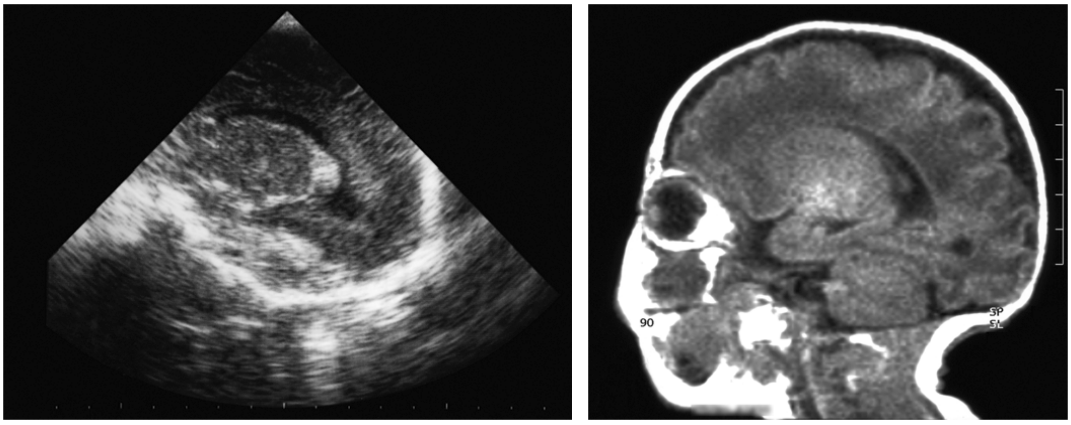
Figure2



Visible group (n=6)

The visible group was defined as neonates in whom cystic PVL can be detected by MRI and ultrasound. The white triangle denotes PVL.

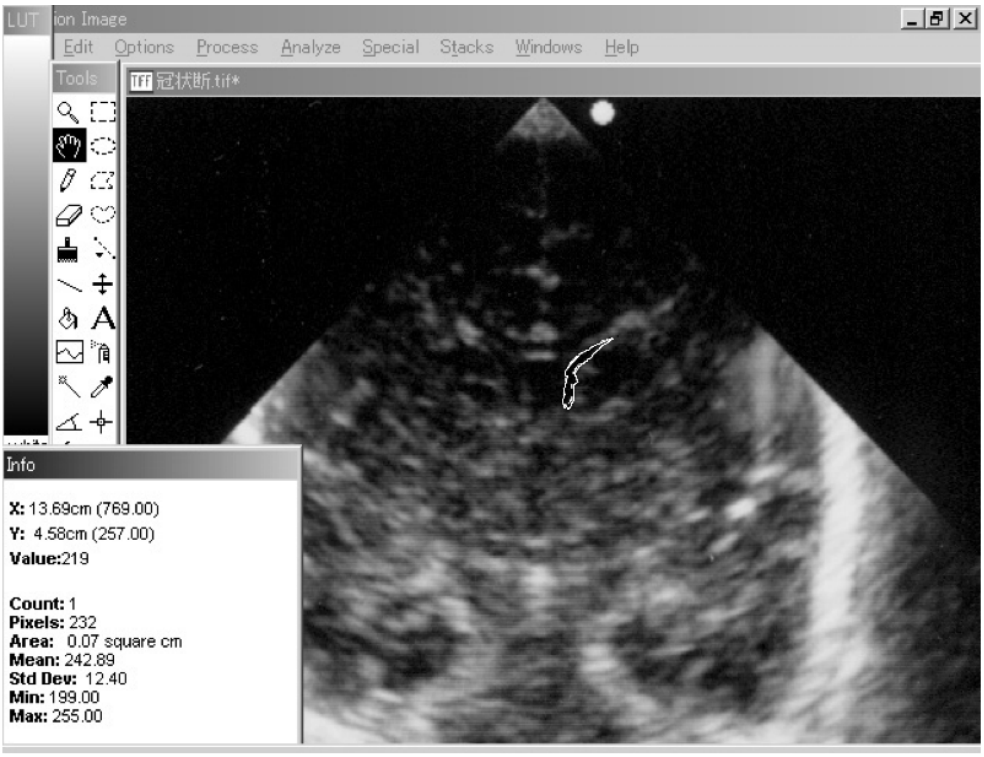
Figure3



Control group (n=11)

The control group was defined as neonates in whom cystic PVL cannot be detected by MRI or ultrasound.

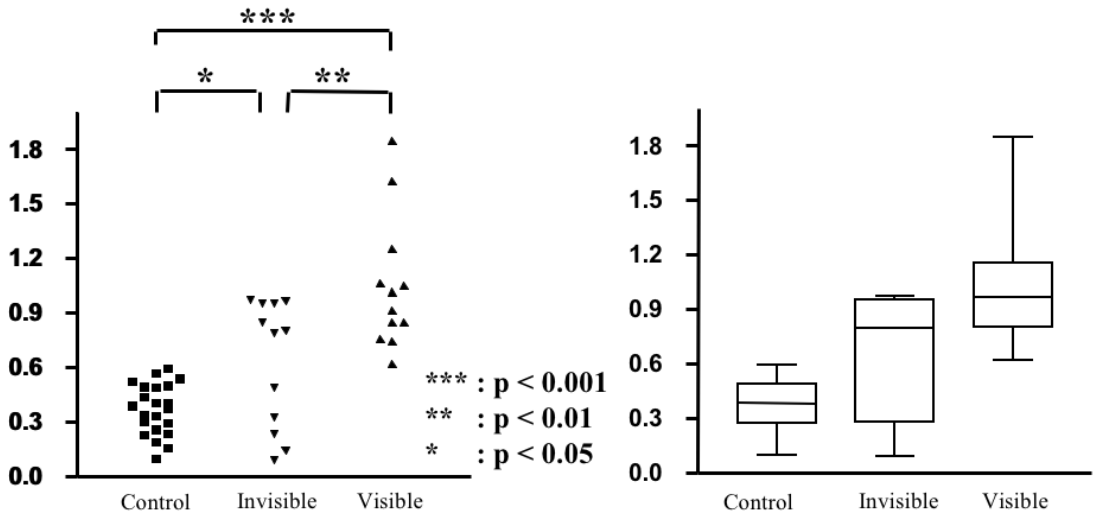
Figure4



This figure shows measurement of the area of the lateral ventricle by ImageJ software. The ratio of the lateral ventricle to head circumference was calculated as

area of lateral ventricle (cm^2)/head circumference (cm) × 100.

Figure5



This figure shows the ratio of the lateral ventricle to head circumference.

The ratio in the invisible group (median 0.79 (range 0.09 to 0.97) $p<0.05$) and in the visible group (median 0.96 (range 0.62 to 1.8) $p<0.001$) was significantly higher than in the control group (median 0.38 (range 0.10 to 0.59)).

Control: neonates in whom cystic PVL cannot be detected by MRI or ultrasound.

Invisible: neonates in whom cystic PVL can be detected by MRI but not by ultrasound.

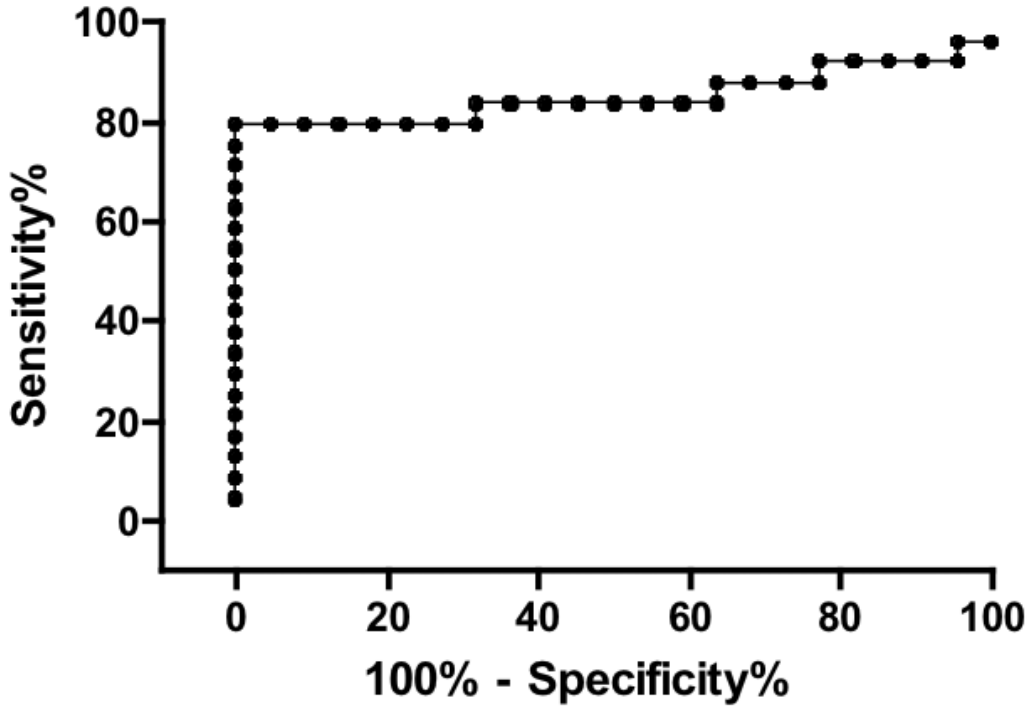
Visible: neonates in whom cystic PVL can be detected by MRI and ultrasound.

PVL: periventricular leukomalacia.

MRI: magnetic resonance imaging.

US: ultrasound.

Figure6



ROC: Receiver operation characteristic curve for the ratio of the lateral ventricle to head circumference (AUC = 0.8466, 95% CI 0.7163 to 0.9769). The suggested cutoff value was 0.6 (sensitivity 79.17%, specificity 100%) to suspect PVL.