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Correlation between Magnetic Resonance Imaging and Clinical Profiles of Periventricular Leukomalacia

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FUJIMOTO, S., TOGARI, H., BANNO, T., TAKASHIMA, S., FUNATO, M., YOSHIOKA, H., IBARA, S., TATSUNO, M. and HASHIMOTO, K. *Correlation between Magnetic Resonance Imaging and Clinical Profiles of Periventricular Leukomalacia.* Tohoku J. Exp. Med., 1999, **188** (2), 143-151 —— Magnetic resonance imaging (MRI) findings of 70 children with periventricular leukomalacia (PVL), examined between 1 year 2 months and 8 years of age (mean: 2 years 4 months of age), were analysed. Neurological assessments were made between 1 year 3 months and 15 years (mean: 4 years 9 months). The possible correlations between MRI findings and clinical profiles of PVL were investigated using three parameters of the MRI findings. The grade of ventriculomegaly correlated well with the severity of cerebral palsy (CP) but not with the severity of mental impairment. The grade of reduction of periventricular white matter correlated well with the severity of CP and mental impairment, and is the most reliable parameter for neurological prognosis. The degree of periventricular hyperintensity on T2-weighted images did not correlate well with severity of CP, but correlated to some degree with mental impairment. There was a significantly lower degree of periventricular

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hyperintensity in children at less than 28 weeks of gestation than at 28 or more weeks of gestation, but no significant difference in other parameters. The periventricular hyperintensity should be evaluated in view of the gestational age.
——— periventricular leukomalacia; magnetic resonance imaging; preterm infant; cerebral palsy; mental retardation

Periventricular leukomalacia (PVL), ischemic lesion of the cerebral white matter, is the most common cause of cerebral palsy (CP) in premature infants. About two-thirds of PVL is diagnosed by ultrasound during the neonatal period, but the remaining third can be diagnosed only by computed tomography (CT) or magnetic resonance imaging (MRI) (Fujimoto et al. 1998).

MRI findings of PVL generally show periventricular hyperintensity on T2-weighted images, atrophy of the cerebral white matter predominantly in the peritrigonal region, and ventriculomegaly with ventricular wall irregularity (Baker et al. 1988; Flodmark et al. 1989). In addition to the above features, enlargement of cerebral sulci, thinning of corpus callosum, delayed myelination and thalamic lesions were also recognized (Truwit et al. 1992; Levinton and Gilles 1996; Yokochi 1997). The periventricular hyperintensity area is thought to reflect gliosis reacting to tissue damage. Although the nervous system of extremely premature infants is incapable of reacting by gliosis to tissue damage (Barkovich and Truwitt 1990), the relationship between periventricular hyperintensity area and gestational age in PVL is still unclear.

There have been several studies on the correlation between MRI findings and clinical profiles in PVL, but most involved only a relatively small number of patients (Feldman et al. 1990; Yokochi et al. 1991; Koeda and Takeshita 1992; DeVries et al. 1993; Fedrizzi et al. 1996; Olsén et al. 1997). The aim of this report is to investigate the relationship between the periventricular hyperintensity area and gestational age in PVL.

We conducted a retrospective study to clarify the possible correlation between MRI findings and clinical profiles in a large number of patients with PVL.

Subjects and Methods

MRIs of 70 patients with PVL were studied. Their birth weights and gestational ages were between 520 g and 2652 g (mean 1342 g), and 22 weeks and 39 weeks of gestation (mean 30.0 weeks), respectively. We evaluated their MRIs performed after 1 year of age, between 1 year 2 months and 8 years of age (mean: 2 years 4 months of age). When MRIs were performed more than once, the latest MRIs were studied. When the patients were given their last neurological examination, their ages were between 1 year 3 months and 15 years (mean: 4 years 9 months).

CP was divided into hemiplegia (arm and leg of one side affected), diplegia (legs more severely affected than arms) and tetraplegia (all four limbs affected, including a mixture of spasticity and dyskinesia). Diplegia was then subdivided into mild (children who can walk before 2 years of age), moderate (children who can walk from between 2 and 4 years of age or can walk with support at 2 years of age), and severe (children who can not walk at 4 years of age or can not walk with support at 2 years of age) according to their motor abilities. No children with diplegia were younger than 2 years of age. Hemiplegia was excluded from statistical analyses, because it was difficult to compare it with diplegia and tetraplegia.

The children's intelligence quotients (IQ) were examined by the Tanaka-Binet test or Wechsler Preschool and Primary Scale of Intelligence. Mental impairment was graded as follows; normal: $IQ \geqq 80$; mild: IQ 50-79; moderate: IQ 30-49; severe: $IQ \leqq 29$ or unmeasurable. IQ tests were not performed in some subjects, who were classified according to their detailed developmental status.

All MRIs were reviewed by one of the authors (S.F.). The ventriculomegaly with ventriclar wall irregularity was graded on a 4-point scale. 0: normal; 1: ventriculomegaly without irregular wall; 2: moderate irregular wall; and 3: severe irregular wall. The degree of reduced volume of periventricular white matter was graded on a 5-point scale. 0: normal; 1: slight loss confined to the peritrigone white matter; 2: moderate or more loss in the peritrigone white matter; 3: reduced white matter adjacent to trigones and bodies of lateral ventricles; and 4: extensive volume loss of white matter adjacent to trigones, bodies and anterior horns of lateral ventricles. The degree of periventricular hyperintensity on T2-weighted images was graded on a 4-point scale. 0: normal white matter; 1: thin hyperintensity area; 2: partially thick hyperintensity area; and 3: extensive hyperintensity.

The relationships between clinical profiles (CP, mental impairment and gestational age) and MRI findings (ventriculomegaly, reduction of periventricular white matter and periventricular hyperintensity) were investigated. Because the nervous system of very premature infants less than 28 weeks of gestation are thought to be incapable of reacting by gliosis to tissue damage (Barkovich and Truwitt 1990), the patients were divided into less or more than 28 weeks of gestational age.

The statistical comparisons were made using Fisher's exact test. A level of $p < 0.05$ was accepted as statistically significant.

Results

Figs. 1-3 showed samples of MRI findings.

Periventricular hyperintensity could not be evaluated in three MRIs because of no or unclear films on T2-weighted images. Fifteen children had no CP. Three had hemiplegia, seven had mild diplegia, eight had moderate diplegia, sixteen had severe diplegia, and twenty-one had tetraplegia. The relationship

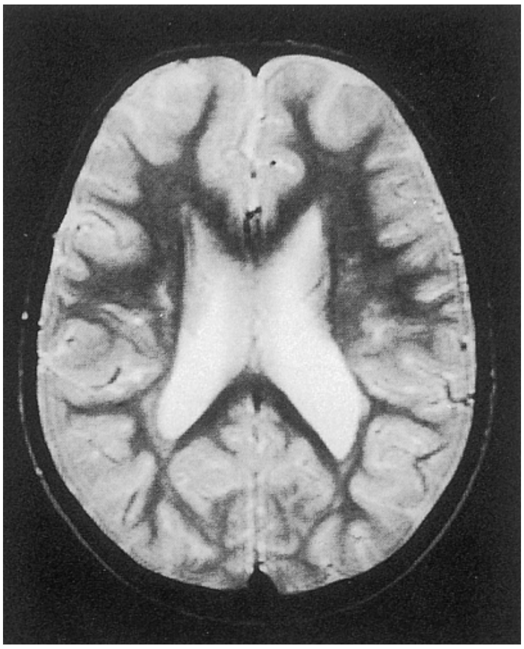

Fig. 1. MRI of a five-year-old girl with mild diplegia and normal intelligence. T2-weighted images (TR: 2500; TE: 90). Ventriculomegaly without irregular wall (grade 1), moderate loss of peritrigone white matter (grade 2), and partially thick periventricular hyperintensity area (grade 2) were noted.

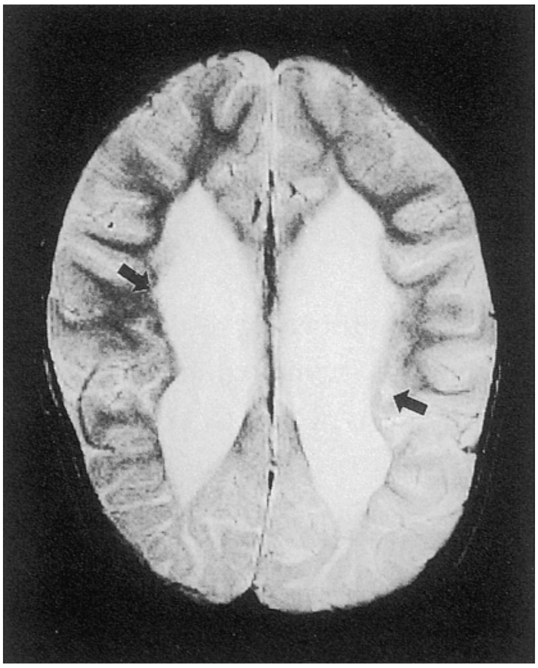

Fig. 2. MRI of a four-year-old boy with tetraplegia and severe mental retardation. T2-weighted images (TR: 2530; TE: 90). Severe irregular wall of lateral ventricles (grade 3), extensive loss of white matter adjacent to trigones, bodies and anterior horns of lateral ventricles (grade 4), and partially thick periventricular hyperintensity area (arrows) (grade 2) were noted.

between MRI findings and severity of CP is shown in Table 1. The grade of ventriculomegaly correlated with the severity of CP. All children with grade 2–3 had CP, whereas half of the children with grade 0–1 had no CP. The grade of

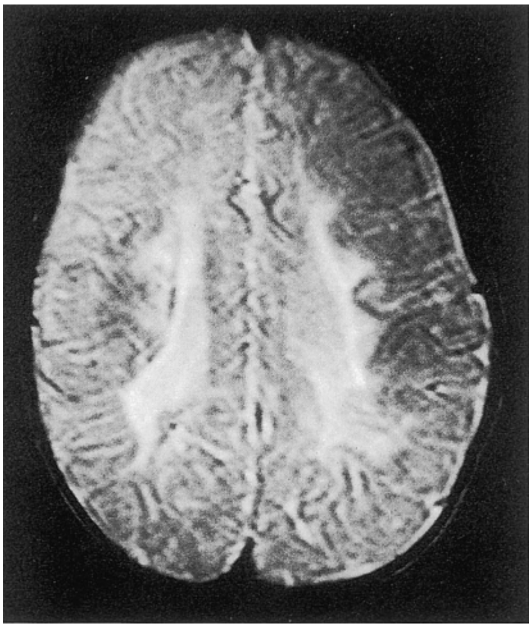

Fig. 3. MRI of a one-year-three-month-old girl. The patient had tetraplegia and moderate mental retardation at 2 years 6 months of age. T2-weighted images (TR: 2300; TE: 100). Moderate irregular wall of lateral ventricles (grade 2) and extensive periventricular hyperintensity area (grade 3) were noted.

TABLE 1. *The relationship between MRI findings and severity of CP*

Grade	Ventriculomegaly[a]				White matter[b]					Periventricular hyperintensity[c]				Total
	0	1	2	3	0	1	2	3	4	0	1	2	3	
CP														
None	9	6	0	0	9	6	0	0	0	1	9	5	0	15
Hemiplegia	0	0	3	0	0	1	1	1	0	0	0	2	1	3
Mild diplegia	2	3	2	0	0	1	6	0	0	0	1	5	1	7
Moderate diplegia	0	2	6	0	0	0	6	2	0	0	2	2	3	8
Severe diplegia	1	4	11	0	0	2	10	4	0	1	2	9	3	16
Tetraplegia	1	2	10	8	1	0	5	7	8	0	2	9	9	21
Total	13	17	32	8	10	10	28	14	8	2	16	32	17	70

Hemiplegia was excluded from statistical analyses.

[a]Enlargement and irregular wall of lateral ventricles. Comparisons were made among grade 0, 1, and 2–3.

[b]Reduction of periventricular white matter. Comparisons wee made among grade 0–1, 2, and 3–4.

[c]Periventricular hyperintensity on T_2-weighted images. Comparisons were made among grade 0–1, 2, and 3.

See text for each grade.

The statistical analyses were made between milder motor deficits (none and mild diplegia) and more severe motor deficits (moderate and severe diplegia and tetraplegia).

$^{**}p<0.01$ (Fisher's exact test).

TABLE 2. *The relationship between MRI findings and mental impairment*

Grade	Ventriculomegaly[a]				White matter[b]					Periventricular hyperintensity[c]			
	0	1	2	3	0	1	2	3	4	0	1	2	3
Mental impairment													
Normal	9	14	14	0	7	9	18	3	0	2	10	20	4
Mild	1	2	8	1	2	1	4	5	0	0	3	6	2
Moderate	1	1	8	1	0	0	5	5	1	0	2	1	7
Severe	0	0	2	6	0	0	0	1	7	0	0	4	4

Two cases with no mental evaluation were excluded.
Periventricular hyperintensity was not evaluated in 3 cases.
[a,b,c]See Table 1.
See text for each grade.
The statistical analyses were made between normal mental ability and mental impairment.
$^{*}p<0.05$, $^{**}p<0.01$ (Fisher's exact test).

TABLE 3. *The relationship between MRI findings and gestational age*

Grade	Ventriculomegaly[a]				White matter[b]					Periventricular hyperintensity[c]			
	0	1	2	3	0	1	2	3	4	0	1	2	3
Gestational age (weeks)													
<28	4	4	7	1	5	2	6	2	1	1	10	3	2
≥ 28	8	13	23	7	5	8	21	10	7	1	6	29	15

Three cases, who were not evaluated for periventricular hyperintensity, were excluded.
[a,b,c]See Table 1.
See text for each grade.
$^{**}p<0.01$ (Fisher's exact test).

reduction of periventricular white matter correlated well with the severity of CP. The degree of periventricular hyperintensity did not correlate well with the severity of CP.

Mental ability was not evaluated in two cases. Thirty-seven were evaluated as having normal mental ability. Twelve had mild mental retardation, eleven had moderate mental retardation, and eight had severe mental retardation. The relationship between MRI findings and mental impairment is shown in Table 2. The grade of ventriculomegaly did not correlate well with mental impairment. The grade of reduction of periventricular white matter correlated well with mental impairment. The degree of periventricular hyperintensity correlated with mental impairment to some degree. Eleven out of 31 children (35%) with grade 2 had mental retardation, while 13 out of 17 children (76%) with grade 3 had mental retardation.

Table 3 showed the relationship between MRI findings and gestational age. Periventricular hyperintensity was significantly lower in very premature children of less than 28 weeks than in those of 28 or more weeks of gestational age. Only five of 16 children (31%) at less than 28 weeks of age had grade 2-3, while 44 of 51 children (86%) at 28 or more weeks had grade 2-3 in periventricular hyperintensity. On the other hand, ventriculomegaly and reduction of white matter showed no significant difference.

Discussion

In this study, we investigated the correlation between MRI findings and clinical profiles of PVL using three parameters of the MRI findings. Ventriculomegaly with ventricular wall irregularity, reduced volume of periventricular white matter, and periventricular hyperintensity was graded according to the shape and extent. These were representative MRI findings of end-stage PVL (Baker et al. 1988; Flodmark et al. 1989).

The pathology of PVL is characterized by involution of cystic lesions, periventricular gliosis, demyelination, and loss of periventricular white matter (Banker and Larroche 1962; Takashima and Tanaka 1978). Peritrigonal white matter is the most commonly affected by PVL. With larger lesions, PVL extends anteriorly from peritrigone to periventricular white matter adjacent to body and anterior horn of lateral ventricles. Corticospinal tracts pass through the periventricular white matter and the leg distribution is close to the ventricles, so that PVL are likely to cause spastic diplegia rather than tetraplegia (Koeda et al. 1990).

The hyperintensity area on T2-weighted images is considered to be MRI expression of glial fibrils or locally increased water content in some but not all areas of astrogliosis (Nelson et al. 1991; Levinton and Gilles 1996). Furthermore, focal or diffuse glial injury by PVL may induce decreased myelinogenesis, which causes a reduced amount of periventricular white matter and ventriculomegaly with irregular wall (Levinton and Gilles 1996).

Our data demonstrated the grade of reduction of periventricular white matter and that of ventriculomegaly with irregular wall correlated well with the severity of CP. As the lesions in white matter extend anteriorly from the trigone, the motor disability is more severe. The degree of periventricular hyperintensity did not necessarily correlate with the severity of CP. These results were in agreement with the previous studies (Yokochi et al. 1991).

The grade of reduction of periventricular white matter correlated well also with mental impairment, but the grade of ventriculomegaly did not correlate well with mental impairment. The degree of periventricular hyperintensity correlated with mental impairment to some degree. A correlation between MRI findings and mental impairment was demonstrated in two earlier studies (Koeda and Takeshita 1992; Fedrizzi et al. 1996), but not in two others (Feldman et al. 1990; Yokochi et al. 1991). Fedrizzi et al. (1996) showed the severity of ventricular dilatation and the degree and extent of white matter reduction correlated significantly with the full scale and performance IQ. Koeda and Takeshita (1992) found that the volume of peritrigone white matter was significantly correlated with the visuo-perceptual impairment. Our data were in agreement with the latter reports.

We investigated the relationship between periventricular hyperintensity area and gestational age, because Barkovich and Truwitt (1990) stated the nervous system of extremely premature infants is incapable of reacting by gliosis to tissue damage. The distinct relationship between periventricular hyperintensity area and gestational age in PVL has not been established. We found a significantly lower degree of periventricular hyperintensity in children at less than 28 weeks of gestation. Our results support the view of Barkovich and Truwitt (1990) that periventricular hyperintensity should be evaluated in view of the gestational age.

The three limitations of our study are as follows. First, the follow-up periods were relatively short for evaluation of CP and mental ability, and minor neurodevelopmental dysfunction was not evaluated. Second, the conditions and timing of MRI were different among the cases. Third, our study is a retrospective one, thus some degree of bias was inevitable.

Despite the above-mentioned limitations, our study provides valuable information in PVL. First, our investigation included the largest number of children with PVL, including 21 with tetraplegia and 15 with no CP. Because of the large number of patients, distinct relationships between MRI findings and motor and mental impairment were found. Furthermore, most of the previous studies handled only children with diplegia (Yokochi et al. 1991; Koeda and Takeshita 1992; Fedrizzi et al. 1996), therefore their clinical utility was limited. Second, this is the first report showing a significantly lower degree of periventricular hyperintensity in extremely premature children. Finally, our data showed that the grade of reduction of periventricular white matter is the most reliable parameter for prognosis of children with PVL.

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References

1) Baker, L.L., Stevenson, D.K. & Enzmann, D.R. (1988) End-stage periventricular leukomalacia: MR evaluation. *Radiology*, **168**, 809-815.
2) Banker, B.Q. & Larroche, J.C. (1962) Periventricular leukomalacia of infancy: A

form of neonatal anoxic encephalopathy. *Arch. Neurol.*, **7**, 386–410.
3) Barkovich, A.J. & Truwitt, C.L. (1990) Brain damage from perinatal asphyxia: Correlation of MR findings with gestational age. *Am. J. Neuroradiol.*, **11**, 1087–1096.
4) De Vries, L.S., Eken, P., Groenendaal, F., van Haastert, I.C. & Meiners, L.C. (1993) Correlation between the degree of periventricular leukomalacia diagnosed using cranial ultrasound and MRI later in infancy in children with cerebral palsy. *Neuropediatrics*, **24**, 263–268.
5) Fedrizzi, F., Inverno, M., Bruzzone, M.G., Botteon, G., Saletti, V. & Farinotti, M. (1996) MRI features of cerebral lesions a nd cognitive functions in preterm spastic diplegic children. *Pediatr. Neurol.*, **15**, 207–212.
6) Feldman, H.M., Scher, M.S. & Kemp, S.S. (1990) Neurodevelopmental outcome of children with evidence of periventricular leukomalacia on late MRI. *Pediatr. Neurol.*, **6**, 296–302.
7) Flodmark, O., Lupton, B., Li, B., Stimac, G.K., Roland, E.H., Hill, A., Whitfield, M.F. & Norman, M.G. (1989) MR imaging of periventricular leukomalacia in childhood. *Am. J. Neuroradiol.*, **10**, 111–118.
8) Fujimoto, S., Togari, H., Takashima, S., Funato, M., Yoshioka, H., Ibara, S. & Tatsuno, M. (1998) National survey of periventricular leukomalacia in Japan. *Acta Paediatr. Jpn.*, **40**, 239-243.
9) Koeda, T., Suganuma, I., Kohno, Y., Takamatsu, T. & Takeshita, K. (1990) MR imaging of spastic diplegia: Comparative study between preterm and term infants. *Neuroradiology*, **32**, 187–190.
10) Koeda, T. & Takeshita, K. (1992) Visuo-perceptual impairment and cerebral lesions in spastic diplegia with preterm birth. *Brain Dev.*, **14**, 239–244.
11) Levinton, A. & Gilles, F. (1996) Ventriculomegaly, delayed myelination, white matter hypoplasia, and periventricular leukomalacia: How are they related? *Pediatr. Neurol.*, **15**, 127–136.
12) Nelson, M.D., Gonzalez-Gomez, I. & Gilles, F.H. (1991) Is gliosis detectable by magnetic resonance imaging? *Am. J. Neuroradiol.*, **13**, 1043.
13) Olsén, P., Pääkkö E., Vainionpää L., Pyhtinen, J. & Järvelin, M.R. (1997) Magnetic resonance imaging of periventricular leukomalacia and its clinical correlation in children. *Ann. Neurol.*, **41**, 754–761.
14) Takashima, S. & Tanaka, K. (1978) Development of cerebrovascular architecture and its relationship to periventricular leukomalacia. *Arch. Neurol.*, **35**, 11–16.
15) Truwit, C.L., Barkovich, A.J., Koch, T.K. & Ferriero, D.M. (1992) Cerebral palsy: MR findings in 40 patients. *Am. J. Neuroradiol.*, **13**, 67–78.
16) Yokochi, K., Aiba, K., Horie, M., Inukai, K., Fujimoto, S., Kodama, M. & Kodama, K. (1991) Magnetic resonance imaging in children with spastic diplegia: Correlation with the severity of their motor and mental abnormality. *Dev. Med. Child Neurol.*, **33**, 18–25.
17) Yokochi, K. (1997) Thalamic lesions revealed by MR associated with periventricular leukomalacia and clinical profiles of subjects. *Acta Paediatr.*, **86**, 493–496.