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# Metabolic Properties of Band Heterotopia Differ from Those of Other Cortical Dysplasias: A Proton Magnetic Resonance Spectroscopy Study

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**Summary:** *Purpose*: To assess the biochemical properties of band heterotopia in comparison with other cortical developmental malformations (CDMs) by using proton magnetic resonance spectroscopy ($^1$H-MRS).

*Methods*: We performed localized single-voxel $^1$H-MRS studies on 13 patients [five band heterotopia (BH), two focal cortical dysplasia (CD), two unilateral CD, one bilateral perisylvian dysplasia, three hemimegalencephaly]. CDMs other than BH were categorized as CD. Spectra were acquired from volumes of interest (VOIs) localized in the CD and in normal-appearing cortex on the contralateral side. In BH patients, the VOIs were the external cortex and the laminar heterotopia. For the BH study, spectra also were obtained from the cortex of age-matched normal volunteers.

*Results*: The spectra of CD lesions were characterized by significantly lower ratios of *N*-acetyl aspartate to creatine (NAA/Cr) and by higher choline to Cr (Cho/Cr) ratios than in the contralateral remote cortex ($p = 0.01$ and 0.01, respectively). The NAA/Cr and Cho/Cr ratios of the external cortex of BH were not significantly different from those of normal volunteers. The NAA/Cr ratio of the laminar heterotopia was not significantly different from that of the external cortex ($p = 0.12$) or normal volunteers ($p = 0.60$), whereas Cho/Cr was significantly higher in laminar heterotopias than in the external cortex ($p = 0.04$) or controls ($p = 0.03$).

*Conclusions*: $^1$H-MRS can distinguish between the metabolic properties of BH and CD. **Key Words:** Cortical dysplasia—Band heterotopia—Proton magnetic resonance spectroscopy.

Cortical developmental malformations (CDMs) are caused by disruption of neuronal proliferation, migration, or cortical organization (1,2). They are clinically important conditions, often accompanied by intractable epilepsy and neurologic developmental deficits (3,4). Band heterotopia (BH) is a CDM that is caused by disruption of neuronal migration, and it is characterized by extensive bilateral plates of heterotopic gray matter just below the normotopic cortex (5). This subcortical heterotopia has unusual functional properties that are not observed in other CDMs. Functional magnetic resonance imaging studies have shown that subcortical heterotopia is activated together with the related external cortex during a motor task, suggesting that the heterotopia may be involved in normal brain activity (6,7).

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Neuropathologic studies have demonstrated that cytoarchitectural derangement occurs in CDMs. The characteristic abnormality in cortical dysplasia lesions is faulty cell differentiation, which produces immature, abnormal cells, such as giant neurons and bizarre glia cells, often referred to as "balloon cells" (8,9). In contrast, the abnormalities in BH are mild. The heterotopic gray matter consists of disarranged, but relatively well-differentiated, pyramidal cells (5). These distinct functional and cytoarchitectural properties that distinguish BH from other CDMs may correlate with different metabolic conditions.

Proton magnetic resonance spectroscopy ($^1$H-MRS) is a noninvasive way to evaluate metabolic conditions in tissues in vivo (10). MRS signals in the brain change in various pathologic conditions, such as metabolic diseases, brain neoplasms, epileptic foci, and CDMs (11), although BH has not been fully addressed. In this study, we used localized single-voxel $^1$H-MRS to investigate the metabolic profile of BH, and compared it with other CDMs.

## METHODS

We studied 13 patients (12 female and one male patients) with different types of CDM (Table 1). The patients' ages ranged from 1 to 34 years (average, 16 years). The objectives of this study were explained to the families and to the patients when possible, and informed consent was obtained.

The disorders were diagnosed from MR imaging (MRI) findings, with reference to a previously proposed MRI classification scheme (12). Because patients 3 and 4 were not strictly classified in the scheme, they were tentatively diagnosed as having unilateral cortical dysplasia. In both cases, the MRI showed hemispheric hypoplasia with multiple abnormal rough shallow gyri. Recently, Caraballo et al. (13) and Pascual-Castroviejo et al. (14) proved that unilateral polymicrogyria consisting of a hypoplastic hemisphere with diffuse abnormal gyri was polymicrogyria by using three-dimensional MRIs and histology. Patients 3 and 4 most likely belong to this category, although further consideration is required. Focal cortical dysplasia (CD), unilateral CD, and bilateral perisylvian dysplasia were categorized as CD and compared with BH.

Proton ($^1$H)-MRS signals are highly age dependent, especially in the first few years of life. Age-dependent changes are prominent in signals of *N*-acetyl aspartate and choline-containing compounds, whereas those of creatine and phosphocreatine are relatively stable throughout life (15). Therefore age-matched controls might be required. Because our CD patient group consisted of young children, the ethical problem of heavily sedating healthy children prevented us from making an age-matched control group. Therefore in this study, we compared the MRS signal of the lesion with that of the remote, putatively normal, contralateral cortex in the same patient by using a paired nonparametric test. By contrast, the BH patients were older, so normal healthy volunteers could be used as age-matched controls for BH. The control group consisted of five normal volunteers: three men and two women, with ages ranging from 8 to 34 years (average, 21 years).

$^1$H-MRS studies were performed at Tohoku University Hospital by using a 1.5-T MR unit that allows both imaging and spectroscopy (Magnetom Vision, Siemens). After obtaining conventional images in the axial, coronal, and sagittal planes, single-volume $^1$H spectra were obtained from a 1.5 × 1.5 × 1.5-cm voxel within CDM lesions and from the contralateral remote cortex as a control. Because of the laminar shape of the subcortical heterotopia of BH, the shape of the voxel was modified to 1.0 × 1.5 × 1.5 cm. Because peak intensity is proportional to the concentration of the substance, the change in voxel shape did not alter the signal ratios (11). Instead, the volume reduction might have reduced the signal-to-noise ratio (11), although the peaks were very recognizable in this modified voxel, as shown in Fig. 3. In the age-matched control group for BH, spectra were obtained from 1.5 × 1.5 × 1.5-cm voxels located in the parietal or occipital cortex. The repetition (TR) and echo (TE) times were 1,500 and 135 ms, respectively. After global and local shimming, and optimization of the water-suppression pulse, data were collected 128 times for each voxel and averaged.

Intense signals in the spectra were noted at 2.0, 3.0, and 3.2 ppm. The signal at 2.0 ppm is thought to be derived from *N*-acetyl–containing compounds, mainly *N*-acetyl aspartate (NAA), whereas the signal at 3.2 ppm is from choline-containing compounds (Cho), and that at 3.0 ppm is from creatine and phosphocreatine (Cr) (13). Because the Cr signal is homogeneously distributed throughout the brain and is relatively stable, even in dis-

**TABLE 1.** *Clinical features of patients with cortical developmental malformations*

| Case | Sex | Age (yr) | Category | MRI diagnosis | Seizure | | | | Mental retardation |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | Onset | Type | Frequency | EEG findings | |
| 1 | F | 1 | CD | Focal CD (R;PL) | 1 yr | BTS | 0/yr | Focal sp (R;aT-mT) | − |
| 2 | F | 9 | CD | Focal CD (bilateral;FL) | 5 yr | CPS | 1/day | Diffuse HVS, focal sp (R;pF) | + |
| 3 | M | 9 | CD | Unilateral CD (R) | 4 yr | GTC | 1/day | Focal sp (R;C) | + |
| 4 | F | 15 | CD | Unilateral CD (L) | 2 yr | GTC | 1/day | Focal sp (L;F, O, R;mT) | + |
| 5 | F | 20 | CD | Bilateral perisylvian CD | 6 yr | CPS | 1/day | Focal sp (Bilat;pT, F-aT) | − |
| 6 | F | 1 | CD | Hemimegalencephaly (R) | 1 mo | SPS | 1/mo | Focal sp, sp-w (R;F, O) | + |
| 7 | F | 19 | CD | Hemimegalencephaly (R) | 18 yr | CPS | 3/wk | Focal sp, sp-w (R;O) | + |
| 8 | F | 27 | CD | Hemimegalencephaly (L) | 2 mo | CPS, GTC, MC | 5/yr | Focal sp, sp-w (L;F) | + |
| 9 | F | 9 | BH | Band heterotopia | 8 mo | CPS | 5/mo | Focal sp (L;pT-O, R;O) | + |
| 10 | F | 14 | BH | Band heterotopia | 2 yr | Multiple (Lennox)[a] | 3/day | Diffuse slow sp-w | + |
| 11 | F | 21 | BH | Band heterotopia | 4 yr | Astatic, CPS | 5/day | Focal sp, sp-w (L;C) | + |
| 12 | F | 24 | BH | Band heterotopia | 6 yr | SPS, CPS | 3/day | Focal sp (L;mT, pT, O) | + |
| 13 | F | 34 | BH | Band heterotopia | 3 mo | Multiple (Lennox)[a] | >10/day | Diffuse slow sp-w | + |

CD, cortical dysplasia (see Methods); BH, band heterotopia; R, right; L, left; PL, parietal lobe; FL, frontal lobe; BTS, brief tonic spasm; CPS, complex partial seizure; GTC, generalized tonic-clonic seizure; MS, myoclonic seizure; SPS, simple partial seizure; sp, spike; sp-w, spike and wave; HVS, high-voltage slow wave.

[a] Multiple seizure types include SPS, atypical absence, atonic, and tonic seizures.

TABLE 2. *$^1$H-MRS metabolite ratios*

| | CD (n = 8) | | BH (n = 5) | | |
|---|---|---|---|---|---|
| | Lesion | Contralateral remote cortex | Heterotopic layer | External cortex | Age-matched control (normal cortex) |
| NAA/Cr | 1.46 ± 0.37 | 2.02 ± 0.46 | 1.65 ± 0.21 | 1.72 ± 0.22 | 1.84 ± 0.09 |
| Cho/Cr | 1.14 ± 0.23 | 0.85 ± 0.14 | 0.87 ± 0.13 | 0.65 ± 0.11 | 0.60 ± 0.53 |

Values are presented as the average ± standard deviation (SD).
CD, cortical dysplasia; BH, band heterotopia; NAA/Cr, *N*-acetyl aspartate to creatine; Cho/Cr, choline to creatinine.

ease, it is often used as an internal standard (11,15). Therefore, the peak amplitudes of these three signals were measured and analyzed in terms of the NAA/Cr and Cho/Cr ratios.

The NAA/Cr and Cho/Cr ratios for CD lesions and for the contralateral side are plotted in the figures, and the summarized data are presented in Table 2 as the average ± standard deviation. Statistical differences between the CD lesions and the contralateral normal cortices were assessed by using the Wilcoxon signed-rank test, a *paired* nonparametric test. This test also was used to compare the subcortical heterotopia with the external cortex of the BH patients. Subsequently, the Mann–Whitney *U* test was used to examine the difference between the external cortex or subcortical heterotopia and the cortex of normal volunteers.

## RESULTS

Figure 1 shows a representative spectrum from CD (patient 3). Because NAA and Cho signals are age dependent (15), the $^1$H-MRS signals of the lesion were compared with those of the contralateral remote cortex in the same patient. Compared with the contralateral remote cortex (Fig. 1A), the NAA/Cr ratio was reduced in the lesion, whereas the Cho/Cr ratio was increased (Fig. 1B). The results for the eight patients with CD are plotted in Fig. 2. The NAA/Cr ratios in the CD lesions were significantly lower than those in the contralateral remote cortex (Wilcoxon signed-rank test, $p = 0.012$; Fig. 2A). In contrast, the Cho/Cr ratios in the CD lesions were significantly higher than in the contralateral remote cortex ($p = 0.012$; Fig. 2B). The average NAA/Cr and Cho/Cr ratios for the CD lesions are listed in Table 2. Patients 1 and 6 were 1-year-old children (shown by open circles in Fig. 2). The NAA/Cr ratios for the contralateral remote cortex (Fig. 2, Contra.) in these cases were lower than those in the older CD patients, whereas the Cho/Cr ratios were higher, which is in line with previously reported developmental changes in MRS signals (15). In these patients, the NAA/Cr ratios also were reduced in the CD lesion, and the Cho/Cr ratios were increased.

The NAA/Cr and Cho/Cr ratios of the external cortex of BH patients were not significantly different from those of the normal cortex of the age-matched controls (Mann–Whitney *U* test, $p = 0.12$ and 0.60, respectively). Figure 3 shows representative spectra from the external cortex and the heterotopic layer of BH (patient 11). The NAA/Cr ratios of the heterotopic layer were not significantly different from those of the external cortex (Wilcoxon signed-rank test, $p = 0.50$) or the control group cortex (Mann–Whitney *U* test, $p = 0.12$; Fig. 4A). By contrast, the Cho/Cr ratios of the laminar heterotopia

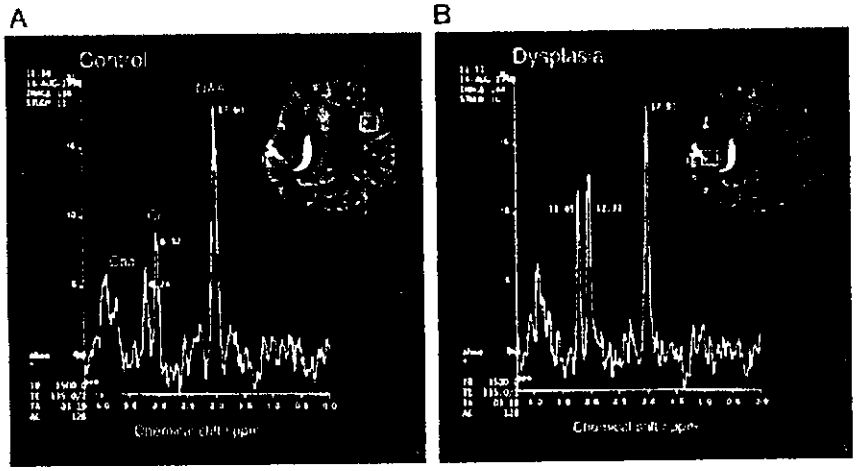


**FIG. 1.** $^1$H-magnetic resonance spectroscopy (MRS) spectrum acquired from a 9-year-old boy with focal cortical dysplasia. The localized volume of interest (VOI) is outlined on the magnetic resonance image (inset). Measurements were made of the remote normal cortex **(A)** and the dysplastic lesion **(B)**. The resonances of choline (Cho) at 3.2 ppm, creatine (Cre) at 3 ppm, and *N*-acetyl aspartate (NAA) at 2 ppm were detected in both cases with different signal-intensity ratios.

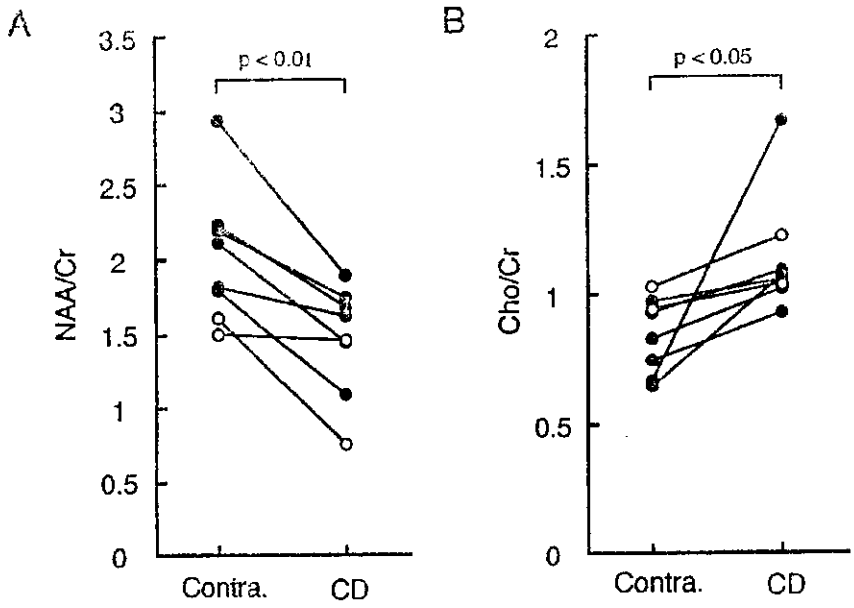


FIG. 2. The summarized $^1$H-magnetic resonance spectroscopy (MRS) results for the cortical dysplasia patients. **A:** *N*-acetyl aspartate (NAA)/creatinine (Cr) ratio in the dysplastic cortex (CD) and in the contralateral remote cortex as a control (Contra). The NAA/Cr ratio in CD was significantly lower than that in Contra ($p < 0.01$). **B:** Cho/Cr ratio in CD and in Contra. The Cho/Cr ratio was significantly elevated in CD ($p < 0.05$). Lines connect the data from the same patient. Open circles are the plots of 1-year-old patients (see text).

were significantly higher than those of the external cortex (Wilcoxon signed-rank test, $p = 0.04$) and the control group cortex (Mann–Whitney *U* test, $p = 0.03$; Fig. 4B). The average NAA/Cr and Cho/Cr ratios of the heterotopic layer, external cortex of BH, and control group cortex are summarized in Table 2.

## DISCUSSION

In this study, the NAA/Cr ratio was significantly decreased in the CD lesions, compared with the contralateral remote cortex. This result agrees with previous MRS reports concerning CD (16–18). CD lesions contain morphologically abnormal neurons, whereas the density of neurons and glia is normal (16). These neurons have unusual electrophysiologic properties (2,19). Immunocytochemically, there is a delay in the developmental switch from the $\alpha_1$ to $\alpha_2$ subunits of γ-aminobutyric acid A ($GABA_A$) receptors, and expression of the 2A (NR2A) *N*-methyl-D-aspartate (NMDA) receptor subunits also is delayed, suggesting functional immaturity of the neurons (20). These abnormalities in neuronal maturation may underlie the reduced NAA signal in the CD lesion, rather than neuronal loss or secondary gliosis.

Another significant finding in CD in our study was the increased Cho/Cr ratio in the lesions. Cho is a constituent of the phospholipid metabolism of cell membranes and may reflect membrane turnover (11). The Cho signal

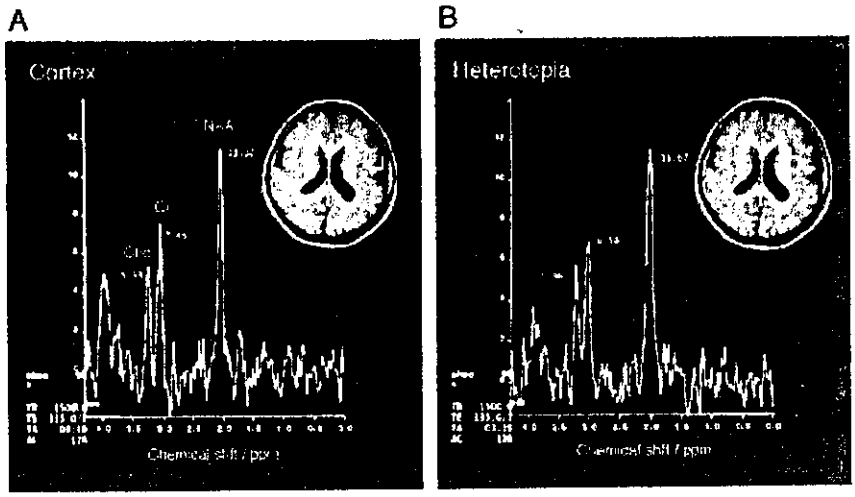


FIG. 3. $^1$H-magnetic resonance spectroscopy (MRS) spectrum acquired from a 21-year-old woman with band heterotopia. The volume of interest (VOI; inset) for the heterotopic area was modified because of its laminar structure (1.0 × 1.5 × 1.5 cm). Measurements of the external control cortex **(A)** and laminar heterotopia **(B)** were made.

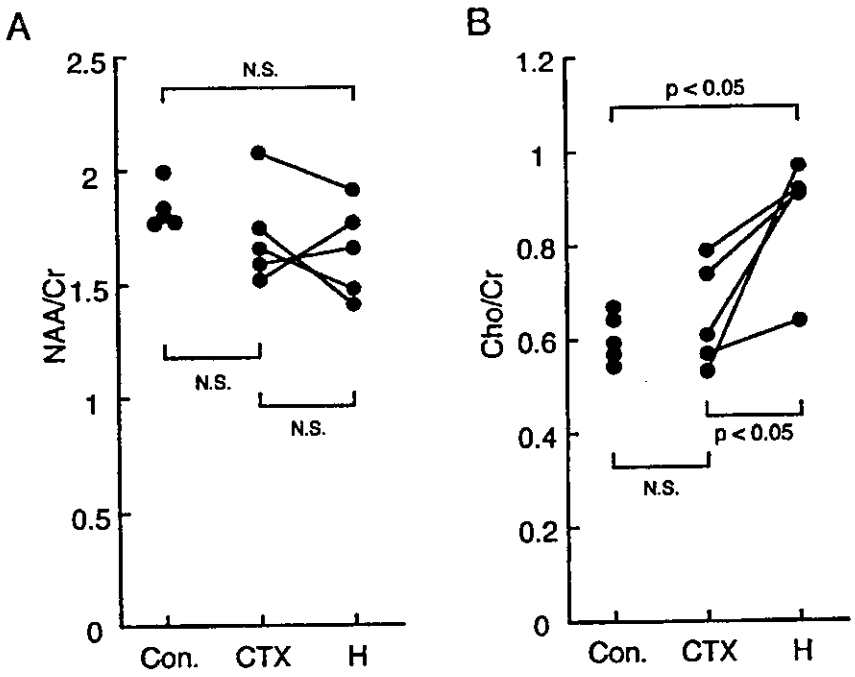


FIG. 4. The summarized $^1$H-magnetic resonance spectroscopy (MRS) results for the band heterotopia patients. A: *N*-acetyl aspartate (NAA)/creatinine (Cr) ratio in the cortex of a normal volunteer (Con.), in the external normal cortex of the patients (CTX), and in the laminar heterotopia (H). There were no significant differences in the NAA/Cr among Con., CTX, and H. B: The choline (Cho)/Cr ratio in CD and Con. The Cho/Cr ratio was significantly higher in H ($p < 0.05$), whereas no significant difference was seen between Con. and CTX. Lines connect the data from the same patient. N.S., no significant difference.

tends to be highest in very young infants (15); therefore the increased Cho/Cr ratio in the CD lesions suggests that there is increased membrane turnover and tissue immaturity. A previous article reported that the Cho signal is decreased in the CD area (18). Although the reason for this discrepancy remains unknown, a possible explanation may lie in the difference in the age of the patients. In our study, the patients with CD were younger than those in the previous report (18). The Cho level in CD might change with age, presumably in a manner different from that of the normal brain. Further study is required to clarify the metabolic differences between other CDMs and to assess age-dependent changes in the MRS signal of CD lesions.

BH is characterized by a laminar heterotopia that is mainly caused by mutations in the *doublecortin* gene in Xq22.3 (21). Histologically, the external cortex appears nearly normal, with the usual six layers (5). The heterotopic band consists of morphologically differentiated pyramidal cells that are randomly arranged (5). Fluorodeoxyglucose positron emission tomography (PET) and single-photon emission computed tomography (SPECT) findings showed similar glucose metabolism and blood flow in the heterotopic band and normal external cortex (22), whereas these studies showed variably abnormal patterns in other CDMs (22,23). These histologic and functional findings imply fewer metabolic abnormalities in BH than in other CDMs. Our study revealed that the NAA/Cr ratio of the laminar heterotopia did not significantly differ from that of the external cortex in BH or of the normal cortex of volunteers. Previous studies have shown that the NAA signal from subcortical heterotopia ranges from normal to below normal, suggesting that the maturity differs from case to case (17). A few cases of BH have had a normal or slightly decreased NAA signal (6,17). A recent functional MRI study reported that finger tapping activated both the normal sensorimotor cortex and the laminar heterotopia facing it, suggesting that the laminar heterotopia of BH has specific synaptic connections with the external cortex (6,7). Synaptic stimulation may facilitate neuronal differentiation in BH (24). By contrast, the Cho/Cr signal was significantly higher in the heterotopic area than in the cortex. The intense Cho signal may result from unusual Cho turnover. Another possible explanation is the presence of bundles of myelinated fibers projecting from the neocortex to remote brain areas, which pass through the laminar heterotopia (5). As shown in MRS spectra of the white matter, myelinated fibers have a relatively intense Cho signal (15); therefore these fibers may enhance the Cho signal from the laminar heterotopia.

This study revealed that the $^1$H-MRS signals of BH were relatively normal, suggesting that neurons in the heterotopic tissue of BH are relatively well differentiated. However, BH is often associated with intractable epilepsy, although the motor and mental impairment in BH is less severe than in other diffuse CDMs. Therefore the results of MRS do not predict the severity of the epilepsy in BH. In CD patients, there also was no obvious correlation between the metabolite ratios and the severity of the neurologic symptoms, as in previous reports (16–18); therefore the MRS data are thought to

correlate more with developmental abnormalities or tissue disorganization than with the clinical severity of the disease in the patients.

The tissue of CD consists of abnormally developed cells and is highly epileptogenic (19,25). By contrast, the heterotopic neurons in BH are relatively differentiated; consequently, the mechanism for the epileptogenicity of BH might be distinct from that of CD. Interestingly, in the *tish* rat, an epileptic model rat for band heterotopia, the heterotopic neurons have aberrant connections with neurons in the external cortex (26), and the external cortex is responsible for initiating the seizure discharges in heterotopic tissue (27). In BH patients, intraoperative electrocorticography with a deep electrode showed that clinical seizures arise in the external cortex, whereas electrical activity in heterotopia does not produce clinical seizures directly (28). Focal surgical removal of the putative epileptogenic tissue in BH patients produces inadequate results, even in the presence of a localized epileptogenic area (28). These experimental and clinical reports suggest that epileptic activity is not simply generated within the heterotopic tissue. The abnormal neuronal network formed by the heterotopic neurons might be responsible for the epileptogenicity in BH. Further investigation is required to clarify the mechanism of epileptogenicity in BH.

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# LONG-TERM FOLLOW-UP STUDY OF WEST SYNDROME: DIFFERENCES OF OUTCOME AMONG SYMPTOMATIC ETIOLOGIES

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**Objectives** To evaluate the outcome of West syndrome and to elucidate the differences in the outcome related to the timing of brain injury.

**Study design** Medical records of 60 patients who were followed regularly for more than seven years were reviewed. The following clinical features were assessed: onset, seizure evolution, electroencephalography and intelligence. Those variables were compared among five groups: cryptogenic, prenatal, preterm, term, and postnatal groups.

**Results** The onset ages of the postnatal group were later than those of the others ($P < .05$). The relapse after adrenocorticotropic hormone therapy of the preterm group was the earliest among the groups ($P < .05$). Regarding encelphalography, the ratio of patients with focal discharges was higher in the postnatal group than in the prenatal group ($P < .05$). The ratios of patients in whom focal epilepsy developed were higher in the term and postnatal group than in the cryptogenic and prenatal group ($P < .05$). The term group showed similar characteristics to those of the postnatal group. Seven of the 60 had normal intelligence, including three girls with tuberous sclerosis.

**Conclusion** The diverse outcomes of West syndrome depending on etiology seemed to be related to the timing of brain injury and brain development. *(J Pediatr 2003;143:231-5)*

West syndrome, an intractable epileptic syndrome, has a wide range of developmental outcomes from normal to profoundly impaired.[1,2] It is classified into cryptogenic and symptomatic groups, and the latter is usually divided further into three categories: prenatal, perinatal, and postnatal groups.[1,2] The *cryptogenic* group includes patients with good outcomes.[2,3] On the contrary, in the *symptomatic* group, some diagnoses (malformation/dysgenesis, early infections, and tuberous sclerosis) have worse outcomes.[3] The varied developmental outcomes of West syndrome are thought to depend on its miscellaneous etiologies. West syndrome is an age-dependent epileptic encephalopathy related to brain maturation. Features such as the electroencephalography (EEG) findings and outcomes are also considered to be associated with brain maturation.[4] However, it is unknown whether the timing of brain injury influences the features and outcome of West syndrome. We investigated the long-term outcomes of 60 patients with West syndrome, and report the outcomes of the perinatal group that differ according to gestational weeks.

## SUBJECTS AND METHODS

We retrospectively reviewed the medical records of 60 patients (32 boys and 28 girls) in whom West syndrome was diagnosed and who were examined regularly for more than seven years by pediatric neurologists at Saitama Children's Medical Center, Saitama, Japan. West syndrome was diagnosed in the patients with both epileptic spasms and hypsarrhythmia. Investigations were performed on every patient to identify the etiologic factor of West syndrome. These included neurologic and ophthalmologic examinations; EEG performed before, during, and after treatment; brain computed tomography (CT) in

| | | | |
|---|---|---|---|
| ACTH | Adrenocorticotropic hormone | EEG | Electroencephalography |
| CT | Computed tomography | MRI | Magnetic resonance imaging |

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Table I. Ages at decision of outcome and onset of 60 patients with West syndrome in each etiologic category

| | Total | Cryptogenic | Prenatal | Perinatal | | Postnatal |
|---|---|---|---|---|---|---|
| | | | | Preterm | Term | |
| No. of patients | 60 | 13 | 23 | 11 | 7 | 6 |
| Gender (M:F) | 32:28 | 6:7 | 13:10 | 5:6 | 5:2 | 3:3 |
| Age at decision of outcome (y)* | 12.3 ± 4.1 | 11.5 ± 4.4 | 12.7 ± 4.8 | 12.2 ± 3.9 | 12.4 ± 2.8 | 12.2 ± 3.5 |
| Preceding seizure | 8/60 | 0/13 | 5/23 | 1/11 | 1/7 | 1/6 |
| Onset age of epileptic spasms (month)* | 6.7 ± 4.1 | 6.5 ± 4.5 | 4.6 ± 1.7 | 8.7 ± 2.8† | 5.8 ± 3.4 | 13.1 ± 5.8‡ |

*Data expressed as mean ± SD.
†Significantly different from cryptogenic and prenatal groups ($P < .05$).
‡Significantly different from cryptogenic, prenatal and term groups ($P < .05$).

all patients and magnetic resonance imaging (MRI) in 47 patients; biochemical and metabolic tests including urine amino acids and organic acids; and chromosomal analysis.

All patients were treated according to the following protocol. First, sodium valproate (30-50 mg/kg) was administered for one to two weeks. If no improvement was obtained, pyridoxine (10-30 mg/kg) and/or clonazepam (0.02-0.04 mg/kg) were added successively. When these administrations during two to four weeks failed to control the spasms, synthetic adrenocorticotropic hormone (ACTH) was given intramuscularly at 0.015 to 0.02 mg/kg/day for two weeks. While the patients were receiving ACTH, the previous medications were continued. Natural ACTH is not commercially available in Japan; therefore, we use a synthetic analog of ACTH considering 1 mg of synthetic ACTH to be equivalent to 40 IU of natural ACTH. The effectiveness of each drug was estimated on the frequency of spasms and interictal EEG findings. "Good response" was defined as both achievement of disappearance of spasms for more than one month and resolution of hypsarrhythmia. If none of the above treatments could control the spasms, various drugs, including gamma globulin and thyrotropin-releasing hormone, were administered.

The medical records of these 60 patients were reviewed for the ages at onset of epileptic spasms, other concomitant/preceding seizures, evolution of seizure type, interictal EEG recordings including, if applicable, ictal recordings, seizure frequency, and developmental status during follow-up. The developmental status was evaluated using several conventional tests appropriate for each developmental state (Tsumori-Inage developmental questionnaire, Kinder infant development scale, Tanaka-Binet Intelligence Scale, Japanese Wechsler Intelligence Scale for Children-Revised (Japanese Wechsler Intelligence Scale for Children-III). The outcome of developmental status was classified by those examinations into four categories: normal (IQ, DQ $\geq$ 75), mild retardation (50 $\leq$ IQ, DQ $<$ 75), moderate retardation (25 $\leq$ IQ, DQ $<$ 50) and severe retardation (IQ, DQ $<$ 25).

The cryptogenic group was defined according to the following criteria: normal pregnancy; normal development and no eventful past history before onset of epileptic spasms; no preceding seizure before epileptic spasms; no abnormality of brain CT and/or MRI; and no focal abnormality on neurologic examinations. The symptomatic group was classified into three etiologic subgroups depending on the timing of presumed causes: postnatal group, perinatal group, and prenatal group. The postnatal group consisted of etiologies that occured after one month, with no perinatal abnormality. The perinatal group included brain insults caused by neonatal asphyxia, intracranial hemorrhage, hypoglycemia, and respiratory distress syndrome. Moreover, we divided the perinatal group into two subgroups: term group (born after 37 gestational weeks) and preterm group (born before 37 gestational weeks). The prenatal group included the patients with etiologies before birth, ie, cerebral dysplasias, chromosomal aberrations, multiple congenital anomalies, intrauterine abnormalities or inherited disorders. When two or more symptomatic etiologies were suspected in one patient, we classified him into an earlier etiologic group; for example, when a patient with a brain anomaly had perinatal asphyxia, the patient was put into the prenatal group.

The Mann-Whitney $U$ test or Fisher's exact probability test were used for statistical analysis. Differences were considered significant with a $P$ value of $\leq .05$.

## RESULTS

Table I shows the number of patients, average ages at decision of outcome, and onset of epileptic spasms in each etiologic category. The prenatal group consisted of tuberous sclerosis (6 patients); Down syndrome (3); progressive encephalopathy with edema, hypsarrhythmia, and optic atrophy syndrome (2); hemimegalencephaly (1); focal cortical dysplasia (1); microcephaly (1); ring 4 chromosome (1); porencephaly (1); and unknown (7). All of these patients presented developmental delay before the onset of the spasms, and three had preceding seizures. Two were also had quadriplegia, and one had congenital visual acuity loss without progressive brainstem-cerebellar atrophy. A family history of epilepsy was presented in one. In the patients classified into the preterm group, two patients were born between 24 to 28 gestational weeks, 6 between 29 to 32 gestational weeks and 3 between 33 to 36 gestational weeks, respectively.

All patients of the preterm group had respiratory distress syndrome and/or asphyxia during the perinatal periods. CT and/or MRI of the patients of the preterm group displayed periventricular leukomalacia in 8 patients, severe brain atrophy

**Table II. Response to ACTH therapy**

| | Total | Cryptogenic | Prenatal | Perinatal | | Postnatal |
|---|---|---|---|---|---|---|
| | | | | Preterm | Term | |
| No. of patients treated with ACTH | 44 | 10 | 18 | 6 | 5 | 5 |
| Good response to ACTH | 36/44 | 8/10 | 14/18 | 5/6 | 5/5 | 4/5 |
| Relapse of any kind of seizures | 29/36 | 7/8 | 8/14 | 5/5 | 5/5 | 4/4 |
| Relapse as epileptic spasms | 13/29 | 3/7 | 4/8 | 3/5 | 1/5 | 2/4 |
| Duration prior to relapse (mo) | 19.5 ± 27.0 | 26.3 ± 29.0 | 23.9 ± 35.9 | 2.9 ± 1.5* | 18.8 ± 24.1 | 20.3 ± 26.9 |

Duration before relapse after ACTH therapy expressed as mean ± SD.
*Significantly different from all the other groups ($P < .05$).

with ventricular enlargement in one, severe brain atrophy with porencephalic cysts in one and severe brain atrophy in one, respectively.

The term group included the patients with lesions caused by neonatal asphyxia in four, intracranial hemorrhage in two and hypoglycemia in one. The postnatal group consisted of 4 patients who suffered from bacterial meningitis and 2 who had subdural hematoma. CT and/or MRI of the term group and postnatal group showed diffuse cerebral atrophy accompanied by varied enlargements of ventricles, with or without focal lesions such as low density/abnormal intensity area in the thalamus, putamen or cerebral cortex, and calcifications.

Preceding seizures before the onset of spasms occurred in five cases in the prenatal group, which was a higher frequency than in the other groups; however, it was not statistically significant (Table I). The onset age of epileptic spasms differed among the groups. The average onset age of the prenatal group was the earliest, followed by those of the term, cryptogenic, preterm, postnatal groups in order of age. That of the postnatal group was significantly later than those of the others. And that of the preterm group was also significantly later than those of the cryptogenic and prenatal groups. Adapting conceptional ages for the preterm group, the average onset age became 6.3 ± 3.0 months old, which was not significantly different.

Initial valproate achieved cessation of spasms and improvement of hypsarrhythmia in three patients and the combination of valproate and clonazepam was effective in 10 patients. One patient responded to vitamin B6. Response to ACTH therapy did not differ between each group, and relapse of spasms after ACTH administration occurred most frequently in the preterm group, but was not statistically significant (Table II). The duration before relapse of seizures of the preterm group was significantly the shortest among the groups (Table II). Regarding the patients in whom ACTH therapy failed to control seizures, effective therapies were ketogenic diet in one patient of four to whom it was administered, and gamma globulin therapy administered to one of 11. Five patients were treated with thyrotropin-releasing hormone; it failed to control seizures in any.

The cryptogenic group comprised three patients with normal development, and the prenatal group included four patients with normal development, respectively (Table III). Six of them with normal intelligence were female, the other one was male and cryptogenic. The patients with normal development of the prenatal group included three with tuberous sclerosis and one with a small porencephalic cyst on the right temporo-occipital border. The patients with severe retardation in the cryptogenic group were significantly fewer than those in the prenatal and the postnatal groups. More than 60% of the patients with symptomatic West syndrome had severe mental retardation.

Regarding follow-up EEG, paroxysmal discharges disappeared in 7 of 13 cryptogenic patients, and that frequency was significantly higher than that in the term group (Table III). Four patients of 6 (66.7%) in the postnatal group and 4 of 7 (57.1%) in the term group manifested focal paroxysmal discharges. The ratio of patients with focal discharges was significantly higher in the postnatal group than in the prenatal group.

Twelve of 60 patients (20.0%) achieved remission of West syndrome and did not relapse during follow-up. In 25 of 60 patients (41.7%), West syndrome developed to localization-related epilepsy. All of the patients in the term group relapsed as localization-related epilepsy. The ratios of patients in whom localization-related epilepsy had developed were significantly higher in the term group and the postnatal group than in the cryptogenic group and the prenatal group (Table III).

Ten patients (76.9%) of the cryptogenic group had no seizures during the last year of follow-up. The ratio of patients without seizure during the last year showed significant differences between the cryptogenic group and the prenatal group, and the postnatal group (Table III). The seizure-free periods of the 10 cryptogenic patients ranged from 4 years 3 months to 12 years 9 months. Their intellectual outcomes were normal in three, mild retardation in two, moderate retardation in four, and severe retardation in two.

## DISCUSSION

This retrospective investigation not only confirmed the poor outcome of patients with West syndrome,[2-9] but also revealed the differences in the outcomes among symptomatic etiologies, especially concerning the perinatal group. Previous studies have examined the long-term outcome of patients with West syndrome, focusing on the effect of the ACTH and

Table III. Outcome of 60 patients with West syndrome

| (n) | Total (60) | Cryptogenic (13) | Prenatal (23) | Perinatal | | Postnatal (6) |
|---|---|---|---|---|---|---|
| | | | | Preterm (11) | Term (7) | |
| Intellectual outcome | | | | | | |
| Normal | 7 | 3 | 4 | 0 | 0 | 0 |
| Mild retardation | 5 | 2 | 1 | 1 | 1 | 0 |
| Moderate retardation | 13 | 5 | 3 | 3 | 1 | 1 |
| Severe retardation | 35 | 3* | 15 | 7 | 5 | 5 |
| Paroxysamal discharge | | | | | | |
| None | 15 | 7† | 5 | 2 | 0 | 1 |
| Diffuse | 9 | 1 | 6 | 1 | 0 | 1 |
| Multifoci | 16 | 0‡ | 8 | 5 | 3 | 0 |
| Focal | 20 | 5 | 4 | 3 | 4 | 4§ |
| Evolution of epileptic syndrome | | | | | | |
| Lennox-Gastaut syndrome | 7 | 1 | 5 | 0 | 0 | 1 |
| Other generalized epilepsy | 16 | 4 | 8 | 3 | 0 | 1 |
| Localization-related epilepsy | 25 | 2 | 6 | 6 | 7‖ | 4§‖ |
| Seizure frequency | | | | | | |
| Daily to weekly | 20 | 2 | 10 | 1 | 3 | 4 |
| Monthly | 12 | 1 | 5 | 3 | 2 | 1 |
| Seizure-free during >1 year | 28 | 10* | 8 | 7 | 2 | 1 |

*Significantly different from prenatal and postnatal groups ($P < .05$).
†Significantly different from term group ($P < .05$).
‡Significantly different from prenatal, preterm, and term groups ($P < .05$).
§Significantly different from prenatal group ($P < .05$).
‖Significantly different from cryptogenic group ($P < .05$).

antiepileptic agents,[6,8] the difference between cryptogenic and symptomatic groups,[9] and various factors probably influencing prognosis, including etiology.[2,3,5] Matsumoto et al pointed out the differences among cryptogenic, prenatal, and perinatal groups.[2] Cryptogenic West syndrome had a better prognosis, as in our study. Concerning the outcome among symptomatic etiologies, Table II showed an obvious discrepancy of relapse after ACTH therapy. The more important findings are that there were significant differences in the duration before relapse between the preterm group and the others (Table II). ACTH therapy may be inadequate for keeping the patients of the preterm group seizure-free. This may depend on factors concerned with cerebral white matter. ACTH therapy likely alters the water content in the white matter, especially periventricular white matter.[10] Another factor is the vulnerability of the brain of preterm infants. The brain injury of preterm infants, will be localized in deep white matter.[11] These relationships have been obscure; however, Konishi et al emphasized a certain connection between epileptic spasms and periventricular hyperintensity.[10] Okumura et al. revealed that West syndrome is one of the common complications of periventricular leukomalacia.[12] Periventricular white matter must have an important role in the facilitation and/or inhibition of epileptic spasms.

Our data has a therapeutic implication. For long-term follow-up, seizures were eventually controlled in more than half of the patients of the preterm group, similar to the cryptogenic group, whereas seizures were controlled in less than half of the other symptomatic groups (Table III). The preterm group showed the tendency of earlier relapse after ACTH therapy and better control of seizures for the long-term compared with the cryptogenic group. ACTH therapy will be occasionally accompanied by complications such as hypertension, brain shrinkage, cardiac hypertrophy, and infections.[10,13-18] Maeda et al reported permanent damage to the developing brain caused by ACTH.[19] Considering the risk of permanent brain damage and the limited effects of ACTH for the patients of the preterm group, other medications should be selected as an initial treatment for the preterm group.

The dosages of ACTH therapy in Japan, in this study also, are less than those used in the United States and Europe because synthetic ACTH has more adverse effects than natural ACTH.[8] Vigabatrin is considered to be a useful agent for West syndrome with tuberous sclerosis[20]; however, vigabatrin has not been available commercially in Japan. Topiramate, lamotrigine, and felbamate also have not been available. Such restrictions may influence the outcomes in this study, especially the outcomes of seizure control. But Ito et al reported that low-dose ACTH therapy is as effective as higher doses of natural ACTH.[8] Lamotorigine, topiramate, and felbamate are usually reserved for cases intractable to ACTH and/or vigabatrin, and vigabatrin is limited because of its retinal toxicity except for the cases with tuberous sclerosis.[21]

Therefore, we considered that differences in therapy had little influence on our results.

In the perinatal groups, the term group showed similar features to those of the postnatal group. Both groups showed the tendency of localized distribution of paroxysmal discharges and evolution to localization-related epilepsy during long-term follow-up (Table III). The differences in onset age among the groups, shown in Table I, also probably indicate necessary periods for regeneration after brain injury and organization of epileptogenicity. The later onset age of the postnatal group would reflect periods to reconstruct neuronal circuits in and around lesions, and that of the preterm group may imply the necessity of brain maturation to some extent for the occurrence of West syndrome.

The three girls in this series with tuberous sclerosis had normal intelligence in this series. The three male patients with tuberous sclerosis had mild to severe retardation. The prognosis for the prenatal group is usually considered to be poor. Riikonen described the group with tuberous sclerosis to have had the worst outcome.[3] However, Yamamoto et al mentioned 4 of 25 patients with tuberous sclerosis accompanied by West syndrome had normal intelligence.[22] We should consider that tuberous sclerosis, which belongs to the prenatal group, will differ from other prenatal etiologies, especially in female patients.

Responses to ACTH, seizure frequency and evolution of epileptic syndrome were different among the symptomatic groups; however, mental outcomes were less different among them (Tables II and III). More than half of the patients of the preterm group had no seizures for one year at least. In the cryptogenic group, 76.9% of the patients had no seizures during one year, and their seizure-free periods ranged from 4 years 3 months to 12 years 9 months. But their intellectual outcomes were not very good. The cryptogenic group comprised four patients with moderate retardation and two with severe retardation. These findings suggest that seizure control is essential, but does not ensure a good outcome.

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# てんかん重積時におけるミダゾラムの有効性

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Midazolam treatment of status epilepticus In epileptic children

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## はじめに

midazolam（MDL）は水溶性のbenzodiazepine（BZP）系薬剤で1980年代後半よりけいれん重積に対する有用性が報告されている。現時点では麻酔前投与，全身麻酔の導入と維持などの効能で薬価収載されているがてんかん，けいれん発作時の効能効果の追加はなされていない。当施設では1997年からてんかん発作重積時に使用しており，これまでの使用経験を後方視的に検討したので報告する。

## 対象と方法

埼玉県立小児医療センター神経科で経過観察中のてんかん患者で，1997年10月1日～2001年12月31日の間にてんかん重積発作で入院しMDLが投与された26例，のべ43回の入院におけるMDL投与機会（以下，機会と略す）を対象として後方視的に検討した。これら43機会のMDLの投与時年齢，投与量，持続静注時間，有効性と副作用を調査し，てんかん診断，てんかん重積の誘因，重積時の発作型が有効性と関連するか検討した。重積時発作型は痙攣性重積発作か非痙攣性重積発作の2群に大別した。

当施設ではけいれん重積時の対応として，DZPを第一選択薬として，以後は担当医の判断でlidocaine，phenytoin（PHT），MDLを適宜使用し，これらで頓挫できない場合にthiopentalを使用することを原則としていた。なお，MDLの使用機会でその有効性が確認された一部の症例では2回目以降の重積時にはMDLを第一選択として用いた。MDLの投与量は通常下記のごとくであり，主治医の判断で適宜増減した。まずMDL 0.15-0.40mg/kgを1～2分かけゆっくり静注し，完全には重積が頓挫しない場合に静注を繰り返しても良いこととした（初期導入静注）。初期導入静注が有効で再発予防が必要と判断した場合に，0.06～0.18 mg/kg/hrの投与量でMDLの持続静注を開始した。持続静注開始後に発作の再発があれば，完全抑制まで15分程度毎に0.06mg/kg/hrずつ増量した。さらに，MDL使用時には呼吸数，心拍とともにパルスオキシメーターで酸素飽和度を全例でモニターし，血圧および呼吸数は適宜計測した。減量に際しては0.03～0.06mg/kg/hrずつ2～3時間毎に減量した。なお，初期導入静注無効例は持続静注を試みることなく，すみやかに他剤を試みた。また，有効性の評価は初期導入静注ではMDL投与後15分以内にけいれん重積が頓挫した場合を有効，持続静注では24時間以上発作の再発を認めず，減量中止後48時間以内に再発を認めないものを有効とした。

なお，midazolamはけいれん発作に対する使用が効能効果として未承認であるため保護者に口頭で同意を得た後に実施した。

## 結果

対象となった症例のてんかん診断とMDL投与時年齢を表1に示した。症候性局在関連性てんかんが34機会と大部分を占め，その半数が前頭葉てんかんだった。43機会における重積前の発作頻度，内服抗てんかん薬数とBZP系薬剤の内服の有無，重積誘因，重積発作型とMDL使用前の抗てんかん薬を表2に示した。なお，MDLの選択順位は22機会において第3選択として使用された。頻度順では次にそれぞれ6機会で第2選択と第4選択，4機会では第1選択，3機会で第5選択，2機会では第6選択薬として使用された。

表1　てんかん診断別のMDL投与機会数、投与時年齢

| 診断名 | | 機会数（症例数） | 投与時年齢（平均） |
|---|---|---|---|
| 症候性局在関連性てんかん | | 34機会（22例） | 0.2～18.4(4.9)歳 |
| | 前頭葉てんかん | 16機会（8例） | 0.8～18.4(5.4)歳 |
| | 側頭葉てんかん | 2機会（2例） | 5.9～8.3（7.1）歳 |
| | 後頭葉てんかん | 10機会（6例） | 0.2～7.8（4.5）歳 |
| | 焦点不明 | 6機会（6例） | 0.9～10.9(3.5)歳 |
| 乳児重症ミオクロニーてんかん | | 9機会（4例） | 1.6～8.9（3.6）歳 |
| 全体 | | 43機会（26例） | 0.2～18.4(4.6)歳 |

37機会で初期導入静注が行われ，初回静注量は0.15～0.40 mg/kgの範囲で平均では0.22mg/kgだった。うち15機会ではさらに1～2回投与し総静注量は0.15～0.90mg/kg，平均で0.35mg/kgとなった。28機会（75.7％）で有効だった。初期導入静注が有効だった28機会のうち10機会は持続静注を要さず，残りの18機会でのみ引き続き持続静注が行われた。18機会の持続静注開始量は0.06～0.24mg/kg/hr，平均0.18mg/kg/hrでだった。発作再発のため7機会で増量され5機会で有効，最大投与量は0.06～0.60mg/kg/hr，平均で0.27mg/kg/hrとなった。持続静注時間は4～288時間，平均で51.3時間だった。持続静注開始後再発し増量により有効となった5機会を含む13機会（72.2％）において持続静注が有効だった。なお，初期導入静注が無効だった9機会では持続静注を行わず他剤が試みられた。

この他に6機会では他剤によってんかん重積発作が頓挫後に再発予防目的でMDLの持続静注が行われた。これら6機会では0.12～0.48mg/kg/hr，平均0.25mg/kg/hrで持続静注を開始し，最大投与量は0.12～0.72 mg/kg/hr，平均0.33mg/kg/hrで，投与期間は3～96時間，平均31.8時間であった。このうち1機会では持続静注開始後に発作が再発し増量によって発作はコントロールできMDL持続静注が有効だった。2機会では再発し，その後も発作はコントロールされず無効，残りの3機会は再発もなく経過した。

副作用はいずれも軽度の酸素飽和度低下（$SpO_2$で70～80台）で，初期導入静注37機会中2機会（5.4％），持続静注24機会中3機会（12.5％）で認めた。初期導入静注時に酸素飽和度が低下した2機会は4p-症候群の重症心身障害児の同一症例で，それぞれ$O_2$を7時間，4時間投与のみで改善した。総投与量は0.5mg/kg，0.4mg/kgで，けいれん重積に関しては前者は有効で，後者は無効であった。この症例はさらに他の2機会で0.45mg/kgと0.3mg/kgの投与が行われたいたが，それらの機会では酸素飽和度の低下を認めず有効であった。

持続静注で酸素飽和度の低下を認めた3機会のうち2機会は同一の脳変性疾患の重症心身障害児例であった。それぞれの持続静注最大投与量は0.24mg/kg/hr（同一症例で同量で2機会），0.48mg/kg/hr（他剤で発作が頓挫後に初期導入静注を受けることなく持続静注が開始された症例）だった。治療としては重症心身障害児の2機会では72時間の酸素投与を必要とし，残りの1機会では発作コントロールのため引き続きthiopentalの使用となり人工呼吸管理となった。

表3に示すようにてんかん症候群分類，重積前発作頻度，内服抗てんかん薬（単剤か多剤か，BZPの有無），投与時年齢，重積誘因，重積発作型に関して有効性の差があるか検討した。感染症を誘因とした21機会の内18機会，85.7％で初期導入静注が有効だったのに対し，誘因のなかった15機会では9機会，60.0％の有効率であったが統計学的な有意差は認められなかった。その他の因子に関しても有意差は認められなかった。

なお，初期導入静注が無効だった9機会において最終的に発作を抑制した薬剤は4機会でlidocaine，それぞれ2機会でPHTとthiopental，1機会でDZPだった。同様に持続静注が無効だった7機会においてはthiopentalが3機会，lidocaineとPHTがそれぞれ2機会で有効だった。

**表2　重積前の発作頻度、内服状況、誘因と重積型**

| | | |
|---|---|---|
| 重積前の発作頻度 | 週に1回未満 | 23機会 |
| | 週に1回以上 | 20機会 |
| 内服抗てんかん薬数 | 単剤 | 14機会 |
| | 2剤以上 | 29機会 |
| BZPの内服 | 内服なし | 26機会 |
| | 内服あり | 17機会 |
| 重積誘因 | 感染症、発熱 | 25機会 |
| | 減量 | 1機会 |
| | 怠薬 | 1機会 |
| | 不明 | 16機会 |
| 重積発作型 | 痙攣性重積 | 38機会 |
| | 非痙攣性重積 | 5機会 |
| MDL使用前抗てんかん薬 | | |
| 坐剤： | DZP坐剤 | 29機会 |
| | PB坐剤 | 4機会 |
| | BZP坐剤 | 3機会 |
| 静注薬： | DZP | 35機会 |
| | lidocaine | 8機会 |
| | PHT | 10機会 |

## 考察

MDLの優れた抗けいれん作用に関しては1980年代から報告されている。1983年にKanekoらがDZPよりすぐれた抗けいれん作用をMDLが有していることを動物実験で示した[1]。1987年にはけいれん発作20例に対しMDLの初期導入静注が試みられ，臨床における有効性が報告された[2]。その後は特にけいれん重積に対するMDLの持続静注の有用性を示す多数の報告がなされた[3-5]。我が国でも皆川らによりMDLの持続静注療法が報告され[6,7]，その有効性と安全性に対する評価は確立しつつある。Riveraらの小児けいれん重積24例の臨床検討では0.15mg/kgの初期導入静注に引き続き，0.06～1.08mg/kg/hr（平均0.138mg/kg/hr）の持続静注を行い全例で有効だった[3]。Koulらの検討でも小児20例に0.15mg/kgの初期導入静注に引き続き，0.06～0.3mg/kg/hr（平均0.12mg/kg/hr）の持続静注を行い95％の有効率だったと報告されている[5]。本邦でも皆川ら，山崎らが小児のけいれん重積にMDLの持続静注を行い副作用はなく80％以上の有効率であったと報告している[7,8]。今回の検討において初期導入静注のみの時点における有効率は75.7％で，初期導入静注に引き続き持続静注行った例では18機会中13機会と72.7

%の有効率だった。これまでの報告の多くは，初期導入静注に引き続き持続静注を行っているためそれぞれを分けて評価することは出来ないが，有効率は概ね同等と思われた。上述のように過去の報告の多くは初期導入静注から引き続き持続静注を行っている。今回の検討では，一部の投与機会を他誌に報告[9]したように初期導入静注が有効であって，脳波検査を行い突発性異常波が充分に抑制されている場合には持続静注を行わなかった。このような初期導入静注のみで持続静注を行わなかった有効機会は，初期導入静注が有効だった28機会中で10機会（35.7％）にのぼった。これまで初期導入静注のみで評価している報告は少ない。しかしGalvinらは，12例のけいれん重積を含む20例のけいれん時にMDLを初期導入静注のみで使用し有効率は100％だったと報告し，一部の症例では初期導入静注のみでも充分な効果があることを示している[2]。本検討における副作用の発生頻度は初期導入静注時では2機会/37機会（5.4％）であったのに対し，持続静注時には3機会/24機会（12.5％）と，持続静注時で副作用の発生頻度が高かった。初期導入静注有効機会の約3分の1は持続静注を行わずに済んだことと，持続静注時に副作用の発生頻度が若干高いことを考えあわせると，持続静注を行うかどうかを必要度に応じ個々の投与機会で判断すべきと思われた。少なくとも急性脳症，脳炎の様な進行性の病態ではないてんかんの発作重積では，初期導入静注で発作が頓挫した場合に持続静注を行わなくても良い機会が多いことに留意すべきであろう。熱性けいれんと急性脳症を対象としたMDL治療の有効性に関する我々の検討[10]ではMDL持続静注の平均持続時間は47.5時間であったのに対し，今回の検討では平均持続時間が31.8時間とより短かった。これはてんかん発作重積において持続静注療法の必要性が少ないことを反映しているのかもしれない。

持続静注を見合わせる判断において脳波所見は重要な役割を果たすと思われる。本検討の一部の症例は，初期導入静注時に脳波検査で突発性異常波の消失を確認した。その結果，持続静注を行わず，その後の発作再発もなかった[9]。ClaassenらもMDL療法時の脳波検査の重要性を訴えており初期導入静注時に脳波検査が可能であれば行い，脳波所見によって，引き続き持続静注を行うか判断する事が好ましいと思われた[11]。さらに引き続き持続静注を開始した場合も，持続静注中止の時期を判断するうえで脳波検査を行うべきであろう[11]。

副作用に関しては酸素飽和度の低下が認められ，持続静注時の頻度が高かったがいずれも軽微で，酸素投与によりすみやかな改善をえた。重度心身障害児で繰り返し認めたことと，同一症例で同量投与された他機会では認められなかったことから，本検討における投与量の範囲では副作用は単に用量に依存しているのではなく，症例の全身状態などその他の要因が大きく，特に重症心身障害児での使用に留意するべきと思われた。この他Riveraら[3]，皆川ら[7]，山崎ら[8]の報告

**表3　臨床要因と初期導入静注と持続静注の有効性**

| | | 初期導入静注 | | | 持続静注 | | |
|---|---|---|---|---|---|---|---|
| | | 有効機会数 | 無効機会数 | 有効率(%) | 有効機会数 | 無効機会数 | 有効率(%) |
| てんかん診断 | 乳児重症ミオクロニーてんかん | 6 | 0 | 100.0％ | 6 | 3 | 66.7％ |
| | 症候性局在関連性てんかん | 22 | 9 | 71.0％ | 11 | 4 | 73.3％ |
| | 前頭葉てんかん | 8 | 5 | 61.5％ | 6 | 1 | 85.7％ |
| | 側頭葉てんかん | 2 | 0 | 100.0％ | 1 | 1 | 50.0％ |
| | 後頭葉てんかん | 8 | 2 | 80.0％ | 3 | 2 | 60.0％ |
| | 焦点未決定の局在関連性てんかん | 4 | 2 | 66.7％ | 1 | 0 | 100.0％ |
| 重積前発作頻度 | 週に1回未満 | 20 | 7 | 74.1％ | 9 | 3 | 75.0％ |
| | 週に1回以上 | 8 | 2 | 80.0％ | 7 | 5 | 58.3％ |
| 内服抗てんかん薬数 | 単剤 | 7 | 5 | 58.3％ | 4 | 1 | 80.0％ |
| | 多剤 | 21 | 4 | 84.0％ | 13 | 6 | 68.4％ |
| BZPの内服 | なし | 18 | 7 | 72.0％ | 9 | 3 | 75.0％ |
| | あり | 10 | 2 | 83.3％ | 8 | 4 | 66.7％ |
| 投与時年齢 | 3歳以上 | 13 | 7 | 65.0％ | 10 | 5 | 66.7％ |
| | 3歳未満 | 15 | 2 | 88.2％ | 7 | 2 | 77.8％ |
| 重積誘因 | 感染症、発熱 | 18 | 3 | 85.7％ | 9 | 6 | 60.0％ |
| | 減量 | 1 | 0 | 100.0％ | 1 | 0 | 100.0％ |
| | 怠薬 | 1 | 0 | 100.0％ | 1 | 0 | 100.0％ |
| | なし | 8 | 6 | 57.1％ | 6 | 1 | 85.7％ |
| 重積発作型 | 痙攣性重積 | 25 | 9 | 73.5％ | 14 | 5 | 73.7％ |
| | 非痙攣性重積 | 3 | 0 | 100.0％ | 3 | 2 | 60.0％ |

では副作用は認めず，Parentらの報告[4]では4例中1例に血圧低下を認めているにすぎない。いずれにせよこれまで報告された範囲内の投与量では，副作用の出現率は比較的低く，あっても重篤なものではなかった。副作用に十分注意して使用すればMDLは安全に用いることができると思われる。

これまで述べてきた如くMDLは重篤な副作用が少なく，安全性と有効性を兼ね備えた優れた抗けいれん薬である。しかし，本邦では2000年7月に集中治療における人工呼吸中の鎮静に対しては効能追加されたのみで抗けいれん作用に対しては効能追加がいまだになされていない。さらに，低出生体重児，新生児，乳児，幼児または小児に対する安全性は確立されていない。MDLの高い有効性と安全性を考え早期に効能効果が追加され，安全性が確立されることが望まれる。

Yoshikawaらはけいれん重積時の第一選択薬としてMDLを試み，その有効性を報告しMDLを第一選択薬として用いるべきと述べている[12]。有効性の判断が数分でできること，人工呼吸管理を要するような重篤な副作用は全く認めなかったことを考えると第一選択薬としての使用をさらに検討すべきであると考えられた。また，初期導入静注のみで充分な効果が得られ持続静注が不要な機会があったこと，投与量が機会毎で差が大きかったことなどから，今後の課題としては，効能効果の追加とともに初回導入静注量と無効時の増量および静注の許容回数，持続静注を開始する判断基準，ならびに投与量と増量の仕方，そして他剤への変更を判断する基準が重要と考えられた。

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＝原著論文＝

# 小児けいれん重積症に対するmidazolam治療の臨床的検討

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要旨 Midazolam（MDL）静注療法の小児けいれん重積症に対する効果を検討した．45症例，53投与機会（以下，機会）でMDL初期導入静注が行われ，総投与量は平均0.35±0.22 mg/kgで，42機会（79.2%）で有効だった．このうち29機会で初期導入静注に続き持続静注が行われた．持続静注量は0.06～0.60 mg/kg/hr（平均0.30 mg/kg/hr）で72.4%が有効だった．持続静注の有効機会のうち72時間以内の投与期間が90.5%だった．また，13機会は持続静注は不要で初期導入静注のみで有効だった．副作用は5機会で酸素飽和度低下，1機会で減量中に不穏状態を呈した．小児けいれん重積症においてMDLは有効性，安全性の両面ですぐれた薬剤であると思われた．

見出し語 midazolam，けいれん重積，抗てんかん薬，てんかん重積，小児

## はじめに

1983年にKanekoらが動物実験によって，midazolam（MDL）にはdiazepam（DZP）よりすぐれた抗けいれん作用があることを示した[1]．1987年のGalvinらの報告以降，けいれん発作，特にけいれん重積に対するMDLの臨床検討が多数なされ[2]~[9]，その有効性と安全性に対する評価は確立しつつある．しかし本邦では2000年7月に集中治療における人工呼吸中の鎮静に対しては効能追加がされたが，抗けいれん作用に対しては効能追加がいまだになされていない．我々の施設では国内外でその有効性と安全性が報告された1997年以降にMDLをけいれん重積症に使用しており，今回はMDLの有効性と安全性を確認するために，これまでの当施設における使用経験をまとめ報告する．

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## I 対象と方法

1997年10月1日～2001年12月31日の間にけいれん重積で入院を要した76症例，のべ98回の入院診療記録より，MDLを使用した45症例（男27例，女18例），のべ62回の入院におけるMDL投与機会（以下，機会と略す）を対象とした．これら62機会の診療記録よりけいれん重積の原因疾患，MDL投与時年齢，初期導入静注量と持続静注量，投与期間，MDL以外に使用した抗てんかん薬，ならびにMDLの副作用とその対応を調査した．

当施設ではけいれん重積時の対応として，DZPを第一選択薬として，以後は担当医の判断でlidocaine，phenytoin（PHT），MDLを適宜使用し，これらで頓挫できない場合にthiopentalを使用することを原則としていた．なお，MDLの使用機会でその有効性が確認された症例では2回目以降の重積時にはMDLを第一選択薬として用いることもあった．MDLは0.15～0.40 mg/kgを1～2分かけゆっくり静注することとし，軽度改善のみで完全には重積が頓挫しない場合に静注を繰り返しても良いこととした（初期導入静注）．初期導入静注が有効で再発予防が必要と判断した場合に，0.06～0.18 mg/kg/hrの投与量でMDLの持続静注を開始し，発作の完全抑制まで15分程度ごとに0.06 mg/kg/hrずつ増量することを原則とした．さらに，MDL使用時には呼

吸数，心拍とともにパルスオキシメーターで酸素飽和度を全例でモニターした．減量に際しては0.03～0.06 mg/kg/hrずつ2～3時間ごとに減量した．なお，有効性の評価は初期導入静注ではMDL投与後15分以内にけいれん重積が頓挫した場合を有効，持続静注では24時間以上発作の再発を認めず，減量中止後48時間以内に再発を認めないものを有効とした．

なお，midazolamは小児への使用に関しては未承認薬であるため保護者に同意を得た．

表1　けいれん重積の原因疾患とMDL投与機会数

| 診断名 | 機会数（症例数） |
|---|---|
| てんかん | 43機会（26例） |
| 症候性局在関連性てんかん | 34機会（22例） |
| 前頭葉てんかん | 16機会（8例） |
| 側頭葉てんかん | 2機会（2例） |
| 後頭葉てんかん | 10機会（6例） |
| 焦点不明 | 6機会（6例） |
| 乳児重症ミオクロニーてんかん | 9機会（4例） |
| 急性脳症，急性脳炎 | 11機会（11例） |
| 熱性けいれん | 7機会（7例） |
| 低酸素性脳症 | 1機会（1例） |
| 合計 | 62機会（45例） |

## Ⅱ　結　　果

### 1．MDL使用機会の臨床的特徴

けいれん重積の原因疾患は表1に示すようにてんかんが投与機会の過半数を占め，複数回の使用機会があった8例はいずれもてんかんだった．投与時年齢は0.2～18.4歳で，平均では3.7歳だった．MDLの初期導入静注および持続静注前に使用された抗てんかん薬はDZP坐剤が44機会，phenobarbital坐剤が7機会，bromazepam坐剤が3機会で投与されていた．静注薬ではDZPが53機会，lidocaineとPHTがそれぞれ15機会で使用されていた．

### 2．初期導入静注について

図1に初期導入静注と持続静注の行われた有効・無効機会の流れと副作用を示す．53機会でMDL初期導入静注が行われた．初回投与量は0.15 mg/kg～0.40 mg/kgで平均では0.22±0.08 mg/kgであった．図1の如く21機会では複数回の静注が繰り返され，1機会あたりの初期導入総投与量は平均0.35±0.22（0.15～0.90）mg/kgで，42機会（79.2%）において有効だった．表2は初期導入静注の初回投与量と総投与量別の機会数を示すが，初回投与量は0.3 mg/kg以下で有効機会の95.2%（40/42機会）を占め，総

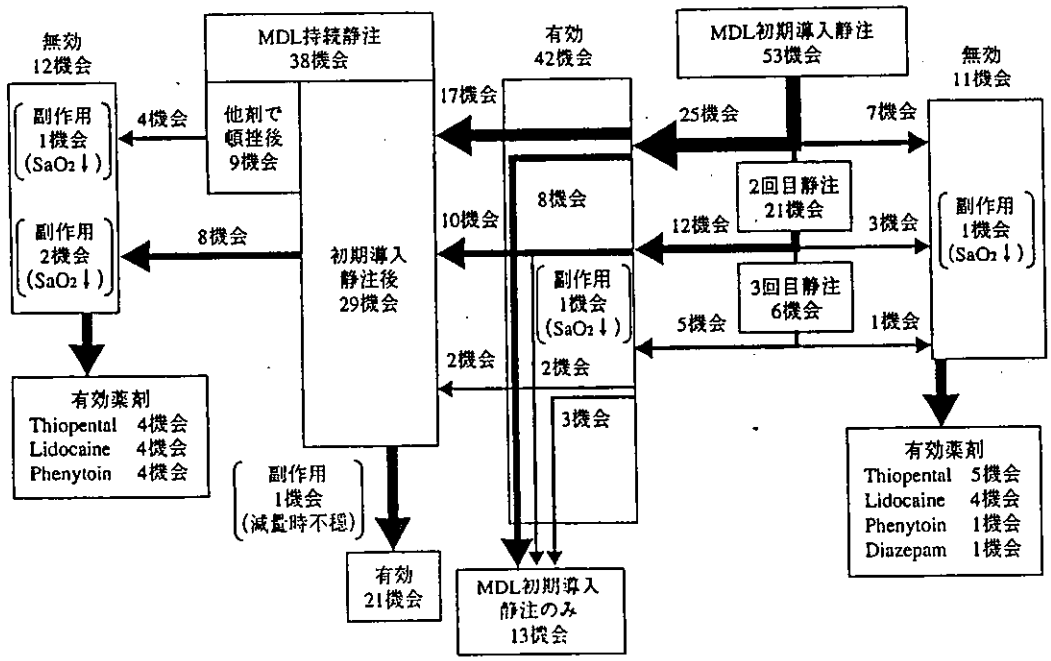


図1　Midazolam初期導入静注と持続静注のフローチャート

投与量は0.5 mg/kg以下で有効機会の88.1%（37/42機会）を占めていた．この中で複数回静注を行い有効となった17機会のうち12機会では初回投与量が0.2 mg/kg以下であった（表2）．

有効だった42機会のうち13機会ではその後の持続静注は行われなかったが，以後の発作の再発も認めずけいれん重積に対する治療は終了となった．これら13機会でも初回投与量は0.3 mg/kg以下が12機会（92.3%）で，総投与量も0.5 mg/kg以下が12機会（92.3%）であった（表2）．

酸素飽和度が低下（$SpO_2$で80%台）する副作用は2機会，4p-症候群の同一症例で認めたが，それぞれ$O_2$を7時間，4時間投与のみで改善した．この2機会の投与量はそれぞれ0.3 mg/kgと0.2 mg/kgの繰り返し後，0.2 mg/kgの2回投与後で，けいれん重積に関しては前者は有効で，後者は無効であった（図1）．この症例はさらにほかの2機会で0.15 mg/kgの2回投与と0.3 mg/kgと0.15 mg/kgの複数回投与が行われたが，それらの機会では副作用を認めず有効であった．

3．持続静注療法について

初期導入静注が有効だった42機会のうち29機会で引き続き持続静注が行われた（図1）．持続静注開始量は0.06 ～ 0.48 mg/kg/hr（平均0.18 mg/kg/hr）で，12機会では持続静注開始後に発作が再発し0.06 ～ 0.42 mg/kg/hr増量され，最大量は0.06 ～ 0.60 mg/kg/hr（平均0.30 mg/kg/hr）となった．有効機会は21機会（72.4%）で，最大量は0.06 ～ 0.60 mg/kg/hrと機会ごとの差が大きく投与量は広く分布した（表3）．持続静注を開始した後に発作の再発を認め，その後増量し発作コントロールを得た8機会中7機会が0.24 mg/kg/hr以下で開始しており，0.30

表2 MDL初期導入静注量別の投与機会数

| 投与量 mg/kg | 投与機会数（有効機会数） | | 複数回投与の有効機会数 | | 初期導入静注のみの有効機会数 | |
|---|---|---|---|---|---|---|
| | 初回投与量 | 総投与量 | 初回投与量 | 総投与量 | 初回投与量 | 総投与量 |
| 0.1 <, ≦ 0.2 | 31 (25) | 16 (13) | 12 | 0 | 8 | 4 |
| 0.2 <, ≦ 0.3 | 19 (15) | 20 (15) | 4 | 4 | 4 | 4 |
| 0.3 <, ≦ 0.4 | 3 (2) | 7 (5) | 1 | 4 | 1 | 1 |
| 0.4 <, ≦ 0.5 | 0 (0) | 4 (4) | 0 | 4 | 0 | 3 |
| 0.5 <, ≦ 0.6 | 0 (0) | 0 (0) | 0 | 0 | 0 | 0 |
| 0.6 <, ≦ 0.7 | 0 (0) | 0 (0) | 0 | 0 | 0 | 0 |
| 0.7 <, ≦ 0.8 | 0 (0) | 1 (1) | 0 | 1 | 0 | 0 |
| 0.8 <, ≦ 0.9 | 0 (0) | 5 (4) | 0 | 4 | 0 | 1 |
| 合計 | 53 (42) | 53 (42) | 17 | 17 | 13 | 13 |

表3 MDL持続静注投与量の投与機会数

| 持続静注投与量 (mg/kg/hr) | 投与機会数*（有効機会数） | | 増量後有効となった機会数 | | 持続静注全機会数** | |
|---|---|---|---|---|---|---|
| | 開始量 | 最大量 | 開始量 | 最大量 | 開始量 | 最大量 |
| ≦ 0.12 | 8 (5) | 4 (4) | 1 | 0 | 10 | 6 |
| 0.12 <, ≦ 0.24 | 18 (14) | 11 (8) | 6 | 0 | 23 | 14 |
| 0.24 <, ≦ 0.36 | 2 (1) | 8 (5) | 1 | 5 | 3 | 10 |
| 0.36 <, ≦ 0.48 | 1 (1) | 1 (1) | 0 | 0 | 2 | 2 |
| 0.48 <, ≦ 0.60 | 0 (0) | 5 (3) | 0 | 3 | 0 | 5 |
| 0.60 <, ≦ 0.72 | 0 (0) | 0 (0) | 0 | 0 | 0 | 1 |
| 合計 | 29 (21) | 29 (21) | 8 | 8 | 38 | 38 |

注，＊：MDL静注後に引き続き持続静注が行われた機会のみ
＊＊：多剤で発作が頓挫した後にMDL持続静注が行われた機会も含む

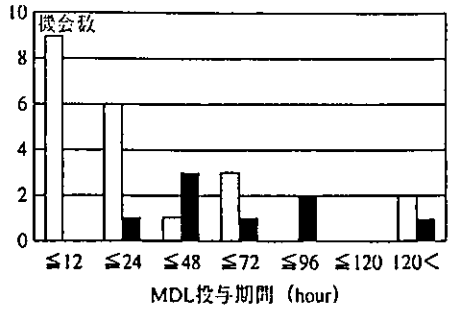


図2 Midazolam持続静注の有効性と投与期間
□有効機会，■無効機会

～0.60 mg/kg/hrまで増量し有効となった（表3）．持続静注の投与期間は4～288時間（平均49.0時間）であった．図2に示すように，持続静注が有効だった21機会のうち投与期間が72時間以内が19機会（90.5%），24時間以内でも15機会（71.4%）を占めていた（図2）．

初期導入静注に引き続き持続静注が行われた他に，他剤で発作が頓挫した9機会においても再発予防目的でMDL持続静注が行われた（図1）．持続静注開始量は0.09～0.48 mg/kg/hr（平均0.21 mg/kg/hr）で，5機会では発作が再発し増量され最大投与量は0.09～0.72 mg/kg/hr（平均0.29 mg/kg/hr）となった．これら9機会の投与期間は3～140時間（平均40.0時間）だった．9機会中4機会では発作の再発もなく，MDL持続静注は減量中止できた．再発した5機会のうち，1機会では増量により発作が頓挫した．2機会は増量が試みられないまま，他の2機会では増量にもかかわらず発作は繰り返し計4機会で他剤に変更となった．

持続静注では4機会に副作用を認めた．最大量0.36 mg/kg/hr，130時間投与した1機会では減量中に不穏状態を呈した．減量を一時中断し，より緩徐に行うことで改善した．残りの3機会（うち2機会は同一症例）においては酸素飽和度の低下（$SpO_2$で70%台）を認めた．それぞれの持続静注の最大投与量は0.24 mg/kg/hr（2機会同一症例），0.48 mg/kg/hr（1機会）だった．この1機会ではMDL持続静注後にthiopental持続投与となり人工呼吸管理となった．残りの同一症例の2機会は72時間の酸素投与を受けた．この症例は原因不明の脳変性疾患で重症心身障害児であった．

## Ⅲ 考 察

けいれん重積におけるMDLの有効性に関してはすでに多数報告され，その有効率は80～100%とされている[2)-9)]．Holmesらはpentobarbital療法と比較し，MDL持続静注の高い有効性とともにすぐれた安全性も強調している[9)]．今回の検討における初期導入静注のみの有効率は79.2%だった．これまでの報告の多くは初期導入静注から引き続き持続静注に連続しており，初期導入静注のみで評価している報告は少ない．Galvinらは12例のけいれん重積を含む20例のけいれん時にMDLを初期導入静注のみで使用し有効率は100%だったと報告している[2)]．我々の検討で13機会においては初期導入静注のみで有効であった．13機会のうち10機会がてんかんであったことから，急性脳症，脳炎などの進行性の病態でない症例においては持続静注を行わなくても良い可能性がある．この持続静注を見合わせる判断において脳波所見は重要な役割を果たすと思われる．本検討の一部の症例は他誌に報告した如く，初期導入静注時に脳波検査で突発性異常波の消失を確認した[10)]．これらの機会には持続静注を行わなかったが発作の再発はなかった[10)]．Claassenらは MDL持続静注の際に脳波で異常が残存している場合は再発する可能性が高いと脳波検査の重要性を訴えている[11)]．今回の検討では副作用の頻度が持続静注でより高かったので，初期導入静注時に脳波検査が可能であれば行い，脳波所見によって引き続き持続静注を行うか判断することが好ましいと思われた．

初期導入静注の投与量に関して，初回投与量が0.2 mg/kgでは複数回静注を必要とする機会が多かった．また，MDLの初期導入静注が有効であった機会の約90%は初回投与量が0.3 mg/kg以下，総投与量が0.5 mg/kg以下であった．さらに初期導入静注のみで持続静注を必要としなかった機会においても92.3%が同量以下であった．よって初回投与量としては0.2～0.3 mg/kgで2回投与を試みることが初期導入静注での効果判定に充分な量と考えられた．

投与量に関しては初期導入静注量を0.15 mg/kgに固定し，引き続き持続静注を行う報告[3)5)-7)9)]の他に，我々と同様に症例ごとに投与量を変えている報告もある．Claassenら[11)]は総投与量として0.03～0.50 mg/kg，Kumarら[12)]は0.02～0.42 mg/kgを初期導入