of CNS dysfunction, including motor dysfunction (70.0% of patients), mental retardation (58.3%), psychiatric symptoms (7.4%) and aphasia (11.8%). These symptoms indicate a diagnosis of RS (Bien *et al.*, 2005). Early diagnosis of RS is essential to improve prognosis. From a clinical perspective, epilepsia partialis continua (EPC) is the most important diagnostic marker for RS patients. However, EPC develops 1.6±2.5 years after the onset of the first seizure (unpublished data) and also occurs in patients with epilepsies other than RS (Oguni *et al.*, 1991). Therefore, EPC is inadequate for specific and early diagnosis of RS. Furthermore, in RS patients without EPC, a definitive clinical diagnosis is difficult even at the advanced stage of RS.

Various autoantibodies against neural molecules (Rogers *et al.*, 1994; Takahashi *et al.*, 2003; Watson *et al.*, 2001; Yang *et al.*, 2000) are found in the serum and cerebrospinal fluid (CSF) of RS patients. Autoantibodies against GluR3 have been studied as an appropriate biomarker, but these autoantibodies are also detected in patients with epilepsies other than RS, and measurement of autoantibodies against GluR3 by ELISA has been suggested to be unreliable (Wiendl *et al.*, 2001; Watson *et al.*, 2004). Therefore, although autoantibodies against CNS molecules may support a diagnosis of RS, they do not serve as hallmarks for this disease.

Due to the difficulties in clinical and laboratory diagnoses of RS, neuroimaging studies have been used to improve clinical diagnosis. Previous MRI studies revealed characteristic hemispheric atrophic lesions with slow progression, and hyperintense lesions on fluid-attenuated inversion recovery (FLAIR) or T2-weighted images (Aguilar and Rasmussen, 1960). Studies on serial MRI changes suggest a unidirectional MRI staging (stages 0-4) system according to volume changes (swelling or atrophic lesions) and signal changes on FLAIR or T2-weighted images. However, we have found more complicated MRI patterns than those encompassed by simple unidirectional staging (Bien *et al.*, 2002a). In the present study, we examined MRI lesions and their evolutionary changes in order to identify the MRI characteristics of RS and thus facilitate early definitive clinical diagnosis.

Materials and methods

Patients

Subjects comprised 15 RS patients at the National Epilepsy Center (Shizuoka City, Japan) and Nishi Niigata Epilepsy Center (Niigata City, Japan), for whom serial MRI images were available *(tables 1, 2A)*. RS was diagnosed based on published diagnostic criteria (Bien *et al.*, 2005), as either fulfilling all three criteria of Part A or two of three criteria of Part B. Part A consisted of clinical findings of focal seizures (with or without EPC) and unilateral cortical deficit; EEG findings of unihemispheric slowing with or without epileptiform activity and unilateral seizure onset, and MRI findings of unihemispheric focal cortical atrophy and either grey or white matter abnormality or ipsilateral caudate head abnormality. Part B consisted of clinical findings of EPC or progressive unilateral cortical deficit; MRI findings of progressive unihemispheric focal cortical atrophy, and histopathological findings of T cell dominated encephalitis and absence of parenchymal infiltration or viral inclusion bodies. Patients were classified as either EPC type (n=8,) or non-EPC type (n=7). Surgical intervention was performed in four EPC and four non-EPC type patients *(table 3)*.

Methods

Axial and coronal MRI images were used to evaluate atrophic lesions (ALs) and high signal intensity lesions (HILs) in all patients, and sagittal MRI images were also examined in some cases. Gadolinium enhancement was not performed in any of the patients. ALs were evaluated primarily on T1-weighted images, while FLAIR or T2-weighted images were also used for the evaluation of HILs. Evolutionary changes in ALs and HILs were studied in all patients. In each patient, MRI was repeated upon the decision of the attending doctor when the patient's seizure condition changed. ALs were classified into three categories according to distribution: focal *(figure 1A)*, unilateral *(figure 1B)* and bilateral *(figure 1C)*. Focal ALs were defined as the presence of ALs in one lobe, and unilateral as ALs in multiple lobes in one hemisphere and bilateral as ALs in both hemispheres, either in one or multiple lobes. HILs were classified into three types by predominant location: white matter dominant *(figure 1D)*, subcortical white matter dominant *(figure 1E)*, and cortex dominant *(figure 1F)*.

Results

Atrophic lesions (ALs)

Atrophic lesions were observed in 13 of the 15 patients (EPC type, n=7; non-EPC type, n=6) *(table 2B)*. Of these, five (EPC type, n=3; non-EPC type, n=2) had focal ALs, four showed unilateral ALs (EPC type, n=3; non-EPC type, n=1), and four showed bilateral ALs (EPC type, n=1; non-EPC type, n=3) at the last examination. Focal and unilateral ALs were observed in the hemisphere with epileptogenic foci. All four patients with bilateral ALs (EPC type: Patient 8; non-EPC type: Patients 9, 13 and 15) had unilateral epileptogenic foci causing

Table 1. Patient characteristics at initial and final examinations.

Pts	Type	Age atseizure onset	Clinical symptoms	EEG	MRI (CT)	Surgery	Final examination			
							Age	Motor status	Seizure status	Mental status
1	EPC	2 Y 8 M	Progressive UCDs+FS+EPC	Right UHS with epileptiform activity, USO	Right HILs	NP	24 Y	Left HP	Daily	MR+++
2	EPC	3 Y 8 M	Progressive UCDs+FS+EPC	Right UHS with epileptiform activity, USO	Right progressive ALs+bilateral HILs	Right FH	8 Y	Left HP	Free	MR+
3	EPC	3 Y 8 M	UCD+FS+EPC	Right UHS with epileptiform activity, USO	Right progressive ALs+right HILs	Right temporal R	9 Y	Normal	Daily	MR+
4	EPC	3 Y 10 M	Progressive UCDs+FS+EPC	Right UHS with epileptiform activity, USO	Right progressive ALs	Right FH	14 Y	Left HP	Free	MR+
5	EPC	3 Y 11 M	Progressive UCDs+FS+EPC	Right UHS with epileptiform activity, USO	Right progressive ALs+right HILs	Right FH	9 Y	Left HP	Free	Normal
6	EPC	4 Y 1 M	UCD+FS+EPC	Left UHS with epileptiform activity, USO → BHS, BSO	Left progressive ALs	NP	21 Y	Right HP	Daily	MR++
7	EPC	6 Y 2 M	Progressive UCDs+FS+EPC	Right UHS with epileptiform activity, USO	Right progressive ALs+right HILs	NP	10 Y	Left HP	Daily	MR+
8	EPC	8 Y 10 M	Progressive UCDs+FS+EPC	Left UHS with epileptiform activity, USO	Left progressive ALs → SE → bilateral ALs + left HILs	NP	18 Y	Right HP	Daily	MR++
9	Non-EPC	0 Y 2 M	Progressive UCDs+FS	Right UHS with epileptiform activity, USO	SE → Bilateral progressive ALs + Bilateral HILs	Right FH	4 Y	Left HP	Free	MR++

Table 1. (*Continued*)

Pts	Type	Age atseizure onset	Clinical symptoms	EEG	MRI (CT)	Surgery	Final examination			
							Age	Motor status	Seizure status	Mental status
10	Non-EPC	2 Y 7 M	Progressive UCDs+FS	Right UHS with bilateral epileptiform activity, USO	Bilateral HILs	Right frontal R	19 Y	Normal	Free	Normal
11	Non-EPC	6 Y 5M	Progressive UCDs+FS	Right UHS with epileptiform activity, USO	Right progressive ALs+HILs	NP	10 Y	Left HP	Daily	Normal
12	Non-EPC	9 Y 0 M	Progressive UCDs+FS	Left UHS with epileptiform activity, USO	Left progressive ALs+HILs	NP	12 Y	Right HP	Weekly	MR++
13	Non-EPC	15 Y 9 M	UCD+FS	Left UHS with epileptiform activity, USO	Bilateral progressive ALs+left HILs	Left frontal R	32 Y	Normal	Weekly	Normal
14	Non-EPC	25 Y 9 M	Progressive UCD+FS	Left UHS with epileptiform activity, USO	Left ALs+HILs	Biopsy	29 Y	normal	Daily	Normal
15	Non-EPC	27 Y 2 M	Progressive UCDs+FS	Right UHS with epileptiform activity, USO	Right progressive ALs+HILs → bilateral progressive ALs	Right front-temporal R	38 Y	Left HP	Weekly	MR+

EPC: epilepsia partialis continua; UCD: unilateral cortical deficit; FS: focal seizure; UHS: unihemispheric slowing; USO: unilateral seizure onset; BHS: bilateral hemispheric slowing; BSO: bilateral seizure onset; ALs: atrophic lesions; HILs: high signal lesions; SE: status epilepticus; FH: functional hemispherectomy; R: resection; HP: hemiparesis; MR: mental retardation; NP: not performed; Y: year; M: month; CT: computed tomography; →: change to; +: mild; ++: moderate; +++: severe.

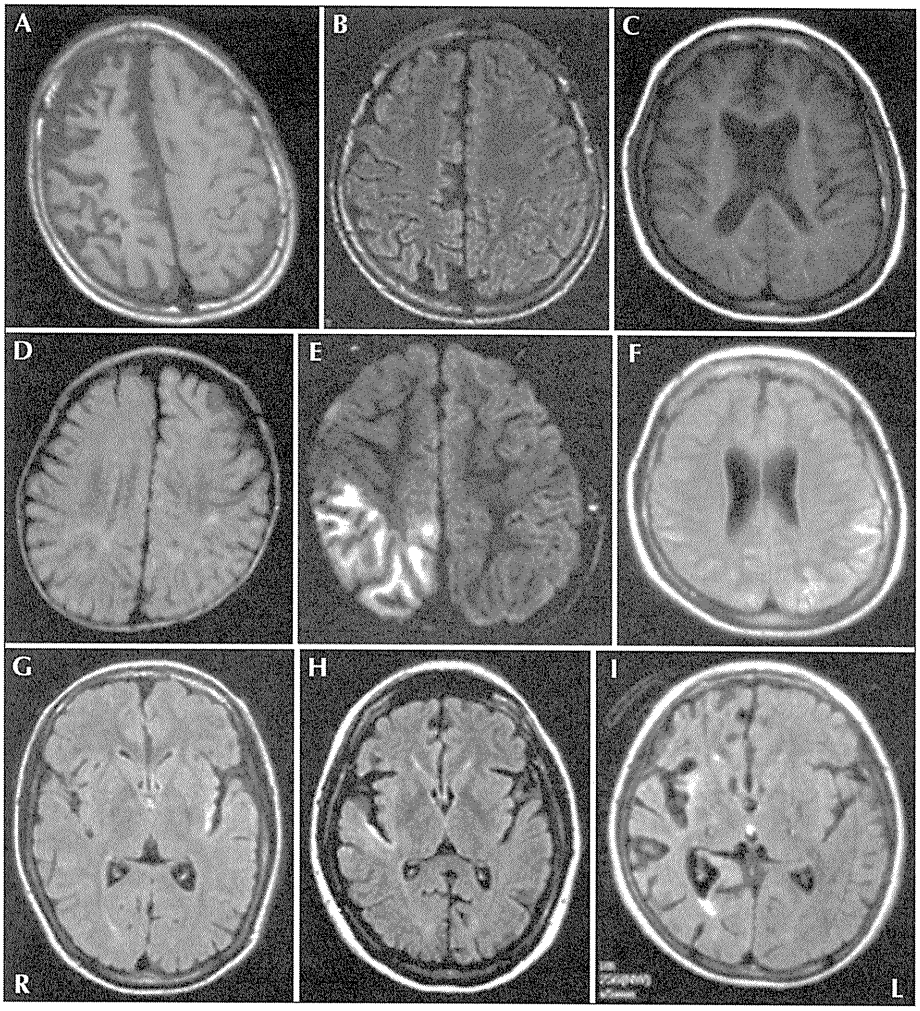

Figure 1. Typical MRI demonstrating atrophic lesions (ALs) and high intensity lesions (HILs).
A) Focal ALs in the right frontal lobe on T1-weighted image.
B) Unilateral ALs on axial fluid-attenuated inversion-recovery (FLAIR) MRI.
C) Bilateral ALs on T1-weighted image.
D) HILs in white matter detected by FLAIR MRI.
E) HILs in subcortical white matter on FLAIR MRI.
F) HILs in cortex on FLAIR MRI.
G) Left insular HILs detected by FLAIR MRI.
H) Right insular HILs on FLAIR MRI.
I) Right insular HILs on FLAIR image.

clinical seizures; two had infantile seizure onset and convulsive status epileptics, while two had seizure onset at age 15 or later and CPS status epileptics, and developed bilateral ALs after surgical intervention which failed to control seizures. Of the three EPC type patients with focal ALs, two had dominant ALs in the frontal lobe (Patients 4 and 8), and one in the temporal lobe (Patient 3). The two non-EPC type patients with focal atrophy both had dominant ALs in the frontal lobe (Patients 12 and 14). Both EPC and non-EPC types exhibited ALs predominantly in the frontal lobe.

High signal intensity lesions (HILs)

High signal intensity lesions were observed in 13 of 15 patients (EPC type, n=6; non-EPC type, n=7), and lesion distribution was variable *(table 2C)*. HILs were localised in the white matter in three patients (Patients 2, 5 and 9), white matter and cortex in one (Patient 10), subcortical white matter and cortex in four (Patients 1, 3, 7 and 11), and cortex only in five (Patients 8, 12, 13, 14 and 15). No significant differences in frequency and distribution of HILs were observed between EPC and non-EPC type patients.

Table 2. Patient background characteristics and lesion frequency on MRI.

	EPC type	Non-EPC type	Total
A. Patient background			
Number of patients examined	8	7	15
Sex (M/F)	7 / 1	2 /5	9 / 6
Seizure onset age (mean±SD, years)	4.6 ± 2.0	12.4 ± 10.8	8.2 ± 8.3
Focal hemisphere (R/L)	7 / 1	5 / 2	12 / 3
Observation period (mean±SD, years)	8.7 ± 7.4	18.1 ± 11.8	13.1 ± 10.5
B. ALs on T1-weighted images at final examination			
Number of patients with ALs	7	6	13
- Focal	3	2	5
- Unilateral	3	1	4
- Bilateral	1	3	4
C. Distribution of HILs on FLAIR or T2-weighted images at final examination			
Number of patients with HILs	6	7	13
Distribution pattern of HILs			
- White matter	2	1	3
- White matter+cortex	0	1	1
- Subcortical white matter+cortex	3	1	4
- Cortex	1	4	5
Insular HILs	3	4	7
Bilateral HILs	1	2	3
D. Early findings of ALs and HILs on MRI			
Number of patients examined	6	3	9
- No lesions	1	1	2
- HILs	2	0	2
- ALs and HILs	2	2	4
- ALs	1	0	1
E. Evolutionary changes of HILs on FLAIR or T2-weighted images			
E-1. Temporal evolution			
Patients without HILs at initial examination	3	3	6
No HIL throughout study	2	0	2

Table 2. (*Continued*)

	EPC type	Non-EPC type	Total
Appearance	1	3	4
- Persistence	1	0	1
- Regression	0	1	1
- Fluctuation	0	2	2
Patients with HILs at initial examination	5	4	9
- Persistence	3	1	4
- Regression	0	2	2
- Fluctuation	2	1	3
E-2. Spatial expansion			
U change to U	3	4	7
U change to B	0	0	0

Onset age: age of seizure onset; side of foci: side of original epileptogenic foci; observation period: period from initial to final MRI examination; EPC: epilepsia partialis continua; ALs: atrophic lesions; HILs: high signal intensity lesions; appearance: number of patients without HILs at the first examinations but with HILs at follow-up examinations; persistence: number of patients with HILs who showed repeatedly no change at follow-up examinations; regression: number of patients with HILs who showed reduction in intensity disappearance at subsequent follow-up examinations; fluctuation: number of patients with HILs showing repeated aggravation and reduction at follow-up examinations; expansion: number of patients with HILs at the first examination, which expanded spatially in follow-up examinations; U: unilateral expansion; B: bilateral expansion.

White matter and subcortical white matter dominant lesions were observed in six of eight (75%) patients with seizure onset before six years or younger and in two of seven (29%) patients with seizure onset at age six years or older. Conversely, cortical lesions were observed in three of eight (38%) patients with seizure onset before six, and in all seven (100%) patients with seizure onset at six or older; a higher rate of cortical lesions was significantly associated with later onset (Fisher exact probability test, p=0.01). Of 13 RS patients with HILs, ten had HILs ipsilateral to the epileptogenic focus, while the remaining three had bilateral lesions (Patients 2, 9 and 10). All three patients with bilateral HILs were diagnosed with unilateral epileptogenic foci based on seizure manifestation and ictal discharges on long-term EEG monitoring. All three patients were treated successfully by surgical intervention.

Early findings

We examined the initial MRI findings in nine patients who underwent MRI examinations in our hospital within one year of seizure onset (mean±SD: 4.7±4.4 months). ALs or HILs were observed in seven of nine patients *(table 2D)*. Two patients (Patients 3 and 8) showed HILs only, four had ALs combined with HILs (Patients 2, 7, 9 and 11), and one (Patient 5) had ALs only. In the patient with ALs only, the initial MRI was taken at three months after seizure onset, and subsequent FLAIR MRI revealed the appearance of HILs.

Evolutionary changes

Serial MRI was conducted in all patients at various intervals depending on clinical progression *(table 2E)*. Many patients showed evolutionary changes in HILs with respect to signal intensity or spatial distribution, independent of immunological therapy. In the six patients without HILs at initial examination, HILs appeared in four patients (66.7%) at 10.8±7.4 months after seizure onset. This suggests that observation of HILs can be anticipated in follow-up MRI, even if HILs are absent in early examinations. On follow-up MRI in these four patients, HILs appeared and persisted in one (Patient 5), appeared then regressed in another (Patient 14), and appeared, regressed and reappeared in two (Patients 13 and 15) *(table 2E-1)*.

Regression (disappearance or decrease in signal intensity) was found in three of 15 patients (20.0%; one without HILs at initial examination [Patient 14] and two with HILs at initial examination [Patients 10 and 11]) at 56.0 ± 56.3 months after onset of seizures. All regression cases were non-EPC type *(figure 2A)*.

Fluctuation (regression followed by reappearance) was found in five of 15 patients (33.3 %; two without HILs at initial examination [Patients 13 and 15] and three with HILs at initial examination [Patients 3, 8 and 12]), and reappearance was found at 70.8 ± 38.0 months after seizure onset *(figure 2B-F)*. The interval from seizure onset to reappearance was not significantly different between EPC type (88.5±51.6 months) and non-EPC type (59.0±32.2 months). Appearance

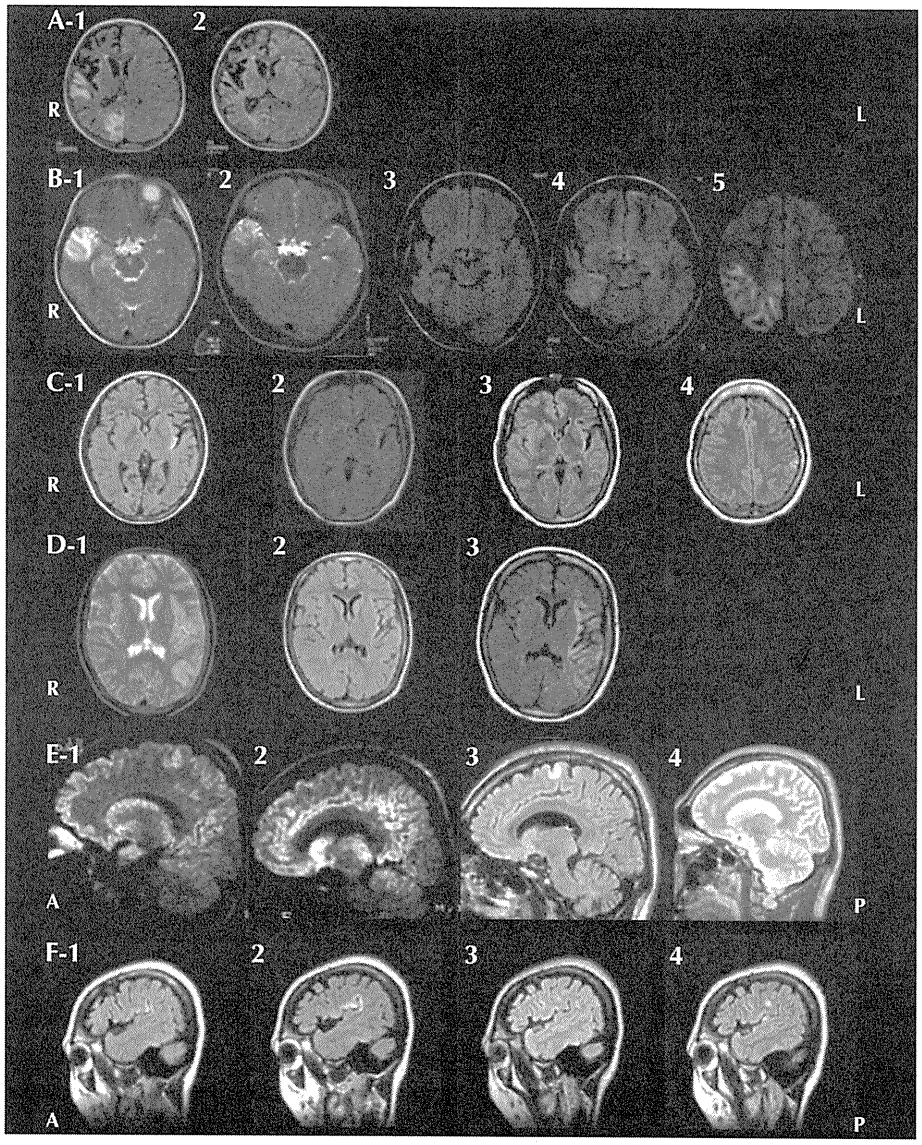

Figure 2. Evolutionary changes in MRI lesions.
A) Axial FLAIR image of Patient 11 taken at 6 months (**A-1**) and 8 months after onset of seizures (**A-2**). HILs in the cortex of the right occipital and temporal lobe and insular region observed in **A-1** are not visible in **A-2**. The patient had daily complex partial seizures (CPS) at **A-1**, and monthly CPS at **A-2**. **B**) Serial MRI of Patient 3 taken at one month (**B-1**, axial T2 image), 2 months (**B-2**, axial T2 image), 4 years 2 months (**B-3**, axial FLAIR image), and 5 years 4 months after onset of seizures (**B-4** and **B-5**, axial FLAIR images). HILs observed in the subcortical white matter of the right temporal lobe (**B-1**) disappeared (**B-2**), then reappeared (**B-3**) and expanded (**B-4** and **B-5**). The patient had CPS status and daily generalised tonic clonic seizures (GTCS) at **B-1**, was seizure-free at **B-2**, had weekly CPS at **B-3**, and showed epilepsia partialis continua (EPC) at **B-4** and **B-5**. This patient underwent epilepsy surgery (right temporal resection) at 8 years of age (4 years 2 months onset of seizures), between the time when **B-2** and **B-3** were taken. **C**) Serial FLAIR MRI of Patient 7 taken at 1 year (**C-1**), 9 years and 2 months (**C-2**), and 10 years 5 months after onset of seizures (**C-3** and **C-4**). HILs observed in the cortex of the left insular (**C-1**) disappeared (**C-2**), then reappeared (**C-3**) and expanded to the left frontal (post-central) lobe (**C-4**). The patient had daily CPS and EPC at **C-1**, weekly CPS and EPC at **C-2**, and weekly CPS and aggravated EPC at **C-3** and **C-4**. **D**) Serial MRI of Patient 12 taken at 3 years (**D-1**, axial T2 image), 3 years and 7 months (**D-2**, axial FLAIR image), and 6 years 11 months after onset of seizures (**D-3**, axial FLAIR image). HILs observed in the subcortical white matter of the left temporal lobe and left insula (**D-1**) disappeared (**D-2**), and then reappeared (**D-3**). The patient had daily CPS at **D-1**, weekly CPS at **D-2**, and daily CPS and quadric paralysis at **D-3**. **E**) Serial MRI of Patient 13 taken at 11 months (**E-1**, sagittal 0.5-Tesla image), one year (**E-2**, 0.5-T image), 8 years 5 months (**E-3**: FLAIR image), and 9 years 6 months after onset of seizures (**E-4**, T2-weighted image). HILs initially observed in the cortex of the left frontal (precentral) lobe (**E-1**) disappeared (**E-2**), then reappeared (**E-3**), and disappeared again (**E-4**). The patient had daily CPS and EPC at **E-1**, weekly CPS at **E-2**, CPS status and EPC at **E-3**, and daily CPS and EPC at **E-4**. **F**) Serial sagittal FLAIR images of Patient 15 taken at 5 years 4 months (**F-1**), 6 years 4 months after onset (**F-2**), 6 years 9 months after onset (**F-3**), and 6 years 11 months after onset of seizures (**F-4**). HILs initially observed in the cortex of the left insula (**F-1**) expanded (**F-2**), then disappeared (**F-3**), and reappeared again (**F-4**). The patient had weekly CPS at **F-1**, daily CPS at **F-2**, weekly CPS at **F-3**, and CPS status at **F-4**.

and reappearance of HILs after initial MRI examination were concordant with aggravation of seizures. Similarly, regression of HILs was concordant with improvement of seizures.
Spatial expansion of the HILs within the same hemisphere was observed in seven of 15 patients (46.6%; EPC type, n=3 [Patients 3, 7 and 8] and non-EPC type, n=4 [Patients 10, 12, 13 and 14]). Although no expansion to the other hemisphere was observed during the clinical course, three patients (20.0%; Patients 2, 9 and 10) showed bilateral involvement of HILs based on the initial MRI examination.

Discussion

In the present findings, while early MRI examinations conducted within one year of seizure onset revealed ALs in 50% and HILs in 60% of RS patients, subsequent MRI examinations depicted ALs and HILs in 87% of patients. The distribution of ALs and HILs was heterogeneous and various combinations of ALs and HILs were observed. Therefore, even in patients with ALs and HILs, a definitive diagnosis of RS cannot be made based on single MRI findings alone.
When we analyzed the evolutionary changes in HILs on MRI after initial examination, appearance (6.7%), regression (20.0%), fluctuation (33.3%), and spatial expansion of HILs (46.7%) were identified. Only a third of the patients (33.3%) showed no evolutionary changes. Although clinical diagnosis is difficult, especially in patients without EPC, all non-EPC type patients (100%) showed dynamic temporal or spatial evolutionary changes. These changes seem to reflect the inflammatory nature of RS and suggest that dynamic MRI evolution may be an important marker for clinical diagnosis.
HILs on T2-weighted or FLAIR images have been reported to be a characteristic MRI finding of RS (Bien *et al.*, 2005; Bien *et al.*, 2002a; Kim *et al.*, 2002; Granata *et al.*, 2003; Takeoka *et al.*, 2003), and may result from inflammatory responses such as reactive astrocyte and T cell infiltration (Bien *et al.*, 2002a). Bien *et al.* (2002a) classified the serial changes of MRI into five unidirectional stages: stage 0, no abnormalities; stage 1, swelling and hyperintense lesions; stage 2, disappearance of swelling; stage 3, appearance of atrophy; and, stage 4, disappearance of hyperintense lesion. According to our MRI data obtained within one year of seizure onset in nine patients, two were classified as Bien's stage 0, two as stage 2, four as stage 3, and one as stage 4. Five of nine patients (55%) had characteristics of Bien's stage 3 and stage 4, early after seizure onset (3-5 months). This indicates that MRI in some patients may show ALs without HILs (characteristic of stage 4) as the initial finding, and that some patients progress from a stage manifesting ALs (stage 4) to a stage manifesting ALs and HILs (stage 3). In previous reports, seven of eight (87.5%) patients showed cortical atrophy as early as within four months of seizure onset (Granata *et al.*, 2003), and three evolutionary patterns of neuroimaging abnormalities were reported, including a pattern of consistent HILs without further changes (Kim *et al.*, 2002). These data also suggest heterogeneity of evolutionary changes of MRI lesions.
Regression of HILs is an important phenomenon, which suggests the inflammatory nature of CNS lesions and a diagnosis of RS. We observed regression in 53.3% of patients around four years after onset of epilepsy. Fluctuation of HILs is even more indicative of the inflammatory process, and further supports a clinical diagnosis of RS. Three of five patients with fluctuation of HILs had typical histological features of RS (Patients 2, 13, 15; *table 3*). Regression and reappearance of HILs were associated with clinical seizure regression and aggravation, respectively. Reappearance was found in 35.3% of patients without immunological treatment around six years after epilepsy onset. In RS pathogenesis, cytotoxic T cells (CTLs) activated by infection seem to cross-react with CNS neurons (Bien *et al.*, 2005; Takahashi *et al.*, 2009; Bien *et al.*, 2004; Takahashi *et al.*, 2009). Reappearance of HILs may be due to reactivation of CTLs by common infection (asymptomatic or symptomatic) and increased infiltration of activated CTLs into the CNS. The observation of HIL fluctuation also indicates that some patients progress not uni- but bi-directionally in Bien's MRI staging.
Evolutionary spatial expansion of HILs is also an important phenomenon suggesting the autoimmune inflammatory nature of CNS lesions; bilateral HILs were observed in 11.8% of the present patients. Although RS is fundamentally a unihemispheric disease, a volumetric MRI study suggests that the unaffected hemisphere is also mildly involved (Larionov *et al.*, 2005). Bilateral HILs sometimes discourage surgical intervention. In the present study, three patients with bilateral expansion of HILs on MRI underwent surgical intervention (functional hemispherectomy, n=2 [Patients 2 and 9] and frontal resection, n=1 [Patient 10]) after confirming that the epileptic seizures originated from unilateral foci, and they remained seizure-free for 3.0±1.6 years, postoperatively. One patient who was treated by non-dominant functional hemispherectomy became seizure-free, irrespective of bilateral expansion of ALs (Patient 9). This supports a previous report that bilateral spreading of HILs is not necessarily a contraindication for surgical intervention (Bien *et al.*, 2005), and suggests that some HILs may not comprise epileptic lesions.
In our study, patients with earlier onset tended to have white matter-dominant HILs, while patients with

Table 3. Surgical interventions and histological features.

Pt	Type	Age at seizure onset	Presurgical diagnosis	Age at surgery	MRI findings at surgery	Type of surgery	Seizure status	Mental status	Histology
2	EPC	3 Y 8 M	RS	4Y 10M	Right ALs and bilateral HILs	Right FH	Free at 8 Y 0 M	IQ 71 at 7 Y 0 M	Typical RS
3	EPC*	3 Y 8 M	TLE	8 Y 0 M	Right ALs and unilateral HILs	Right temporal resection	Daily at 9 Y 0 M	IQ 71 at 9 Y 0 M	Typical RS
4	EPC	3 Y10 M	RS	9 Y 0 M	Right ALs	Right FH	Free at 14 Y 0 M	IQ 56 at 9 Y 3 M	Typical RS + FCD
5	EPC	3 Y11 M	RS	5 Y 7 M	Right ALs and unilateral HILs	Right FH	Free at 8 Y 11 M	IQ 94 at 7 Y 7 M	Typical RS
9	Non-EPC	0 Y 2 M	RS	2Y 10 M	Bilateral ALs and HILs	Right FH	Free at 4 Y 3 M	DQ 53 at 3 Y 1 M	Typical RS
10	Non-EPC	2 Y 7 M	FLE	14Y 3 M	Bilateral HILs	Right frontal resection	Free at 19 Y 0 M	IQ 82 at 16 Y 3 M	Typical RS + FCD
13	Non-EPC	15 Y9 M	RS	26Y	Bilateral ALs and left HILs	Left frontal resection	Weekly at 32 Y 0 M	IQ 80 at 28 Y	Typical RS
15	Non-EPC	27 Y2 M	FLE	34Y	Bilateral ALs and right HILs	Right front-temporal resection	Weekly at 38 Y 0 M	PIQ 74 at 38 Y 0M and aphasia	Typical RS

Pt: patient; EPC: epilepsia partialis continua; RS: Rasmussen syndrome; TLE: temporal lobe epilepsy; FLE: frontal lobe epilepsy; Y: years; M: months; ALs: atrophic lesions on T1-weighted MRI; HILs: high signal intensity lesions on FLAIR or T2-weighted images; FH: functional hemispherectomy; IQ: intelligence quotient; DQ: deviation intelligence quotient; PIQ: performance IQ; FCD: focal cortical dysplasia.

later onset tended to present with cortical lesions. Although there has been no detailed study of the relationship between HILs and age of epilepsy onset, a histopathological study of 45 patients who underwent hemispherectomy has shown that longer disease duration and earlier onset are associated with increased severity of histological changes and spreading of lesion from the cortex to the white matter (Pardo *et al.*, 2004). The age-dependent severity of histological findings and spreading suggested by Pardo *et al.* (2004) may contribute to our observation of age-dependent distribution of high intensity lesions. Rapid progression and poor prognosis in a case of infant seizure onset has been previously reported (Bien *et al.*, 2002b) and we also reported three cases of infant onset of RS showing a very serious clinical course (Takahashi *et al.*, 1997). Age appears to have a considerable impact on RS evolution.

In the present study, around 60% of non-EPC type patients had HILs in insular regions. Several reports have described insular changes in RS, including initial inflammatory lesions in two of 13 patients (Bien *et al.*, 2002b), HILs in three of seven patients (Kim *et al.*, 2002), HILs in eight of 13 patients (Chiapparini *et al.*, 2003) and frequent atrophic changes at onset (Granata *et al.*, 2003). However, it is unclear why the insula is susceptible to autoimmune inflammation in RS. In a patient with postinfectious autoimmune-mediated encephalitis, HILs on MRI and contrast enhancement on computed tomography were found in the insular cortex (Joos *et al.*, 2003). The blood-brain barrier in the insular cortex may be vulnerable to inflammatory factors. Further studies are needed to confirm the frequent involvement of the insula.

Conclusion

The present study indicates that dynamic evolutionary changes in MRI lesions (regression, fluctuation and expansion of HILs) may be a diagnostic feature of RS. □

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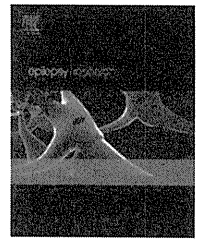

Versive seizures in occipital lobe epilepsy: Lateralizing value and pathophysiology

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KEYWORDS
Versive seizure;
Occipital lobe epilepsy;
Lateralizing sign

Summary To clarify the value of versive seizures in lateralizing and localizing the epileptogenic zone in patients with occipital lobe epilepsy, we studied 13 occipital lobe epilepsy patients with at least one versive seizure recorded during preoperative noninvasive video-EEG monitoring, who underwent occipital lobe resection, and were followed postoperatively for more than 2 years with Engel's class I outcome. The videotaped versive seizures were analyzed to compare the direction of version and the side of surgical resection in each patient. Moreover, we examined other motor symptoms (partial somatomotor manifestations such as tonic and/or clonic movements of face and/or limbs, automatisms, and eyelid blinking) associated with version. Forty-nine versive seizures were analyzed. The direction of version was always contralateral to the side of resection except in one patient. Among accompanying motor symptoms, partial somatomotor manifestations were observed in only five patients. In conclusion, versive seizure is a reliable lateralizing sign indicating contralateral epileptogenic zone in occipital lobe epilepsy. Since versive seizures were accompanied by partial somatomotor manifestations in less than half of the patients, it is suggested that the mechanism of version in occipital lobe epilepsy is different from that in frontal lobe epilepsy.

Introduction

Eye and/or head deviation is frequently observed during epileptic seizures, and the lateralizing significance of these symptoms has been a topic of debate (Ochs et al., 1984; Robillard et al., 1983). Although version is also frequently observed in occipital lobe epilepsy (OLE), subjective symptoms such as visual auras are considered as hallmarks in the diagnosis of OLE, and detailed studies using video-EEG monitoring of objective seizure symptoms in OLE are rare

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Table 1 Clinical characteristics of 13 patients.

Patient	Age at onset (years)	Age at surgery (years)	Aura	EEG		Laterality of lesion	Histology	Follow-up (years)	Outcome (Engel)
				Interictal	Ictal				
1	15	28	elementary visual	Lt O, Lt T	Lt T	Lt	cephalocele	15	Id
2	9	17	cephalic	Lt pT-O	Lt pT-O	Lt	CD	12	Ib
3	6	17	elementary visual, ocular sensation	Rt O	Rt O	Rt	CD	12	Ic
4	7	17	visual illusions	Rt T	Rt pT-O	Rt	ulegyria	10	Ic
5	9	17	none	Lt mT-pT, Rt O	Lt pT	Lt	CD	8	Id
6	9	26	blurred vision	Lt aT, Rt aT	Lt T-P	Lt	CD	7	Ia
7	8	22	amaurosis, blurred vision	Rt aT, Rt O	Nonlateralizing	Rt	ulegyria	7	Ia
8	5	28	cephalic, amaurosis(rare)	Rt O, Rt T	Lt T	Rt	ulegyria	6	Ic
9	3	14	amaurosis	Lt O-pT	Lt O-pT	Lt	CD	5	Id
10	11	17	epigastric, visual illusions, somatosensory	Lt aT-mT	Lt aT-mT	Lt	DNT	5	Ia
11	9	35	chilly feeling, nausea	Bil T	Lt T	Rt	ulegyria	4	Ic
12	5	28	none	Rt T	Rt hemisphere	Rt	ulegyria	3	Ia
13	2	13	visual illusions	Rt O	Rt hemisphere	Rt	ulegyria	3	Ia

CD: cortical dysplasia, DNT: dysembryoplastic neuroepithelial tumor, Rt: right, Lt: left, Bil: bilateral, aT: anterior temporal, mT: mid temporal, pT: posterior temporal, T: temporal, O: occipital, P: parietal.

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Table 2 The direction and character of version, and association of version with other motor activities.

	Version			Other motor activities accompanying version			
Patient	Number of seizures	Direction	tonic or clonic	None	Partial somatomotor	Automatism	Blinking
1	3	contralateral[a]	clonic	3	0	0	0
2	5	contralateral	both	3	2	0	0
3	2	contralateral	both	0	0	1	2
4	3	contralateral	tonic	3	0	0	0
5	4	contralateral[a]	both	0	4	0	0
6	5	contralateral	tonic	1	0	4	0
7	4	contralateral	both	0	4	0	0
8	4	bidirectional, contralateral	both	3	1	0	0
9	7	contralateral	both	0	7	0	1
10	4	contralateral	tonic → clonic	0	0	4	2
11	3	contralateral[a]	clonic	0	0	3	0
12	2	contralateral	tonic	0	0	0	2
13	3	contralateral	both	3	0	0	0

[a] Preceded by ipsilateral head turning.
None = without somatomotor manifestation, automatism, or blinking.

(Fogarasi et al., 2003; Munari et al., 1984; Williamson et al., 1992). The propagation of ictal discharges into the frontal eye field (FEF) is generally considered to be responsible for versive movements in OLE, however, the true pathophysiology and lateralizing significance of version has not been clarified. In this study, videotaped versive seizures in patients who were successfully treated by occipital lobe resection were analyzed retrospectively to confirm the value of version in lateralizing and localizing epileptogenic zone, and to clarify pathophysiology of version.

Methods

A total of 40 patients in our Center underwent occipital lobe resection for the treatment of intractable epileptic seizures as of December 2008. Of the 40 patients, 13 who had at least one versive seizure recorded during preoperative non-invasive video-EEG monitoring, and were followed for more than 2 years with Engel's class I outcome were included in the present study (Table 1). The ages at seizure onset ranged from 2 to 15 (mean 7.5) years and ages at surgery from 13 to 35 (mean 21.5) years. The postoperative follow-up durations ranged from 3 to 15 (mean 8.7) years.

Nine patients had visual auras including amaurosis or blurred vision in four, illusions in three, and elementary visual hallucination in two. Two patients had no aura. In the remaining two patients without visual aura, one had cephalic auras, and another had autonomic auras characterized by chilly feeling and nausea. Interictal EEG revealed epileptiform discharges in the temporal or posterior regions on the lesion side in ten patients. In the remaining three patients, epileptiform discharges were seen bilateral independently. Ictal EEG showed regional or lateralized seizure activities on the lesion side in ten patients. In two patients, ictal discharges were predominant in the contralateral temporal region. Ictal discharges were nonlateralizing in the remaining patient.

Histopathology of resected specimens revealed ulegyria in six patients, cortical dysplasia in five, dysembryoplastic neuroepithelial tumor in one, and cephalocele in one. According to the definition by Wyllie et al. (1986), versive seizures are defined as clonic or tonic head and eye deviations, unquestionably forced and involuntary, resulting in sustained unnatural positioning of the head and eyes. Epileptic nystagmus (Beun et al., 1984) was excluded. The direction of versive movements and the side of surgical resection were compared in each patient. Moreover, other motor symptoms (partial somatomotor manifestations such as tonic and/or clonic movements of face and/or limbs, automatisms, and eyelid blinking) that preceded or appeared simultaneously with version were analyzed, and motor symptoms that appeared after versive movements were excluded from analysis.

Results

Forty-nine versive seizures were analyzed. Table 2 shows the number of versive seizures in each patient, the direction and character (tonic or clonic) of versive movements, and the presence or absence of other motor symptoms.

Both head and eye versive movements were observed except one seizure of Patient 2 with isolated eye version.

In 12 patients, the direction of versive movements was always contralateral to the side of surgical resection. In three (Patients 1, 5, 11) of them, version was preceded by ipsilateral non-versive head and eye turning. For example, in Patient 5 who had an epileptogenic lesion in the left occipital lobe, his head was first turned to the left at about 90°. About 20 s later, this was followed by clonic movements of the right arm and face, and versive movements of

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the head and eyes to the right. Then generalized jerking started. In the remaining patient (Patient 8), four versive seizures were recorded. In two of the four seizures, versive movements were directed towards the side contralateral to the resection, whereas ipsiversive movements interrupted contraversive movements in the remaining two seizures.

As for the character of versive movements, it was both tonic and clonic in seven patients, tonic followed by clonic in one, tonic only in three, and clonic only in two.

Partial somatomotor manifestations (partial tonic and/or clonic movements of face and/or limbs) accompanying version were observed in five of 13 patients. In three of the five patients, versive movements were always accompanied by clonic movements of the arm on the side to which version was directed. Eight patients had no accompanying partial somatomotor manifestations. Automatisms were associated with versive movements in four patients: two showed manual automatisms, one had manual and oral automatisms, and one crossed his arms over his chest and wiggled his body during version. Partial somatomotor manifestations and automatisms never appeared simultaneously. In four patients, eyelid blinking preceded version or occurred simultaneously with version.

Discussion

Wyllie et al. (1986) defined versive seizures as clonic or tonic head and eye deviations, unquestionably forced and involuntary, resulting in sustained unnatural positioning of the head and eyes. They studied 37 patients who had head and eye turning during 74 spontaneous epileptic seizures and correlated videotaped seizures with the EEG location of seizure onset. Contralateral versive head and eye movements occurred during 61 seizures in 27 patients comprising 10 with frontal foci, 14 with temporal foci, two with parietal foci, and one with occipital focus. No ipsilateral versive movements were observed. They suggested that version was primarily due to transcortical propagation of the seizure discharge to frontal contraversive centers in the hemisphere of seizure onset.

In OLE, the direction of version is generally considered to be contralateral to the epileptogenic zone. Ludwig and Ajmone-Marson (1975) reported that the direction of version was always contralateral to the EEG foci in the occipital region; however, their study was not based on video-EEG monitoring. Rosenbaum et al. (1986) studied a man with repeated seizures characterized by deviation of the head and eyes to the left, and demonstrated a right occipital focus on ictal EEG. Munari et al. (1984) reported 49 seizures with early ocular deviation during stereo-EEG investigations of 16 patients, and reported that the ocular deviation was contralateral to the discharge in 48 of 49 seizures. In the study of Williamson et al. (1992), however, eye deviation was observed in 16 of 25 patients who underwent OLE surgery; the direction was contralateral to the seizure foci in 13 cases, and ipsilateral in the remaining three. In our study, we carefully analyzed the videotaped versive seizures of 13 patients in whom location and laterality of the epileptogenic zone were proven by the results of surgery. In 12 of 13 patients, versive movements were always directed towards the side contralateral to the epileptogenic zone. Therefore, it can be concluded that version has lateralizing significance also in OLE. In the remaining patient (Patient 8), version was directed contralateral to the epileptogenic zone in two of four recorded versive seizures, whereas ipsiversive movements interrupted contralateral versive movements in the remaining two seizures. In another three patients, ipsilateral non-versive head and eye turning preceded contralateral version. Although the mechanisms of these phenomena are unknown, inhibition of the ipsilateral hemisphere may cause ipsilateral non-versive turning due to hemineglect (Kernan et al., 1993).

Version may be associated with seizures arising from any cortical region. The localizing value of version has not been clarified, and the character of version in OLE has not yet been identified. In the study of Munari et al. (1984), ocular deviation was 'tonic' in most cases (44 of 49 seizures). However, it is known that both saccadic and smooth eye movements are evoked by electrically stimulating FEF or supplementary eye field in monkeys (Tian and Lynch, 1996). The parietal lobe also plays a major role in both saccades and smooth pursuit (Shibutani et al., 1984; Goldberg, 2000). In our patients with OLE, both tonic and clonic components were observed. Therefore, the character of eye movements does not differentiate the location of seizure onset. As regards the timing of version onset, Bleasel et al. (1997) reported that version occurs earlier in extratemporal seizures than in temporal seizures. Early onset of version may suggest extratemporal seizure focus, but does not differentiate frontal lobe epilepsy from parietal or occipital lobe epilepsy. As for the accompaniment of other motor symptoms with version, of ten patients with frontal lobe foci included in the study of Wyllie et al. (1986), posturing and clonic movements of the arm were observed during version in six, and tonic or clonic contraction of the face was seen during version in eight. On the contrary, we observed partial somatomotor manifestations (partial tonic and/or clonic movements of face and/or limbs) accompanying version in only 5 of 13 patients with OLE, and partial somatomotor manifestations invariably accompanied version in only three patients. Partial somatomotor manifestations associated with version was much less frequent in patients with OLE than in those with frontal lobe epilepsy studied by Wyllie et al. (1986). Based on the findings from cortical stimulation, activation of the FEF (Foerster, 1931; Godoy et al., 1990) or the supplementary eye field is generally considered to be responsible for versive movements. Also in OLE, propagation of the ictal discharge into frontal contraversive areas has been suggested to be the most important mechanism of version. As regards the involvement of cortices posterior to the central sulcus, activation of intraparietal area (Muri et al., 1996) or striate cortex (Bodis-Wollner et al., 1997) during voluntary saccades has been reported using functional MRI. Penfield and Jasper (1954) elicited contralateral eye deviation by stimulating Brodmann's area 19. Our finding that versive movements were accompanied by partial somatomotor manifestations in less than half of our patients contradicts the theory that frontal propagation is the main mechanism of version in OLE. Horizontal ocular movements are mediated by the paramedian pontine reticular formation (PPRF), which receives parallel input from the FEF and the superior colliculus (Schiller et al., 1980). The superior colliculus receives converging inputs

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from frontal, prefrontal, parietal, temporal, and occipital cortices (Sparks and Nelson, 1987). Therefore, two pathways may convey impulses for conjugate eye movements during cortical stimulation or in seizures: (1) extrafrontal cortex → frontal cortex → PPRF; and (2) cortex → superior colliculus → PPRF (Blume, 2001). In seizures arising from the occipital lobe, version may be elicited via the superior colliculus and PPRF without engaging frontal contraversive areas, although frontal propagation may play a major role in some patients.

In conclusion, versive seizure is a reliable lateralizing sign indicating contralateral epileptogenic zone in OLE. Since versive seizures were accompanied by partial somatomotor manifestations in less than half of the patients, it is suggested that the mechanism of version in OLE is different from that in frontal lobe epilepsy.

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ランチョンセミナー

重症心身障害児(者)のてんかんの薬物治療
―抗てんかん薬の使い方の実際―

須貝研司

表1 重症児（者）のてんかんへの対応

1. 詳しい発作症状に基づいた薬剤選択
   類似の発作の場合、脳波をもとに全般発作か部分発作かを鑑別
2. 看護記録、看護師・指導員・保育士・学校教員への聞取りによる発作症状の確認
3. 発作とまぎらわしい行動異常、奇妙な癖は発作時脳波を発作症状がその脳波異常で（部位や形）で説明できるかを検討し、てんかん発作か否かを判断
4. 最低限脳波があればできるような薬剤選択マニュアル
   脳波では強直発作や暴れるような過動発作ではFz、Cz電極が必要
5. 臨床薬理を応用した治療
   1）発作の好発時間に血中濃度が高くなるように、ピーク時間（Tmax）と半減期（T1/2）を考慮して薬剤選択と投与時間を
   2）多剤併用や不要な薬剤を整理
   発作型から不適当と思われる薬剤、血中濃度が著しく低い薬剤は中止
   3）相互作用で互いに血中濃度を下げ合う組み合わせの場合、その発作型に効果が少ないと思われる薬剤を中止
6. 副作用の熟知
   重症児（者）にとって不利益がありうる薬剤はなるべく避け、使用時は副作用に注意
7. 可能ならCT/MRIで脳内病変をチェック
   脳内病変がある場合は重症児・者でも手術を検討

よび新たな41例（前頭葉てんかん37例、側頭葉てんかん1例、頭頂葉・後頭葉てんかん3例、部分発作が1種類が22例、2種類が14例、3種類が5例）に対する前方視的検討を合わせて、具体的な発作症状（強直、二次性全般化強直間代、間代、hypermotor（過動）－暴れる/走り出す、陰性運動野発作－脱力/陰性ミオクロニー、意識減損・消失/動作停止、その他－感覚発作/自律神経発作など）に分けて有効な薬剤を検討し、10例以上投与した薬剤における反応率：responder rate（RR：発作が半分以下に減少した例の割合）を算出して、反応率≧75％を第一選択薬、反応率74～50％を第二選択薬、反応率49～25％を有効の可能性あり（第三選択薬）、反応率＜25％を無効薬（不適当薬）とした[3]。

2）全般発作

全般発作に関しては、筆者の経験的印象に、臨床的な実情に合うと感じる英国のNICE（National Institute for Clinical Excellence）のてんかん治療ガイドライン[4]（表4）を加味して、第一選択薬、第二選択薬、第三選択薬、不適当薬とした。

4．薬剤調整の具体例

症例1：35歳、West症候群後のLennox-Gastaut症候群、体重38kg。

発作症状：①全身を硬く突っ張る、②急に崩れ落ちる、③ピクンと両上肢を挙げる。

治療の現状：バルプロ酸（VPA）1,100mg分3（血中濃度100μg/ml）、クロナゼパム（CZP）5mg分3（33ng/ml）、カルバマゼピン（CBZ）600mg分3（10.0μg/ml）で、発作が月に15回前後あり、特に朝の起きて間もなくや、日中眠くなると起こしやすい。

脳波：やや前頭部優位だが左右対称性でほぼ全般性の多棘波（いわゆるrapid rhythm）と全般性の棘徐波が頻発（図3）。

MRI：両側の前頭部から頭頂部、後頭部まで傍矢状部（大脳半球の内側）の大脳白質の中に皮質があり、後頭部の皮質には脳溝が認められず、多小脳回または厚脳回を示す奇妙な皮質形成異常があり、また小脳も下半分が小さく、押し上げられたような形の形成異常を示している。

脳波から全般性の発作であり、また脳波の形状と合わせて、発作型は、①は強直発作、②は脱力発作、

表2 重症児（者）てんかん治療マニュアル（三訂案）

Ⅰ．治療前評価
・発作症状の確認：観察、看護記録、看護師・指導員・保育士・学校教員への聞き取り
・抗てんかん薬の血中濃度
・脳波検査
・可能ならMRI/CT検査。脳形成異常等の局在病変で極めて難治な場合は手術も考慮。

Ⅱ．発作症状と脳波（一部分から起こるか全般性か）から発作型診断と薬剤選択

1．脳波の発作波

発作波の部位	脳波焦点
一部分か、そこから周辺に広がる、時に全体に広がる	部分起始
離れた場所で2カ所以上だが一側性、または両側性だが全体に広がらない	部分起始
2カ所以上だが、両側に同時に出現し、頻回に全体に広がる	全般性
おもに全体に出ていて、時に一部分にも出現	全般性

2．発作症状と薬剤選択

発作症状	発作型	薬剤
体全体や一部を突っ張る、力が入る、強く倒れる（前後左右）	強直発作	部分起始：ZNS、PB、KBr、CLZ 全般性：　VPA、PB、ZNS、KBr （判断困難なら初めはVPA）
体全体や一部ををがくがくさせる	強直間代発作	
びくびくさせる	間代発作	部分起始：CBZ、CLB、PHT、CZP 全般性：　VPA、CLB
びくんびくん、びくっ、頭・体幹・足がかくんと落ちる	ミオクロニー発作*	部分起始：ZNS、PB
	陰性ミオクロニー発作*	全般性：　CZP、CLB、VPA
ぼうとして動作停止	複雑部分発作	部分起始：CBZ、CLB
	非定型欠神発作	全般性：　VPA、ESM
力がはいらず倒れる、頭部前屈	脱力発作*	部分起始：ZNS、PB 全般性：　CZP、CLB、VPA
暴れる様に上下肢を振り回す、走り出す	過動発作	部分起始：PHT、CBZ

抗てんかん薬の略号：AZM：アセタゾラミド、CBZ：カルバマゼピン、CLB：クロバザム、CLZ：クロラゼプ酸、CZP：クロナゼパム、ESM：エトサクシミド、KBr：臭化カリウム、NZP：ニトラゼパム、PB：フェノバルビタール、PHT：フェニトイン、VPA：バルプロ酸、ZNS：ゾニサミド

＊：部分起始のミオクロニー発作、陰性ミオクロニー発作、脱力発作は陰性運動野（脳波では、一見全般性に見えるが前頭～中心部の正中部Fz、Czから前頭部優位に棘波、棘徐波と、まれにF-C）の発作で起こりうる。かくんと前屈や脱力、あるいは前後左右にゆっくり倒れる。

Ⅲ．薬剤変更方法
1．病棟では定期処方からはずし、1週間ごとの臨時処方に。
2．最も多いか、生活に支障があるか、止めやすいと思われる発作型を選ぶ。
3．ねらった発作型に対して無効と思われるか量が少ない薬剤は中止またはその発作型に対する薬に変更、あるいは効くと思われる薬を追加。量が少ないが効くと思われる薬は増量。多剤併用の場合は、抗てんかん薬同士の相互作用に注意。
4．発作の好発時間、薬のピーク時間と半減期を考慮し、薬の時間、分服方法（分1、分2、分3など）と偏服（朝1，夜2の割合など）のやりかたを決める。
5．その薬で発作がもっとも減少するまで少量、中量、多量と3段階で増量。半減期が短いか中等度の薬剤（VPA，CBZ、PHT）は1～2週おきに、半減期が長い薬剤（PB、ZNS、KBr、ESM）、代謝産物の半減期が長いCLB、および増量時に副作用が出やすいが1週間以内に軽減するCZPは2週間ごとに増量。
6．発作が消失しなければ、血中濃度を測定し、治療域の上限まで増量。副作用がなければ上限を超えて増量。それでも発作が消失しなければ次の薬剤に置換するか追加。
7．その発作が1カ月以上なければ、著効と判断して、次の発作に移る。すべての発作が1カ月以上なければ定期処方にもどす。
8．種々の薬でもその発作が消失しない場合は、その発作が最も少なくなった時の薬と量にもどし、次の発作に移る。
9．副作用が出たら、減量するか他の薬に変更。
10．多剤併用の整理：マニュアルから見てその発作症状に合っていない薬、部分発作でその発作症状に無効が多い薬（表3）、全般発作で不適当薬（表3）、投与量が著しく少ない（維持量の半分以下）か血中濃度が著しく低い（治療域下限の半分以下）薬を中止の対象とし、1～2週毎に1/3～1/4ずつ減量して中止し、発作が増える場合は発作症状が合っている他の薬剤に変更。

（文献2を改訂）

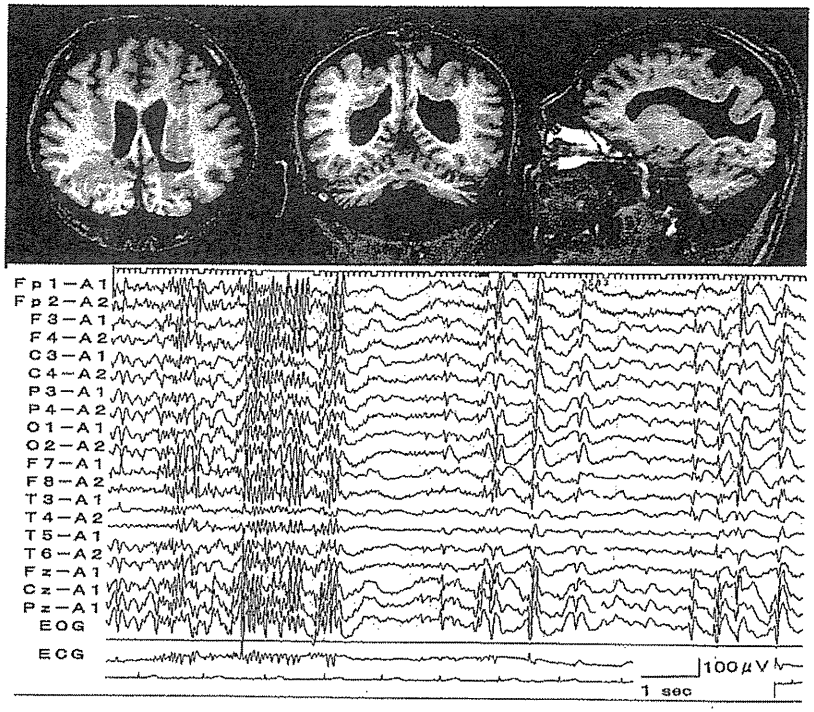

図3 症例1

③はミオクロニー発作または短い強直発作、と判断される。

服用中の抗てんかん薬はいずれも血中濃度は十分高いが、発作波抑制されていなかった。VPA、CZP、CBZのうち、発作型から見て、CBZは発作①、②、③のいずれに対しても選択薬とはならず、また表3からは、むしろいずれの発作にも不適当薬である。

まず、全般発作の強直発作に対して二次選択薬であるゾニサミド(ZNS)に変更し、増量した。

2週間ごとに ZNS 200→300→400mg分2

CBZ600mg分2→400→200mg→0

発作①は半分以下に減少したが残ったので、全般発作の強直発作に対して二次選択薬であるフェノバルビタール(PB)を追加、60→90mg分2としたところ、発作①は消失した。しかし、②、③は残ったので、ミオクロニー発作および脱力発作の第一選択薬であるVPAを1100→1250mg分2に増量したところ、③は消失し、全体で②が月1回以内まで減少した。しかし、眠気があり、活動性がやや乏しく、また眠いときに発作②が起るので、CZPを2週ごとに5→4→3→2mg分2と減量したところ発作②が増加したため、3mg分2に戻した。以上により、発作は②が月に1～2回におさまり、眠気もなく、活動性も上がっている。。

症例2：34歳、ヘルペス脳炎後遺症、右片麻痺、前頭葉てんかん、体重37kg

発作症状：①全身を硬くする、突っ張る、②時に全身をがくがくさせる

治療の現状：CZP 5mg分2（血中濃度50ng/ml)、VPA 800mg分2（74μg/ml)、フェニトイン（PHT）200mg分2、ZNS 200mg分2で週に2-3回、時に群発。

脳波：左前頭極Fp1から棘波がきわめて頻発し前側頭部F7に伝播し、また右前頭部F4からも棘波、鋭波が頻発し、前頭中央部Fzに伝播している(図4)。

CT：左の前頭部～中側頭部の萎縮があり、左半球が小さい。

発作①は強直発作で、時に②全身性強直間代発作、と判断されるが、脳波では脳炎後遺症なので両側前頭部に発作波が見られるものの、両側同期ではなく個々に局在しており、部分起始の強直発作とその二次性全般化発作と判断される。

服用中の抗てんかん薬のうち、マニュアルからはVPA、CZPは部分起始強直発作、二次性全般化発作の選択薬ではなく、また表3からは、①にはVPAは不適当薬であり、CZPも第三選択薬にも入らず、②にはVPAは第三選択薬にも入らない。ZNSはマニュアルで選択薬、表3でも第一選択薬に入っているが、量が少ない。

まず、VPAは減量中止し、ZNSを200→300→400mgまで増量し、発作は週1-2回に減少したがまだ残った。CZPを①、②に対する第二選択薬であるPBに変更し、60→80mg分2として発作は週1回以下に減少したが、まだ抑制できなかったので、KBrを追加し、700→1000→1200→1400mg分2として完全に抑制された。歯肉増殖がひどかったため、PHTを2週間ごとに1/3ずつ減量し、中止したが、発作は再発しなかった。

Ⅲ 薬物治療がうまくいかない場合の対応(表5)

薬物治療がうまくいかない原因で最も多いのは薬が合っていない場合であり、それにはてんかん分類や発作型診断が誤っている場合と、薬剤選択が誤っている場合とがあるが、重症児(者)の場合は、てんかんとまぎらわしい行動異常や癖も大きな原因になっている。これに対しては、発作症状の確認、脳波異常がその発作症状を説明できるか、そして可能ならば発作時脳波を検査するなど、診断の見直しを行う。

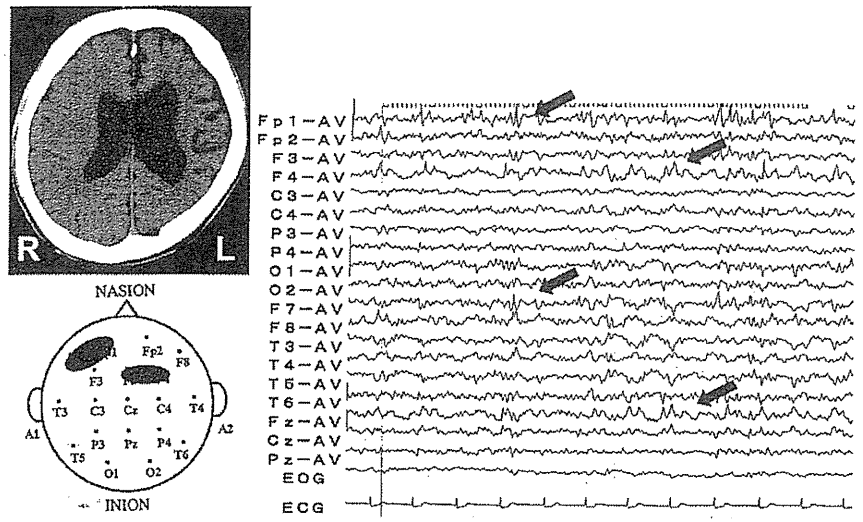

図4 症例2

表5 薬物治療がうまくゆかない場合の問題点と対応

1. 薬が合っていない → 診断
   - てんかん分類や発作症状の診断の誤り
   - 抗てんかん薬の選択が不適切
   - 偽発作であるか、その混在
2. 薬の量が少ない → 薬理動態
   - 投与量不足、血中濃度が有効域だが低い
   - 不適当な多剤併用：血中濃度を下げる組み合わせ
   - 不適当な分服数と服薬時間：半減期、ピーク時間を考慮せず
   - 発作が多い時間に血中濃度が低い
   - 抗てんかん薬の耐性
   - 自己誘導：CBZ
2. 真に難治 → 治療の工夫、専門家への相談、手術
   - 既存の治療法に難治なてんかん症候群
   - 器質的病変を持つ局在関連てんかん
   - 症候性全般てんかん

表6 新規抗てんかん薬の有効な発作型

発作型・症候群	GBP	TPM	LTG	LEV
部分発作	+	+	+	+
二次性全般化発作	+	+	+	+
原発性全般性強直間代発作	−	+	+	+
欠神発作	X	−	+	+
ミオクロニー発作	X	+	+*	+

GBP：ガバペチン、TPM：トピラマート、LTG：ラモトリギン、LEV：レベチラセタム

+：有効、−：無効、X：無効で時に悪化、*：乳児重症ミオクロニーてんかんで悪化

（文献7）より引用、改変）

次いで多いのは、薬の量が不十分な場合である。これには、絶対量や通常の血中濃度が低い場合だけではない。重症児(者)のてんかん治療で多い多剤併用による相互作用や、ピーク時間、半減期と服用する時間、分服方法などをチェックし、発作が多い時間帯に血中濃度が高くなっているか否かを検討する。

さらに、もともと重症児(者)のてんがんには難治が多いので、上記の検討によっても改善しない場合は、治療の工夫や専門家への相談が必要になり、場合によっては手術を考慮することもある。

Ⅳ 新規抗てんかん薬に関して

この5年間に、わが国でも4種類の新規抗てんかん薬(ガバペチン、トピラマート、ラモトリギン、レベチラセタム）が部分発作に対する併用薬として認可されたが、まだ経験が十分でないので、どんな具体的な発作症状に効くかがはっきりしない。そこで、文献報告[5)6)]をまとめ、有効とされている発作型をまとめた(表6)[7)]。また、使いやすいように新規抗てんかん薬を含めて発作型に対する第一選択、第二選択、不適当薬を示している英国のNICE (National Institute for Clinical Excellence) のてんかん治療ガイドライン(表4)を示す。

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＝原著論文＝

機能的半球切除術により日常生活動作に著しい改善を認めた小児 Rasmussen 脳炎の3例

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要旨 機能的右半球切除術を施行した Rasmussen 脳炎（Rasmussen encephalitis；RE）3小児例の発作，精神・神経学的および運動機能の回復過程について検討した．手術直前には抗てんかん薬，免疫療法に抵抗性の持続性部分てんかん発作（epilepsia partialis continua；EPC）と進行性片麻痺により坐位保持も困難であった．術後 EPC は消失し，片麻痺は残存したが，理学療法により 1.5 から 5 カ月で補助具での歩行が可能になり，日常生活活動（activities of daily living；ADL）は回復した．健側半球の覚醒時脳波では後頭部 α 波を認め，知能検査では退行の阻止を確認した．RE では発作，片麻痺が進行し，ADL が低下してきた場合，早期に機能的半球切除術を考慮すべきと考えた．

見出し語 Rasmussen 脳炎，機能的半球切除術，日常生活活動，予後，てんかん発作

はじめに

Rasmussen 脳炎（Rasmussen's encephalitis；RE）[1]は，難治性部分てんかんを主徴とし，生後 14 カ月から 10 歳に好発する，進行性の慢性局在性脳炎である．主症状として薬物療法に抵抗性の一側性部分発作，持続性部分てんかん発作（epilepsia partialis continua；EPC）とともに進行性片麻痺，知的退行を認める[2)3)]．治療としては抗てんかん薬や，免疫グロブリン大量療法，ステロイド大量療法，tacrolimus hydrate などを用いた免疫療法，それらが無効の場合には，てんかん外科治療が試みられている．しかし，抗てんかん薬には抵抗性で，免疫療法の効果も一時的とされており，最終的には侵襲は強いが，発作抑制効果が 62.5 から 85% と高い患側の大脳半球切除術を考慮する必要がある[4)5)]．以前は解剖学的半球切除術が行われていたが，約3分の1に水頭症，ヘモジデローシス，頭蓋内血腫などの術後晩期合併症を認め，機能的半球切除へ移行した[6)]．半球切除術自体は，もともと機能廃絶した大脳半球を切除するという発想であり，術後も大きな神経学的後遺症は残さないとされる[6)]．しかしながら，RE の場合には一側半球の一部より脳炎が進展，拡大していくので，手術時期によってこの後遺症の程度は変化しうる[7)]．RE の半球切除後の発作，神経学的変化について簡単な記載はあるものの，どのような過程を経てどの程度回復するのか詳細な記載はない．特に日本においては，RE の報告自体少なく，RE に対する半球切除術の予後について参考となる報告もない．

我々は3例の RE に機能的右半球切除術を行い，良好な発作抑制，運動機能の回復，知的退行の阻止を得たのでその詳細を報告する．

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I 症 例

症例1 13 歳女児

家族歴・既往歴 特記すべきことなし

現病歴 明らかな先行感染の既往はなく，5 歳 3 カ月に左半身けいれんで発症し，5 歳 6 カ月には嘔吐，顔面紅潮する自律神経発作が加わった．6 歳 1 カ月には EPC が出現し，軽度の左不全痙性片麻痺を認めた．ステロイド大量療法の効果は一時的であった．術前の頭部 MRI では，進行性の右半球萎縮と T2 強調・FLAIR 画像で右後頭葉の一部に高信号を呈していた（図 1a）．臨床経過と画像所見より RE と診断した．片麻痺の進行に加えて，EPC の頻発により立位保持，座位保持不能の状態が持続したため，6 歳 10 カ月に機能的右半球切除術を施行した．

脳波所見では，術前に右半球に多量の多型性 δ 波と臨床発作を伴わない頻回の発作発射放電を認め，健側左半球では 6-7 Hz と徐波化していた．術後しばらくはてんかん波や発作発射放電が持続していたが，機能的半球切除術のため患側に限