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# Multiple band frequency analysis in a child of medial temporal lobe ganglioglioma

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**Abstract** We report a 1-year 6-month-old girl with ganglioglioma in the right medial temporal lobe who showed epileptic spasms in clusters. Spasms occasionally followed a dazed and fearful gaze. Interictal electroencephalography (EEG) showed diffuse bursts of slightly irregular high-voltage spikes and slow waves without hypsarrhythmia. The findings on ictal EEG, single-photon emission computed tomography, and F-18 fluorodeoxyglucose positron emission tomography indicated focus on the right medial temporal lobe. Ictal fast rhythmic activity analysis of scalp EEG by multiple band frequency analysis showed gamma rhythms at 65–80 Hz with a high spectral power around the tumor area. Epileptic spasms completely disappeared after tumor resection. These findings suggest that the cerebral cortex may be a source of epileptic spasms and indicate the possibility of usefulness of fast activity analysis in this condition.

**Keywords** Multiple band frequency analysis (MBFA) · Gamma rhythms · Epileptic spasms · Periodic spasms · Ganglioglioma

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## Introduction

Numerous patients suffer from epileptic spasms in clusters apart from West syndrome patients. Although the pathogenesis of epileptic spasms is not widely understood, the cerebral cortex is assumed to play an important role [1]; however, conventional electroencephalography (EEG) has been ineffective for tracking the propagation of seizure discharges in epileptic spasms. Recent progress in digital EEG recording techniques, including multiple band frequency analysis (MBFA), developed to characterize the precise frequency spectral density for visually evoked potentials, has overcome this limitation. These techniques have detected very fast rhythmic activities in focal cortical areas during epileptic spasms in West syndrome and related disorders, and have implicated that the cerebral cortex plays a major role in developing epileptic spasms [2–4]. Here, we report a patient with ganglioglioma in the right medial temporal lobe who showed epileptic spasms in clusters without hypsarrhythmia on EEG. These spasms completely disappeared after tumor resection. We performed EEG, single-photon emission computed tomography (SPECT), F-18 fluorodeoxyglucose positron emission tomography (FDG-PET), magnetoencephalography (MEG), and analyzed the ictal fast activities on scalp EEG by MBFA. Results suggested that the cerebral cortex might be a source of epileptic spasms, and this finding indicated the possibility of usefulness of analyzing fast activities in this condition.

## Case report

A girl was uneventfully born to healthy Japanese parents, and psychomotor development was normal until the onset

of illness. At 1 year 3 months of age, she developed epileptic spasms in clusters consisting of a brief symmetrical contraction of axial muscles associated with intense head nodding and often falling down, which were occasionally preceded by a dazed and fearful gaze. Since the onset of spasms, she became autistic and lost social smile. Interictal EEG recordings showed diffuse slightly irregular high-voltage spikes and slow waves occasionally. Treatment with vitamin B6 and zonisamide resulted in only partial reduction of seizures. Computed tomography and magnetic resonance imaging (MRI) of the brain revealed a calcified mass lesion and cyst in the right medial temporal lobe involving the hippocampus, amygdala, parahippocampal gyrus, and fusiform gyrus (Fig. 1).

She was referred to our hospital at 1 year 6 months of age. On admission, her developmental quotient was 61. Ictal ethyl cysteine dimer (ECD)-SPECT revealed hypoperfusion in the right mesial temporal lobe area. Interictal FDG-PET revealed hypometabolism in the same area. On MEG recordings, the spike sources were located over the bilateral angular gyrus, spreading to the surrounding temporal and parietal areas. On ictal EEG recordings, a diffuse high-voltage slow wave complex with superimposed fast rhythms was observed with frontal area predominance (Fig. 2a). She underwent tumor resection at 1 year 9 months of age. Since then, her seizures have not recurred, and neuropsychological development has resumed. Her histopathological finding was consistent with that of ganglioglioma.

#### Multiple band frequency analysis

Ictal scalp EEG recordings were obtained with a digital sampling frequency of 500 Hz using Nihon Kohden

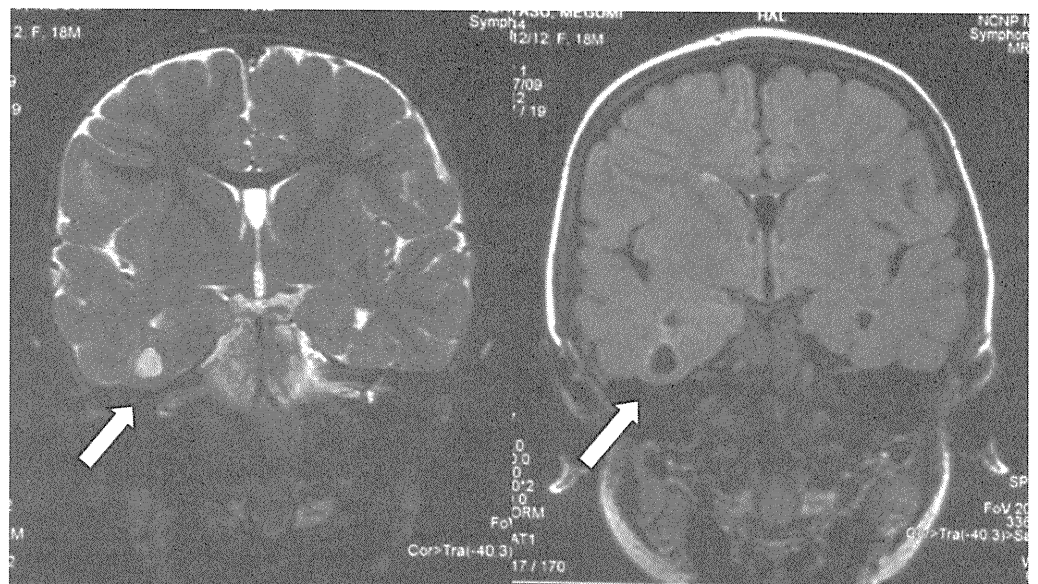
Neurofax (EEG-2000). The international ten to 20 electrode system was used. We identified fast rhythmic activities on EEG from 40 s before a spasm when she looked dazed and fearful. Fast activities were localized to the right middle temporal (T4) and frontal areas (Fp2, F8) (Fig. 2a, b). We were not able to correctly analyze the fast activities because of electromyogram artifacts after the spasm. We performed MBFA using Short-Spectrum Eye software (Gram, Saitama, Japan) to analyze the frequency and distribution of fast activities. MBFA deconstructed EEG waveforms into a sequence of frequency bands. We analyzed the power spectrograms of frequency bands between 1 and 150 Hz with a frequency resolution of 2 Hz and a temporal resolution of 20 ms. By MBFA, we measured the amplitude of each frequency to calculate the power in micro square Volts. It showed gamma rhythms at 65–80 Hz with a high spectral power predominantly over the right middle temporal (T4) and frontal areas (Fp2, F8) (Fig. 2c).

#### Discussion

Although epileptic spasms are typically associated with West syndrome, some cases fail to satisfy the criteria for West syndrome. Among them is a subgroup of patients with localization-related epilepsies with spasms in clusters in which cortical mechanisms play a critical role in their pathophysiology [1].

In our case, dazed and fearful gazes preceding spasms, ictal EEG with focal onset, spasm-related fast activity superimposed on slow waves, and lack of hypersarrhythmia were compatible with the findings of periodic spasms in patients, which were first described by Gobbi et al. in 1987

**Fig. 1** Brain MRI showing a slightly hyperintense lesion with a cyst in the right medial temporal lobe involving the hippocampus, amygdala, parahippocampal gyrus, and fusiform gyrus on T2-weighted (left) and FLAIR (right) images



**Fig. 2** **a** Ictal EEG recording. At first, fast activities are localized to the right middle temporal (T4) and frontal areas (Fp2, F8) (*upward arrowheads*). When a spasm occurs, a diffuse high-voltage slow wave complex with superimposed fast rhythms is seen with frontal area predominance (*arrow*). **b** An expanded EEG. Horizontal bar (1 s) **a** was expanded in **b**. Fast rhythmic waves are seen especially on T4 (*upward arrowheads*). **c** A representative power spectrogram. Frequency analysis was performed in the window of dotted line (200 ms) in **b** by MBFA. Gamma rhythms at 65–80 Hz with a high spectral power are predominantly seen over the right middle temporal (T4) and frontal areas (Fp2, F8). Each square corresponds to each EEG electrode. Vertical axis indicates frequency; horizontal axis indicates time course and colors indicate power ( $\mu\text{V}^2$ )

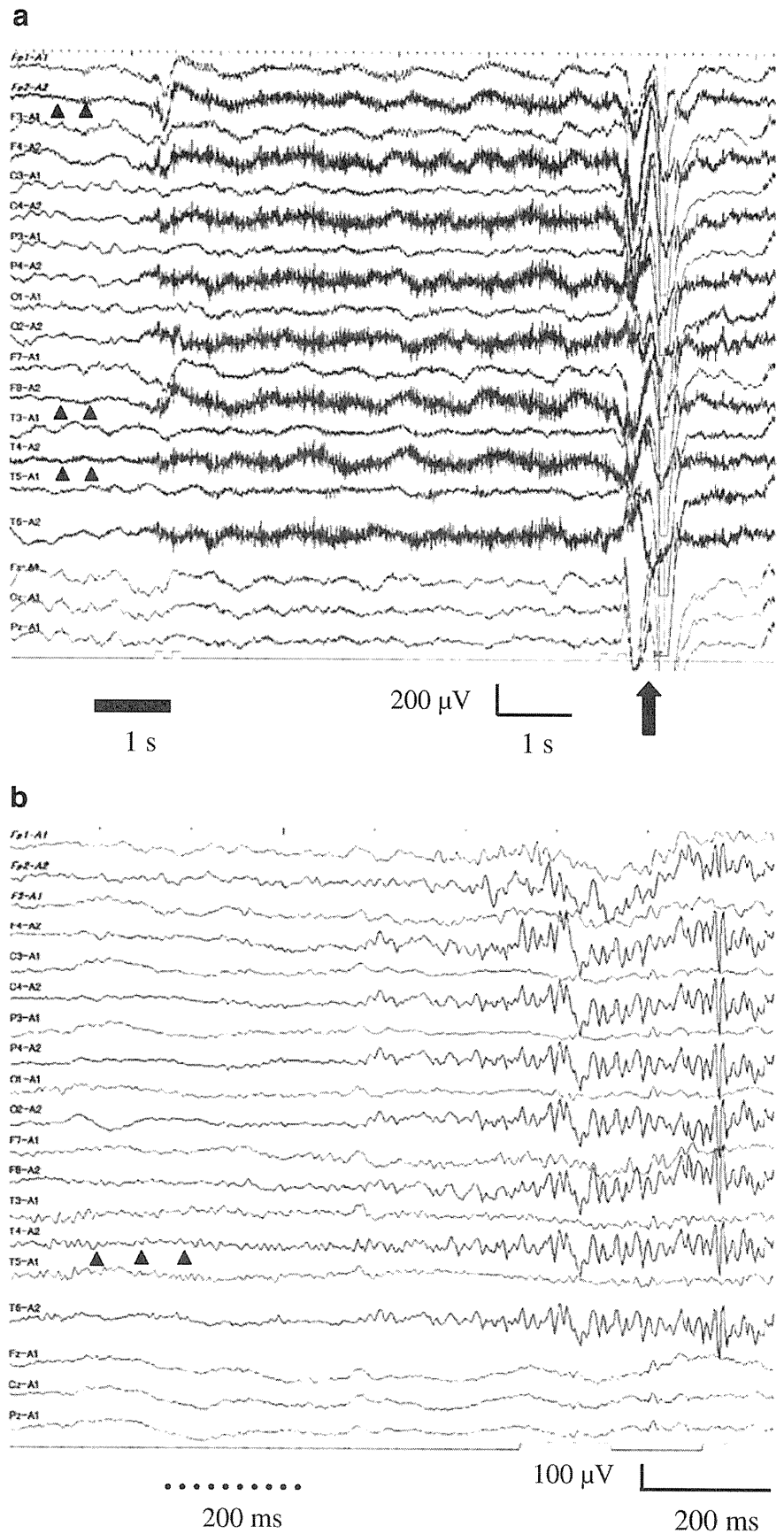
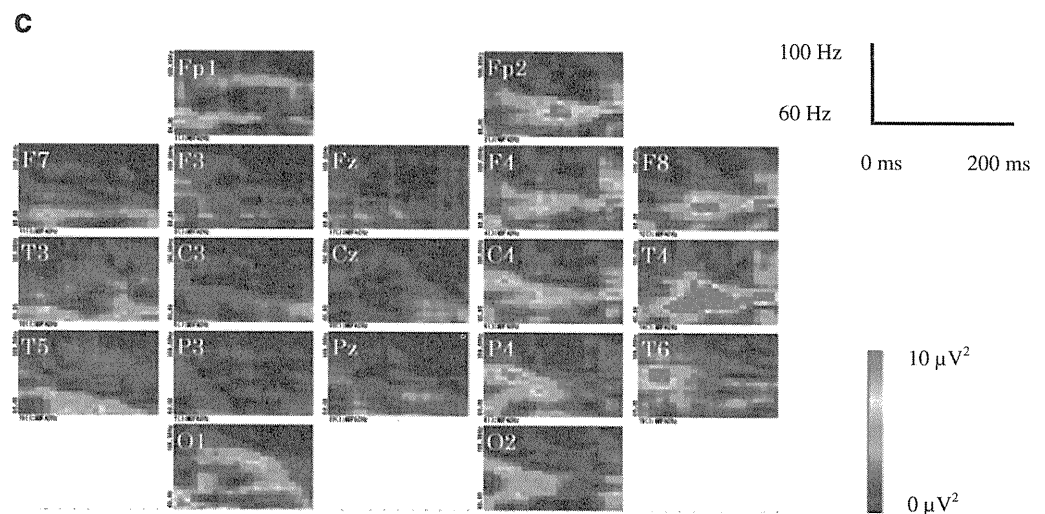


Fig. 2 (continued)



[5]. They showed that periodic spasms consist of a series of epileptic spasms following a focal seizure. Interictal EEG recordings mainly show multifocal spikes or spikes and waves without hypsarrhythmia, and ictal EEG recordings show a diffuse high-voltage slow wave with a superimposed fast rhythm or brief polyspike burst. They suggested that periodic spasms were partial seizures with a particular type of secondary generalization and were associated with abnormal interactions between the cerebral cortex and subcortical structures.

Periodic spasms with a brain tumor have not been reported. Because the concept of periodic spasms is not widely accepted, some cases may be categorized as epileptic spasms. Very fast activity associated with clinical spasms has recently raised significant concern. The progress in digital EEG recording techniques has facilitated detailed analysis of this activity. Gamma activity was indicated to be related with the behavior of inhibitory interneurons, especially gamma-aminobutyric acid-ergic interneurons, in hippocampal or neocortical networks or with electrical coupling between principal neurons via axonal gap junctions based on animal experiments and/or computer simulations. Kobayashi et al. discovered the gamma rhythm with a frequency ranging from 51 to 98 Hz during episodes of spasms in West syndrome and related disorders by digital scalp EEG. They speculated that the ictal gamma rhythm might reflect neocortical dysfunction and that the cortex played a major role in generating epileptic spasms [3]. Akiyama et al. also showed that high frequency oscillations (HFOs) defined as electroencephalographic activities above 100 Hz occurred over the localized cerebral cortex during epileptic spasms recorded by intracranial EEG, and these focal cortical HFOs clinically triggered spasms [4]. Furthermore, they reported that low-amplitude HFOs at 80–120 Hz started 4–15 min before clinical spasms were

apparent on the video, and location of the HFOs was consistent with that of the ictal phase.

In our case, fast activities were localized to the right middle temporal and frontal areas from 40 s before the spasm. Although the focus of the seizure was not clear by usual EEG or MEG, fast activity analysis may define the focus. The pathomechanisms of epileptic spasms has been studied by various methods. In the present report, we provided evidence for the close relationship between the cerebral cortex and epileptic spasms. First, seizures disappeared completely after tumor resection, which suggests that a tumor was important for the onset of spasms. Previous reports have described that tumors in the temporal lobe or other sites cause epileptic spasms, including West syndrome [6–8]. Second, according to the findings of ECD-SPECT, FDG-PET, and ictal fast activities by MBFA, the focus of spasms is located in the tumor area, and the spasms generate from the cerebral cortex.

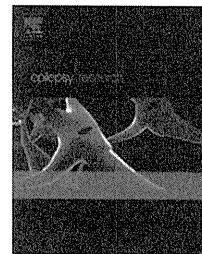
Another issue is the propagation of seizure activities during spasms. Based on MRI and PET findings, Juhasz C et al. hypothesized that in West syndrome, cortical epileptic discharges triggered the brainstem raphe nuclei, and the prominent serotonergic raphe-striatal and descending spinal pathways might be responsible for secondary generalization resulting in relatively symmetric spasms [9]. Asano et al. recorded dynamic ECoG changes associated with epileptic spasms and hypothesized that spasm-associated fast-wave bursts might be derived from a corticosubcortical pathway rather than corticocortical pathway because fast-wave bursts are rapidly and extensively involved in the noncontiguous neocortex simultaneously [10].

In conclusion, considering our case, we hypothesized that the focal fast activities spread to the corticocortical pathway and induced spasms via the corticosubcortical pathway. Further study is needed to elucidate the mechanism of propagation of fast activities during spasms.

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SHORT COMMUNICATION

## Effects of acetazolamide on epileptic apnea in migrating partial seizures in infancy

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### KEYWORDS

Apnea;  
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Temporal lobe;  
Acetazolamide

**Summary** We report two cases of migrating partial seizures in infancy complicated with intractable epileptic apnea with severe desaturation. Ictal electroencephalography revealed migrating foci of epileptiform discharges, which spread to bilateral temporal areas resulting in the onset of apnea. Magnetoencephalography detected dipole sources at bilateral perisylvian areas. Single photon emission tomography revealed a significant ictal change in perfusion at bilateral anterior temporal lobes in one patient. Addition of acetazolamide to the regimen resulted in complete disappearance of epileptic seizures.

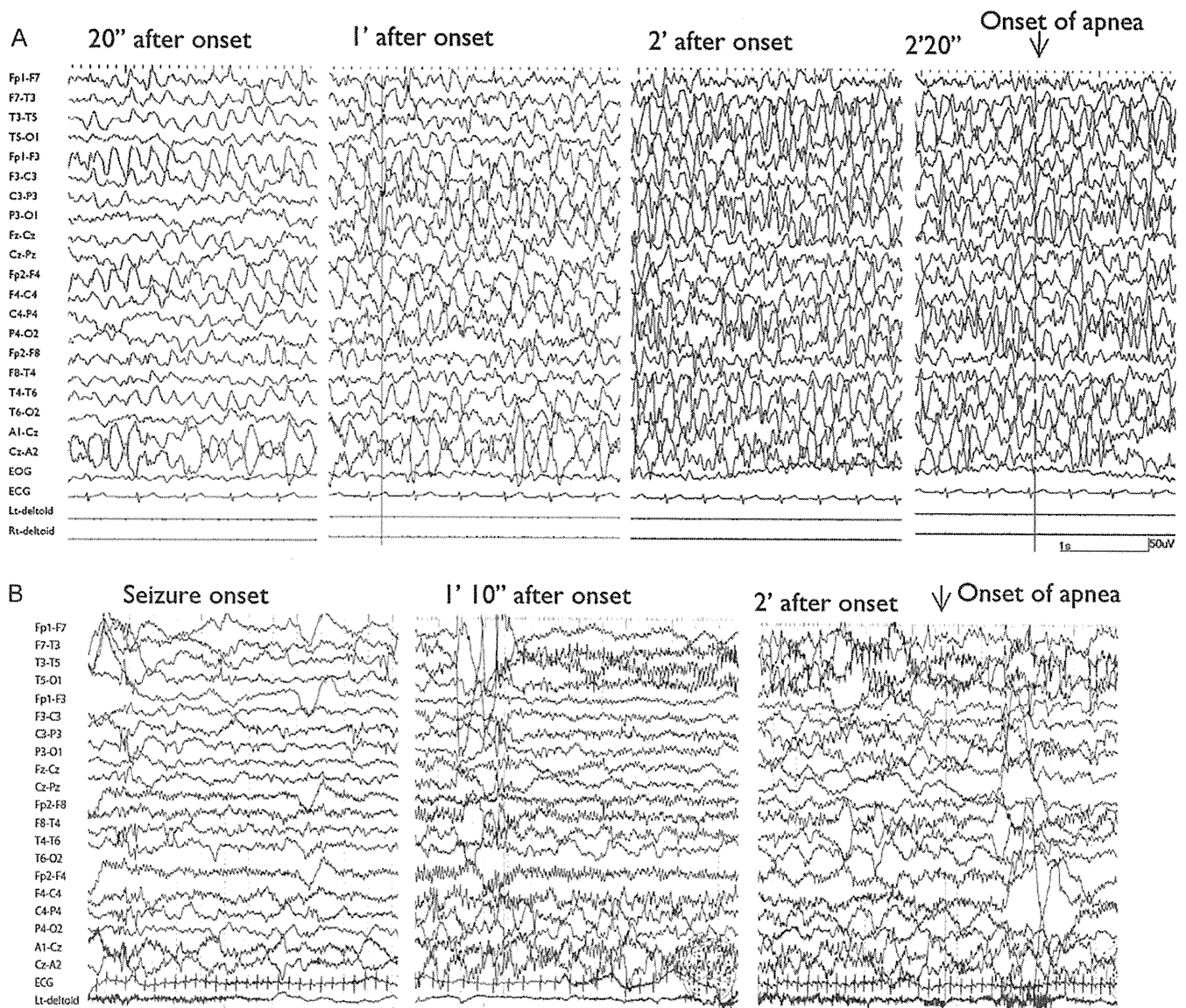
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### Introduction

Migrating partial seizures in infancy (MPSI) is a rare epileptic syndrome characterized by onset before six months of age, continuous migrating polymorphous focal seizures, ictal epileptic discharges arising independently and sequentially from both hemispheres, marked intractability to antiepilep-

tic drugs, and developmental arrest after the onset of disease (Coppola et al., 1995; Caraballo et al., 2008). Autonomic manifestations including apnea, flushing, and cyanosis often accompany or predominate the ictal phenomena (Coppola et al., 1995; Caraballo et al., 2008). Apnea as a manifestation of epileptic seizures is also observed in patients with localization-related epilepsy (Watanabe et al., 1982; Akaike et al., 2008). This type of seizure can appear during sleep or wakefulness, can necessitate resuscitation and can also be lethal (Ramelli et al., 1998), and has been assumed to be partly responsible for sudden unexpected death in epilepsy. Within these seizures, ictal activity usually consists of rhythmic focal alpha to theta activity

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**Figure 1** Ictal electroencephalography (EEG) for epileptic apnea. (A) Patient 1. At seizure onset with motion arrest, theta activities appeared in the right frontopolar area. These theta activities spread to the ipsilateral temporal and contralateral frontal regions within 20 s of the onset. One minute later, epileptiform activities further appeared in the left centroparietal region. Two minutes after the onset, theta activities involved the left temporal region. Two minutes and 20 s after the onset (20 s after the spread of theta activities in the bilateral temporal regions), apnea was observed. (B) Patient 2. Fast activity appeared in the right frontotemporal areas, which spread to the left temporal areas at 1 min and 10 s later. Epileptic activities in different frequency bands, 1 Hz in the right posterior and 5–6 Hz in the left centrottemporal areas, predominated at 2 min after the onset when apnea was observed.

originating in the temporal lobes (Watanabe et al., 1982). Limbic structures are densely connected to the respiratory center in the brainstem, primarily through ipsilateral descending pathways (Hopkins and Holstege, 1978). Therefore, bilateral temporal lobe involvement is significantly linked to ictal desaturation during complex partial seizures in temporal lobe epilepsy (Seyal and Bateman, 2009).

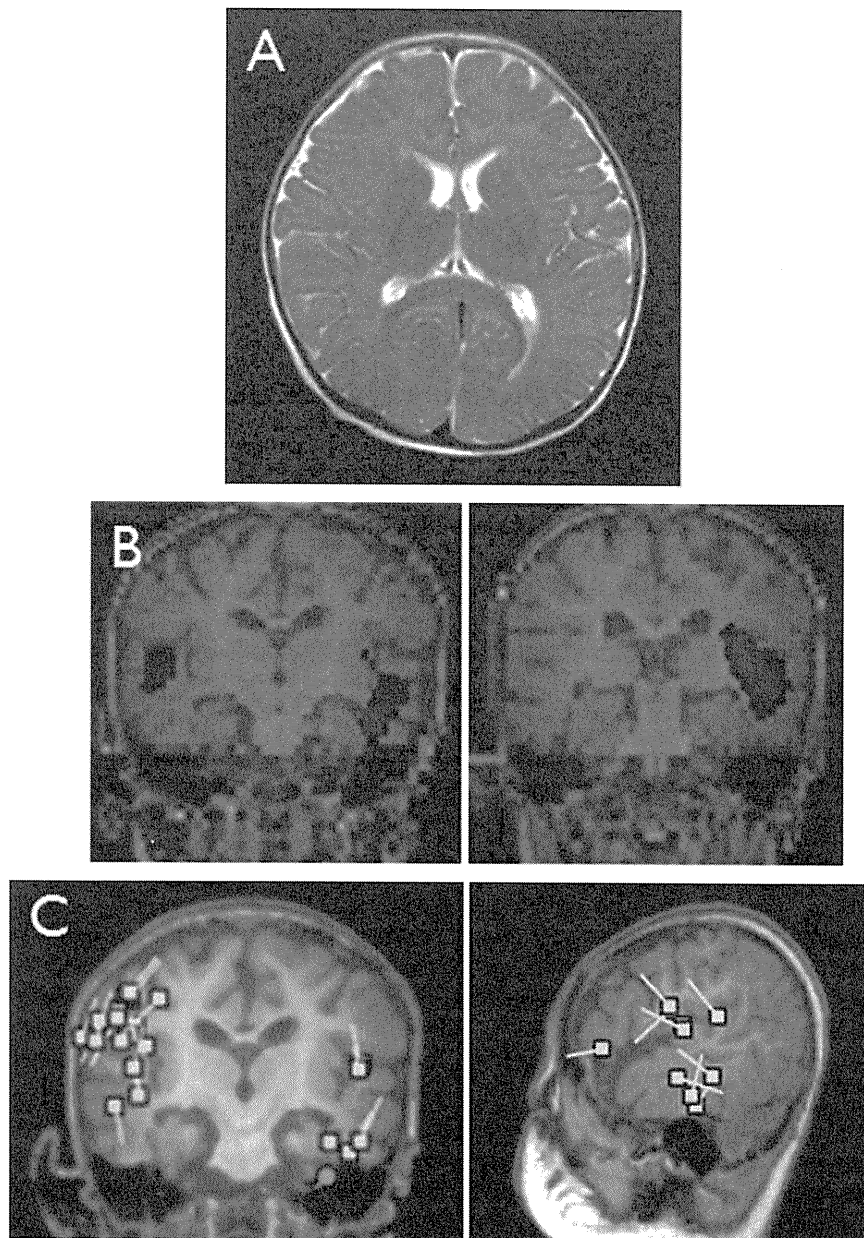
Here we report two cases of infants with MPSI who suffered from intractable epileptic apnea accompanying ictal discharges of bilateral temporal areas. Acetazolamide (AZA) administration produced significant effects on these seizures, which is the first demonstration of its usefulness in the treatment of MPSI.

## Case reports

### Patient 1

The one-year-old girl was born uneventfully and at term. Growth and development were normal until six months of age, when she experienced recurrent episodes of motion arrest and subsequent cyanosis with or without clonic movements of the upper limbs beginning on the right side. Although no abnormality was noted on interictal electroencephalogram (EEG), valproate (VPA) treatment was initiated. Blood and urine analyses found no evidence of metabolic disorders, and computed tomography (CT) of

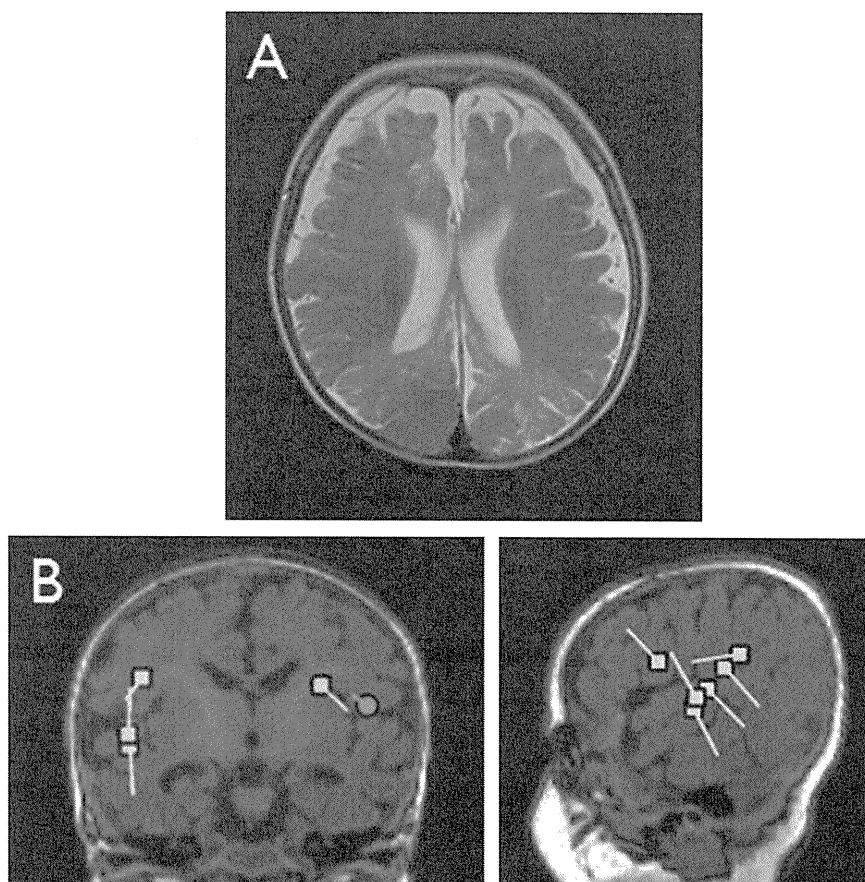




**Figure 2** Neuroimaging of patient 1 during admission (A) magnetic resonance imaging, (B) subtraction ictal single-photon emission computed tomography coregistered with magnetic resonance imaging, and (C) magnetoencephalography. (C) Interictal EEG at this period showed periodic appearance with bursts of polymorphic 1–5 Hz widespread slow waves, lasting 1–5 s with intervals of several seconds, mixed with multifocal spikes that were distributed at Fp1, Fp2, F3, F4, P4, T4, T5 and O1 areas (not shown).

the head showed normal results. At seven months of age, the frequency of motion arrest with severe desaturation increased, and SpO<sub>2</sub> levels as low as 50% were noted. EEG revealed occasional bilateral fronto-parietal spikes, and VPA was replaced by carbamazepine (CBZ). However, cluster seizures recurred daily and were refractory to phenytoin (PHT), diazepam, a high therapeutic dose of phenobarbital (PB), clobazam (CLB), lamotrigine (LTG), zonisamide (ZNS), potassium bromide (KBr), and continuous intravenous midazolam (MDL). The patient was admitted to our hospital at the age of nine months. At this point, she had lost the social smile response and the ability to sit alone, but was able to roll over, gaze, and track moving objects with her eyes. Each episode of epileptic apnea with desaturation typically lasted 1–5 min and was accompanied by limb

atonia, slight tongue thrust, facial flushing, and lacrimation. This type of seizures daily occurred 10–20 times as single and isolated episodes, as well as in clusters of a couple of times, each composed by 6–10 seizures. Ictal EEG showed rhythmic sharp waves originating from either the left or right frontal region and spreading to the ipsilateral and contralateral temporo-parietal regions, with apnea initiating after the bilateral involvement of the temporal regions (Fig. 1A). Magnetic resonance imaging (MRI) showed frontal dominant cerebral atrophy without abnormal signal intensity (Fig. 2A). Subtraction ictal single photon emission computed tomography (SPECT) co-registered to MRI (SISCOM) revealed elevated blood flow in the bilateral temporal lobes (Fig. 2B). Magnetoencephalography (MEG) showed dipole sources distributed in the bilateral



**Figure 3** Neuroimaging of patient 2 (A) magnetic resonance imaging and (B) magnetoencephalography. In (A), high signal change on T2-weighted magnetic resonance imaging, involving both gray and white matter and accompanied by regional atrophy, is noted in the parieto-occipital areas bilaterally. Less severe changes are also observed in the frontal lobes anterior to the lateral ventricles. These changes correspond to the distribution pattern of lesions due to watershed brain injuries. (B) Interictal EEG at this period revealed multifocal spikes predominantly at Fp2, F4, C3, T3 and P3 areas (not shown).

perisylvian areas, predominantly in the temporal lobes (Fig. 2C). The patient was diagnosed with MPSI. Seizures were refractory to regimens of KBr (50 mg/kg/day) and PB (10 mg/kg/day) and clobazam (CLB) (1 mg/kg/day) and levetiracetam (LEV) (30 mg/kg/day). Additional continuous infusion of lidocaine worsened the seizures. However addition of AZA (20 mg/kg/day) at 9.5 months of age resulted in complete disappearance of seizures within several days after initiation. EEG at this period showed dysrhythmic background activity with occasional spikes at T5 and O1 areas, which were markedly decreased in frequency compared to the previous records. The patient remained seizure-free for six months thereafter.

### Patient 2

Some clinical data regarding this patient, focusing on the bromoderma, have been previously published (Nabatame et al., 2010). This boy, now one year and 11 months old, was born uneventfully and at term. Growth and development were normal until three months when he suffered a febrile episode manifested with repeated loss of consciousness, ocular deviation, and unilateral limb thrashing, lasting several minutes. Blood, urine, and cerebrospinal fluid

analyses found no evidence of infection or metabolic disorders and brain MRI was normal. The seizures were refractory to PHT, PB, lidocaine, CBZ, and ZNS, but continuous intravenous MDL was partially effective. The patient lost the skills of visual pursuit and social smile within several weeks. He was admitted to our hospital at the age of four months. At this point, he suffered apneic episodes without convulsive symptoms several times daily, which increased to more than 50 times per day within 2 months after admission. An ictal EEG revealed fast activity, which spread from the right frontal to the ipsilateral temporal areas. Apnea was then observed after epileptic activity spread to the contralateral temporal regions (Fig. 1B). MRI showed cerebral atrophy predominantly of the bilateral parieto-occipital areas (Fig. 3A). MEG identified dipole sources in the bilateral perisylvian areas (Fig. 3B). Interictal SPECT revealed hypoperfusion over the right frontal and left lateral parietal lobes. The patient was diagnosed with MPSI. Initiation of KBr (60 mg/kg/day) and AZA (10 mg/kg/day) treatment in addition to a regimen of PB (5 mg/kg/day) and CLB (0.3 mg/kg/day) resulted in a significant reduction in seizure frequency. However, KBr administration was terminated because of the emergence of severe bromoderma (Nabatame et al., 2010). Thereafter, the occurrence of epileptic apnea increased to 30 times daily, and the dose of AZA was increased to

15 mg/kg/day at eight months of age. The epileptic apnea disappeared within one month, and the patient remained seizure-free for 12 months. Although still severely disabled, he has regained the abilities of social smile and ocular tracking. Follow-up EEG initially showed dysrhythmic background activity in low voltage, which improved in synchrony and amplitude at the age of 1 year and 10 months. Distribution of residual spikes has been limited to the Fp1/F3, C4 and T5 areas.

## Discussion

Epileptic apnea without convulsive symptoms can be regarded as a type of complex partial seizure (Watanabe et al., 1982). Apart from patients with neonatal seizures, this type of seizure has been mainly observed in infancy. Because decreased consciousness is often difficult to assess precisely at this age, accompanying motion arrest and minor signs such as grimacing, drooling, or flushing provide clues to the diagnosis of epilepsy. EEG reveals that these seizures most frequently originate in the temporal areas and less frequently in the frontal areas (Seyal and Bateman, 2009). This pattern of localization parallels the distribution of cortical sites, which are observed to inhibit respiration when electrically stimulated (Kaada and Jasper, 1952). The symptomatology of epileptic apnea found in MPSI may share a common mechanism with these experimental findings. As in the present patients, a close correlation has been observed between the bitemporal spread of epileptic activity on EEG (Seyal and Bateman, 2009) and the emergence of apnea, and ictal perfusion changes in the temporal lobe have also been identified in non-MPSI epileptic apnea (Lee et al., 1999).

Seizures in the present patients were quite intractable, whereas apneic seizures in other epilepsies have been responsive to medications including PB, CBZ, PHT, VPA, LTG, ZNS, or continuous infusion of MDL. Apnea with severe desaturation presumably resulted in the parieto-occipital lesions observed in patient 2. Although there are a couple of reports that have described the beneficial effects of KBr and LEV in MPSI (Caraballo et al., 2008; Hmaimess et al., 2006), these medications showed little effect or had to be terminated because of serious side effects in the present patients. Since we have observed the effects of AZA on epileptic apnea originating from the temporal region (Akaike et al., 2008), we tried this agent, which resulted in unexpectedly excellent seizure control. AZA is believed to achieve anticonvulsant action through inhibition of carbonic anhydrase, possibly by reduction of GABA-mediated depolarization, and suppression of the excitatory action of NMDA receptors (Thiry et al., 2008). AZA is also effective against non-epileptic central apnea by induction of metabolic acidosis that results in stimulation of central chemoreceptors. The effect of AZA on both epileptic and non-epileptic apnea is interesting, but it is unclear whether these antiapneic actions are the result of common symptogenic pathways modulated by these or other unidentified AZA mechanisms. The implication of exclusive response to AZA may further elucidate the pathophysiology of MPSI. In any case, the usefulness of AZA in preventing serious complications secondary to hypoxia and promoting improved neurological development in MPSI should be broadly recognized.

Epileptic foci in MPSI, as assessed by ictal EEG, have been often described simply as multifocal. However, a recent report suggested a classifying scheme of ictal electroclinical patterns in MPSI as (1) simple focal motor seizures, (2) complex focal seizures without obvious motor manifestations and (3) complex focal seizures with tonic phase, each type of phenomena being attributed to rhythmic epileptic activity at perirolandic, temporo-occipital and frontotemporal regions, respectively (Caraballo et al., 2008). The apneic seizures of present patients may represent the second type seizure in this classification. The SISCOM study suggested the significance of bilateral temporal lobe involvement in the exaggerated apneic phenomena in this seizure phenotype, whereas interictal EEG and MEG revealed that epileptogenic activity distributed to the areas corresponding to all of these three subgroups even when a single seizure type predominated in these patients. These facts that were obtained through close inspection of individual cases would contribute to extend our understanding of the pathophysiology of MPSI.

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# Surgical management of cavernous malformations presenting with drug-resistant epilepsy

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Cerebral cavernous malformations (CMs) are dynamic lesions characterized by continuous size changes and repeated bleeding. When involving cortical tissue, CMs pose a significant risk for the development of drug-resistant epilepsy, which is thought to be result of an altered neuronal network caused by the lesion itself and its blood degradation products. Preoperative evaluation should comprise a complete seizure history, neurological examination, epilepsy-oriented MRI, EEG, video-EEG, completed with SPECT, PET, functional MRI, and/or invasive monitoring as needed. Radiosurgery shows variable rates of seizure freedom and a high incidence of complications, thus microsurgical resection remains the optimal treatment for CMs presenting with drug-resistant epilepsy. Two thirds of patients reach Engel I class at 3-year follow-up, regardless of lobar location. Those with secondarily generalized seizures, a higher seizure frequency, and generalized abnormalities on preoperative or postoperative EEG, show poorer outcomes, while factors such as gender, duration of epilepsy, lesion size, age, bleeding at the time of surgery, do not correlate consistently with seizure outcome. Electrocorticography and a meticulous removal of all cortical hemosiderin – beyond pure lesionectomy – reduce the risk of symptomatic recurrences.

**Keywords:** epilepsy surgery, cavernous malformation, drug-resistant epilepsy, electrocorticography, partial onset epilepsy

## INTRODUCTION

Cerebral cavernous malformations (CMs), also known as cavernous angiomas, cavernomas, or cavernous hemangiomas, were first described in the central nervous system by Virchow in 1863 (Iza-Vallejo et al., 2005) and characterized microscopically by McCormick (1966). These mulberry-like lesion consist of intertwined clusters of thin-walled vascular sinusoids lined by a thin endothelium lacking smooth muscle, elastin, and intervening parenchyma, surrounded by hemosiderin deposits and gliosis (Raychaudhuri et al., 2005). CMs account for about 10% of all symptomatic vascular malformations, being the most frequent angiographically occult intracranial vascular malformations (Gomori et al., 1986), with an estimated frequency of 0.4–0.9% (Ottens et al., 1989; Brown et al., 2005), and an annual bleeding rate laying somewhere between 0.7 and 1.4%/lesion/year, or 0.25–3.1%/person/year of exposure (Kim et al., 1997; Stefan and Hammen, 2004; Ferroli et al., 2006).

Their occurrence can be sporadic, or as an autosomal dominant condition with variable expression and incomplete penetrance. The first recognized gene association (*CCM1*), was mapped in the long arm of chromosome 7 (*7q11* to *7q12*), upon studying the familial form of CM in a Hispanic family (Dubovsky et al., 1995). Three genes implied in the pathogenesis have been identified, all of them expressed in neurons rather than in blood vessels, suggesting an impaired signaling between these structures (Revenu and Vakkula, 2006).

It is well recognized the changing nature of CMs. This dynamism is determined by both extrinsic – hemorrhage,

calcifications, thrombosis, and intrinsic factors – pseudotumoral growth of the cavernous matrix – that result in growing or shrinking of established malformation; and by pathologic angiogenic factors in *de novo* appearing lesions (Houtteville, 1997).

## CMS AND EPILEPSY

Clinical manifestations, when present, are variable and include headache, seizures, hemorrhage, and sudden onset focal neurological deficits (FND; Raychaudhuri et al., 2005). The latter are the most common presentation of brainstem lesions, whereas seizures are the most frequent manifestation of supratentorial lesions (Awad and Jabbour, 2006; Van Gompel et al., 2010).

Epileptic seizures linked to CMs are often drug-resistant (Robinson et al., 1991; Kim et al., 1997). Cortical involvement is the most relevant risk factor for epilepsy. A greater diameter, the absence of edema, and localization in the left hemisphere are also associated with the occurrence of epilepsy. Mesiotemporal archicortical CMs pose a significantly higher risk for the development of epilepsy than neocortical lesions, a group that shows no differences regarding lobar location (Yeon et al., 2009; Menzler et al., 2010). Patients with peri-limbic or anterior temporal lesions may show signs of dual pathology, consistent in macroscopically – hippocampal sclerosis – microscopically, or only functional abnormalities within the mesial temporal lobe (Cendes et al., 1995; Stefan and Hammen, 2004).

The mass effect does not completely account for CMs' high epileptogenicity, as the clinician may appreciate when dealing with larger lesions, namely other kinds of AVMs – in the absence of

prior hemorrhage or FND – and gliomas, which are less likely to present with seizures (Awad et al., 1991; Josephson et al., 2011). This feature, referred to as secondary epileptogenesis (Morrell, 1985), has been studied in CMs. Williamson et al. (2003) performed intracellular recordings from neurons adjacent to gliomas and cavernomas, finding that neurons adjacent to CMs were more likely to show large complex spontaneous synaptic events than neurons adjacent to tumors. These neurons also showed more pronounced responses to synaptic stimulation, e.g., multiple action potentials riding on prolonged excitatory postsynaptic potentials were evoked in the majority of these cells, as opposed to those belonging to the tumor group (Williamson et al., 2003).

Intralesional bleeding is another factor to consider. This event may partially destroy the CM, leaving residual cysts, and calcifications (Pozzati et al., 1989). It is thought that the breakdown of blood products results in gradual deposition of hemosiderin and hemin in the cerebral tissue surrounding the malformation (Kim et al., 1997); ultimately leading to biochemical abnormalities that become more prevalent and significant as the duration of epilepsy continues. The latter might explain why a longer history of epilepsy is a predictive of poorer results following pure lesionectomy, i.e., restricted surgical removal of the CM, respecting the hemosiderin-stained gliotic perilesional tissue (Ferroli et al., 2006). In addition, reactive glial proliferation may be epileptogenic.

## PREOPERATIVE EVALUATION

A detailed preoperative epileptological and radiological work-up tailored to the individual's pathology allows the clinician to classify seizures according to the ILAE guidelines. Clinical history, neurological examination, epilepsy-oriented MRI, scalp EEG, and video-EEG are essential (Von Der Brélie and Schramm, 2011). Spin echo and gradient echo sequences using T1 and T2-weighted MRI provide useful information on the CM hemodynamics; and also permit to classify them in four types according to the findings focused on signal characteristics (Zabramski et al., 1994).

Complementary studies include interictal and/or ictal SPECT, PET, functional MRI, magnetoencephalography (Stefan et al., 2004), intracarotid amobarbital testing (Stefan et al., 2004; Yeon et al., 2009), electrocorticography (ECoG), or implantation of intracerebral or subdural grid electrodes when needed (Siegel et al., 2000; Ferrier et al., 2007). Computer tomography with contrast enhancement (Stavrou et al., 2008) or angiography can also be used, although the latter usually fails to identify CMs (Gomori et al., 1986; Stavrou et al., 2008).

## MANAGEMENT

Radiosurgery leads to the progressive obliteration of CMs by endothelial cell proliferation, with consequent luminal closure. This process takes 1–3 years on average to complete (Schneider et al., 1997), a period of time during which the risk of hemorrhage remains. Moreover, serious complications are not uncommon, with as much as 41% of patients presenting neurological deterioration after treatment and 27% requiring microsurgical extirpation (Karlsson et al., 1998). In fact, pathological studies on previously radiated patients undergoing surgery show that radiation does not always warrant complete vascular obliteration (Gewirtz et al., 1998).

Although seizure freedom is reported to reach 52% (Regis et al., 2000), there is still a lack of consensus on the indications for radiosurgery and the appropriate dose of irradiation, let alone the limited evidence supporting a protective role against rebleeding (Kim et al., 1997; Pollock, 2008). For these reasons, excision remains the optimal therapeutic strategy for patients with drug-resistant epilepsy. Standard microsurgical technique is widely accepted, and variations in surgical behavior exist among different groups. For instance, some of them describe the routine (Ferroli et al., 2006) or occasional (Kivelev et al., 2011) use of a stereotactic device or frameless neuronavigation system. A mini-invasive transulcal approach has been described (Ferroli et al., 2006); alternatively, a transylvian approach may be useful for anteromedial temporal CMs, or transcortical excision, at times using intersulcal dissection, for other locations (Kivelev et al., 2011). Neurophysiologic monitoring, in the form of direct cortical mapping and monitoring of neurological functions are used for CMs in eloquent locations (Ferroli et al., 2006).

The amount of resected tissue is also a matter of discussion. For instance, Yeon et al. (2009) take into account seizure frequency, opting for more aggressive approaches for drug-resistant epilepsy, i.e., extended rather than simple lesionectomy in patients without mesial temporal lesions; and tailored resection rather than standard temporal lobectomy for mesiotemporal CMs (Yeon et al., 2009). On the other hand, Ferroli et al. (2006) endorse a two-step surgical policy for patients with epilepsy secondary to CMs, attempting at first a pure lesionectomy, followed by invasive localization and tailored removal of the epileptogenic zone in those patients with drug-resistant seizures at 1–2 years follow-up (Ferroli et al., 2006).

## GENERAL OUTCOME

Up to 17% of patients may develop neurological symptoms (sensorimotor deficits and homonymous hemi or quadrantanopsia) immediately after the operation (Ferroli et al., 2006; Stavrou et al., 2008). Nonetheless, at follow-up, the rate of neurological deficits including severe headache, slight dysphasia, sensory disturbances, ataxia, severe hemiparesis, pontocerebellar degeneration, descends to 2.6–8% (Zevgaridis et al., 1996; Baumann et al., 2006; Ferroli et al., 2006; Stavrou et al., 2008; Kivelev et al., 2011). No mortality related to the procedure is reported.

Data is still limited regarding neuropsychological outcome. In one study, 15% of patients complained of postoperative memory deficits, the half of these presented with only temporary short-term memory decline. The rest underwent neuropsychological evaluation, reporting new memory deficit (4%) or worsening of previous symptoms (4%). Postoperative depression and fatigue were also assessed, finding a 9.4% rate of new-onset symptoms (Kivelev et al., 2011).

## SEIZURE OUTCOME

It is not easy to systematically evaluate seizure outcome due to the following limitations: several studies include patients whose main complaint was not epilepsy; definitions for intractability are not always clear; group subdivision is not uniform among studies regarding the evolution, frequency, and/or severity of seizures; control groups are compared against lesionectomy or epilepsy

surgery, but rarely both. Finally, standardized classifications – Engel et al. (1993), ILAE (Wieser et al., 2001) – are yet to be universally adopted.

#### OVERALL SEIZURE OUTCOME

The largest series to date, including 168 patients, showed an Engel I rate of 70% (48% IA) after 1 year. This figure declined to 68 and 65% for the second and third, respectively (Baumann et al., 2007), a phenomenon previously described by Kim et al. (1997), arguably due to the lack of follow-up for patients who became seizure-free. In contrast, smaller series report up to 82–84% seizure freedom rates (Casazza et al., 1996; Cappabianca et al., 1997).

#### LENGTH OF FOLLOW-UP

As commented above, slight differences on outcome are to be expected as follow-up lengthens, namely after the third year (Baumann et al., 2007; Von Der Brelie and Schramm, 2011), while this is not a constant finding (Yeon et al., 2009).

#### LOBAR LOCATION

There seems not to be any correlation between the lobar location nor the side of CMs and seizure freedom (Cappabianca et al., 1997; Baumann et al., 2007). At 1-year follow-up, the outcome was better for patients with mesiotemporal cavernomas and worst for neocortical locations (Baumann et al., 2007), but subsequent comparisons showed no differences.

Lesion location within the temporal lobe does not correlate with epilepsy outcome, i.e., patients with mesial or lateral lesions have the same chance of having a favorable seizure outcome (Yeon et al., 2009; Kivelev et al., 2011).

#### SIZE OF LESION

A size of less than 1.5 cm diameter has been associated with better seizure control during the first 2 years but no differences arise at longer evaluation (Baumann et al., 2007; Englot et al., 2011), a finding confirmed later on (Yeon et al., 2009; Englot et al., 2011).

#### TYPE OF SEIZURES

Patients with simple partial and complex partial seizures are more likely to become asymptomatic than patients affected by secondarily generalized seizures, although this analysis is not routinely performed by most of studies (Baumann et al., 2007; Englot et al., 2011).

#### DURATION OF EPILEPSY

The theory of secondary epileptogenesis states that a prolonged preoperative history of epilepsy brings an increased risk for worse seizure outcome as a result of developing remote epileptogenic foci (Morrell, 1985; Cohen et al., 1995; Cappabianca et al., 1997). The impact of this variable is controversial, for there are series that correlate the duration of epilepsy with seizure outcome, i.e., they report a slightly (Stavrou et al., 2008) or significantly (Cohen et al., 1995; Casazza et al., 1996; Zevgaridis et al., 1996; Cappabianca et al., 1997; Schroeder et al., 1997; Moran et al., 1999; Hammen et al., 2007; Englot et al., 2011) poorer outcome for patients with more than 1–2 years of seizure history, with the notable exception of patients with sporadic seizures over a long period of time. On

the other hand, others report similar results for patients with 0.5 to more than 10 years of seizure history (Baumann et al., 2007; Kivelev et al., 2011).

Yeon et al. (2009) did a sub-analysis within their non-lesionectomy group, for which duration of illness showed statistical significance only when Engel class IA was set aside and compared to the other classes considered as a whole (Yeon et al., 2009).

#### GENDER

Gender differences on outcome, when present, show that men seem to have a higher chance to become seizure-free (Cohen et al., 1995; Cappabianca et al., 1997; Stavrou et al., 2008), but, once again, it is not a constant finding (Baumann et al., 2007; Yeon et al., 2009).

#### AGE

Some studies show a better outcome in patients whose first seizure occurred after age 30 (Cohen et al., 1995; Baumann et al., 2007) or 40 (Cappabianca et al., 1997). In contrast, others considered age at onset to be irrelevant (Moran et al., 1999; Stavrou et al., 2008; Yeon et al., 2009). Baumann et al. (2007) found better seizure control for patients aged 30 or more at the time of surgery.

#### PREOPERATIVE EEG

There is a reported correlation between epileptiform abnormalities after the first unprovoked seizure and seizure recurrence (Van Donselaar et al., 1992). Subjects with normal findings on preoperative scalp EEG have better odds of being seizure free (Kivelev et al., 2011), as opposed to patients with multifocal epileptic activity (Baumann et al., 2007).

#### POSTOPERATIVE EEG

Kivelev et al. (2011) found no correlation between neurophysiological evaluation and epilepsy control, but an earlier study described an association of interictal epileptiform activity and seizure persistence (Di Gennaro et al., 2004).

#### LESION BLEEDING AT THE TIME OF SURGERY

Perilesional bleeding – old or recent – whether documented on MRI or directly observed during surgery, did not affect outcome on Baumann et al. (2007) study, but was considered as negative prognostic factor by Stefan et al. (2004) and Stefan and Hammen (2004).

#### FREQUENCY AND NUMBER OF SEIZURES

In two studies patients were classified according to the total number of seizures in three groups, i.e., 1, 2–5, and >5 seizures, achieving a seizure-free rate of 100, 69–100, and 62.5–69%, respectively (Cappabianca et al., 1997; Kivelev et al., 2011).

A high seizure frequency before surgery has been shown to worsen the postoperative outcome in some series (Cohen et al., 1995; Cappabianca et al., 1997; Moran et al., 1999; Stefan and Hammen, 2004; Ferroli et al., 2006; Englot et al., 2011) but had no effect in others (Casazza et al., 1996; Baumann et al., 2007; Stavrou et al., 2008). In their study, Yeon et al. (2009) named “intractable” those patients presenting >1 monthly seizure over a 1-year period.

Seventy-two percent of these patients were in Engel I class (54.5% IA), as opposed to 89.5% (84.2% IA) of subjects with sporadic seizures (Yeon et al., 2009).

### THE ROLE OF "PURE" LESIONECTOMY

The extension of excision is subject of controversy. Several studies report a better outcome when surrounding gliosis and hemosiderin are removed (Piepgras et al., 1993; Yeh et al., 1993; Cohen et al., 1995; Casazza et al., 1997; Kim et al., 1997; Siegel et al., 2000; Stefan and Hammen, 2004; Baumann et al., 2006; Hammen et al., 2007; Stavrou et al., 2008; Menzler et al., 2010), while others fail to find significant differences (Casazza et al., 1996; Zevgaridis et al., 1996; Cappabianca et al., 1997).

The problem arises when trying to compare techniques due to the lack of a control group – one of medical treatment – that can be compared with *both* lesionectomy and more extended resections in the same study. For instance, Yeon et al. (2009) found no difference between lesionectomy and other methods; but the decision of what procedure to perform was predetermined by their protocol, which, in turn favors the use of a more aggressive approach for patients with intractable epilepsy, a group in which blood degradation products are thought to play a major role in the aforementioned mechanisms of seizure propagation and secondary epileptogenesis (Morrell, 1991; Yeh and Privitera, 1991).

Lesionectomy alone appears to be beneficial for patients with sporadic seizures or evolution shorter than 1 year (Acciarri et al., 1995; Cohen et al., 1995; Casazza et al., 1996; Zevgaridis et al., 1996; Cappabianca et al., 1997; Ferroli et al., 2006). In this subset of individuals, it has been suggested to reserve a more invasive approach for persisting or relapsing cases (Yeon et al., 2009).

Growing evidence both in clinical and basic grounds suggests that resection of all *cortical* hemosiderin might improve seizure outcome, whereas incomplete removal of *subcortical* hemosiderin to spare eloquent tracts might not influence postoperative seizures (Siegel et al., 2000; Baumann et al., 2006; Menzler et al., 2010).

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In particular, transoperative ECoG-guided resection is associated with more extensive resections and, more importantly, is a good prognostic factor for seizure freedom when compared to patients without ECoG (Sugano et al., 2007; Komotar et al., 2008; Van Gompel et al., 2009).

### CONCLUSION

Comprehensive research is still needed to reach fully understanding of CMs on the molecular level and its implications on clinical grounds (Raychaudhuri et al., 2005).

Early microsurgical resection is an effective and safe therapy for patients with CMs and symptomatic epilepsy, let alone CMs' well known inherent risk of bleeding. For this purpose, the seizures must be carefully classified; the site of the lesion and the presence/absence of dual pathology accurately determined; and the focal epileptic activity, the risk of bleeding, and neuropsychological status carefully evaluated (Stefan and Hammen, 2004).

It is strongly recommended the complete lesion removal including the neighboring epileptogenic brain tissue for drug-resistant epilepsy, performing transoperative neurophysiological monitoring (ECoG), because subtotal removal of a CM is associated with a high risk of symptomatic recurrences (Kim et al., 1997; Baumann et al., 2006; Hammen et al., 2007; Englot et al., 2011).

Published case series and reviews emphasize the need of further prospective studies with homogeneous inclusion criteria with the purpose of generating comparable data (Von Der Brélie and Schramm, 2011). In this spirit, we suggest that upcoming studies adhere to the revised definition of drug-resistance (Kwan et al., 2010), state clearly the demographics of the group studied, the type and number of seizures, illness duration, history of bleeding, neurological examination, paraclinical findings – MRI, EEG, video-EEG, and, when suitable, metabolic and/or functional studies, size, location, surgical approach, resection type, transoperative clinical and paraclinical findings, transient and permanent neurological deficits, the use of Engel and/or ILAE outcome classifications, and the length of follow-up.

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# Dravet syndrome with an exceptionally good seizure outcome in two adolescents

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**ABSTRACT** – We present two children who exhibited the characteristics of Dravet syndrome during infancy and young childhood, with *SCN1A* mutation, but nevertheless achieved seizure freedom for at least four years during adolescence. These patients had no episodes of convulsive status epilepticus with a duration of more than 30 minutes and their overall favourable seizure outcome may be related to the prevention of convulsive status epilepticus.

**Key words:** *SCN1A* mutation, severe myoclonic epilepsy in infancy, Dravet syndrome, convulsive status epilepticus, prognosis, adolescence

Dravet syndrome, or severe myoclonic epilepsy in infancy, is one of the severest types of childhood epilepsy and is characterised by age-dependent occurrence of a unique combination of intractable seizure types and myoclonus (Dravet *et al.*, 2005). Dravet syndrome is a channelopathy, usually resulting from a mutation of *SCN1A* (Claes *et al.*, 2001). Affected patients are expected inevitably to have persistent seizures with cognitive impairment (Dravet *et al.*, 2005); however, we have examined two patients who exhibited the characteristics of Dravet syndrome during infancy and young childhood but nevertheless had an unusually favourable seizure outcome.

This study was approved by the Ethics Committee of Okayama

University and written informed consent was obtained from the patients' parents.

## Case reports

### Patient 1

A female patient was born via normal delivery after an uneventful pregnancy. There was no seizure disorder in her family.

Generalised tonic-clonic seizures (GTCS) and unilateral seizures involving either side of the body started at six months of age with frequent provocation by fever. She was initially treated at local hospitals with sodium valproate (VPA), phenobarbital (PB) and phenytoin (PHT), although detailed

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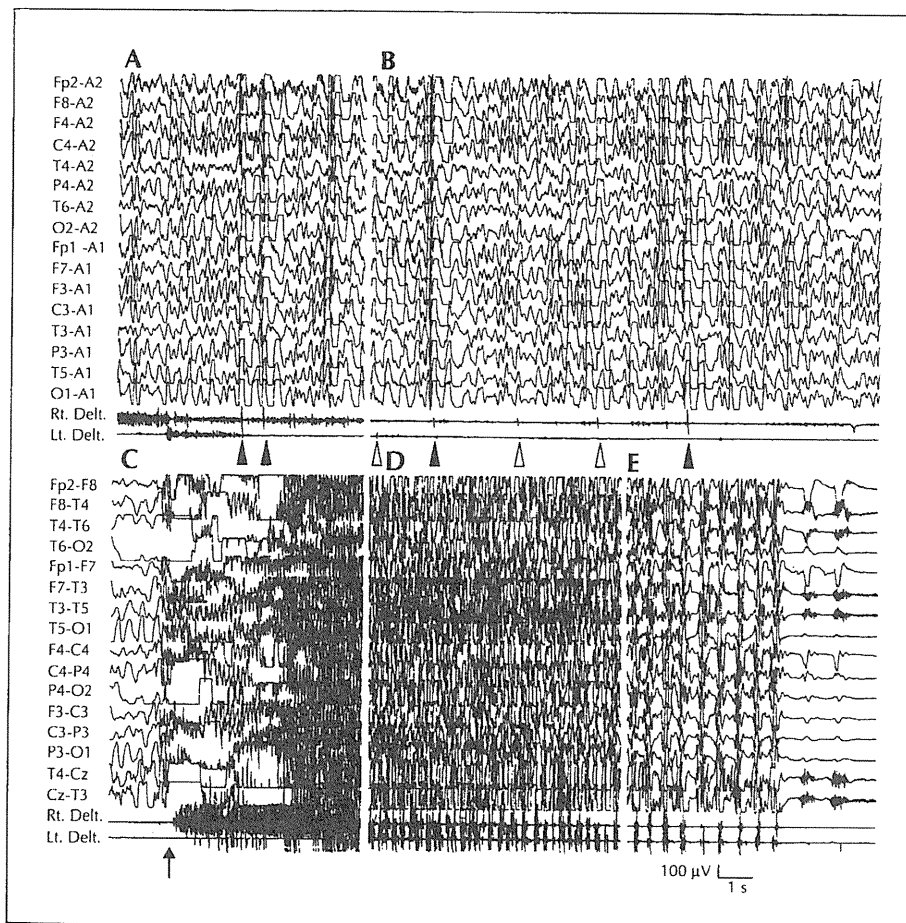
information was unavailable. Carbamazepine (CBZ) was transiently used but shortly discontinued because of skin eruption. Her EEG was reported as normal during infancy. Convulsive seizures occurred almost weekly, but their maximum duration was only 15 minutes. Her development was normal during infancy.

At five years and six months of age, the patient was admitted to Okayama University Hospital and appeared mentally slow. She had two episodes of non-convulsive status epilepticus (obtundation status) which were characterised by prolonged disturbance of consciousness with erratic segmental myoclonus and EEG findings of persistent diffuse high-voltage slow waves with multifocal spikes. Generalised myoclonic seizures were observed in association with generalised polyspike-wave discharges on EEG (figure 1A, B). She also had weekly GTCS (figure 1C, D, E). She did

not show photosensitive seizures or photoparoxysmal responses on EEG.

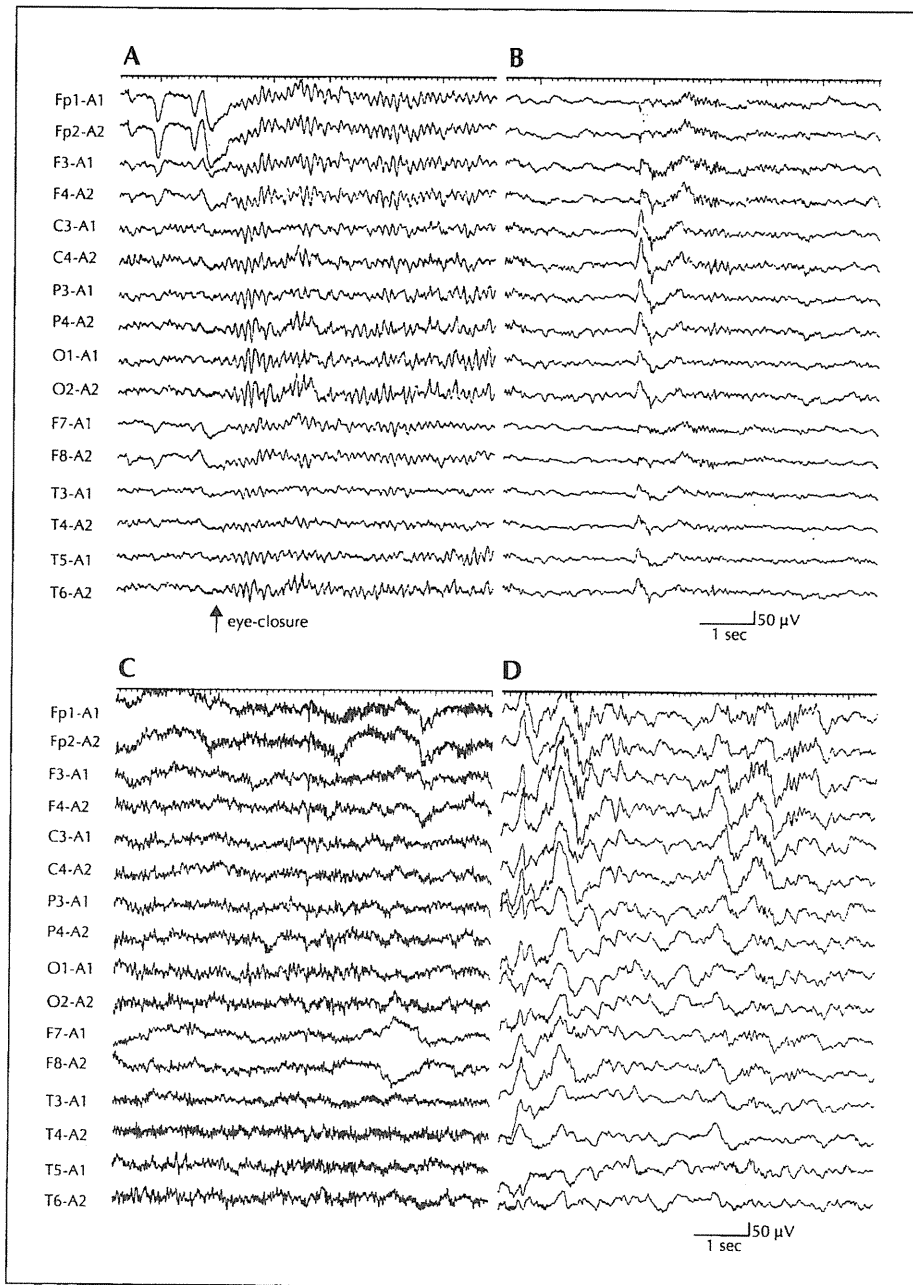
While on a combination therapy consisting of VPA, zonisamide (ZNS), potassium bromide (KBr) and acetazolamide, after discontinuation of PHT and PB, the patient had several febrile GTCS per year, from six to eight years of age. EEG during this period showed irregular alpha activity in the background and multifocal spikes without generalised discharges. She experienced only one febrile GTCS per year, from eight to 11 years of age. After 11 years and seven months of age, the patient's seizures disappeared and have not recurred as of her last follow-up at 16 years and three months of age. Treatment with VPA and ZNS is still ongoing. EEG spikes also disappeared at the age of 12 (figure 2A, B).

MRI was normal and her intelligence was borderline according to the Wechsler Intelligence Scale



**Figure 1.** Ictal EEGs of Patient 1.

A-E) EEGs recorded at five years of age. Diffuse high-voltage slow waves continued on EEG during an obtundation status with persistent impairment of consciousness (A, B). Myoclonic seizures occurred in association with generalised spike-and-wave complexes (closed arrowhead), and erratic segmental myoclonus appeared with no concomitant EEG changes (open arrowhead). A generalised tonic-clonic seizure started at the time point indicated by the arrow and lasted for 60 seconds (C, beginning; D, middle; E, end).



**Figure 2.** Intercictal EEGs during seizure remission.

In Patient 1, waking EEG (A) and sleep EEG (B) at 15 years of age were normal with no epileptic discharges.

In Patient 2, waking EEG (C) at 11 years of age showed an increase in fast waves, but no epileptic discharges were observed during either wakefulness or sleep (D).

(WISC)-III (full IQ 78, verbal IQ 75, performance IQ 86) at 15 years of age. Genetic analysis detected a missense *SCN1A* mutation (E788K); no analysis was performed on the parents.

**Patient 2**

A male patient was born with neonatal asphyxia after 33 weeks of gestation, but his development was normal

during infancy. His sister had a single simple febrile seizure at two years of age and developed normally with no subsequent seizures.

The patient's initial seizure was a left hemiconvulsion with a duration of 25 minutes associated with mild fever at seven months of age, and was suppressed by intravenous diazepam (DZP); thereafter he experienced monthly GTCS with frequent provocation by fever or exposure to hot water. He was initially treated