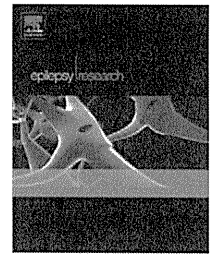
Epilepsy Research (2011) 96, 185–189

journal homepage: www.elsevier.com/locate/epilepsyres



SHORT COMMUNICATION

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

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Received 8 April 2011; received in revised form 6 May 2011; accepted 8 May 2011
Available online 1 June 2011

KEYWORDS
Apnea;
Malignant migrating partial seizures;
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.

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 antiepileptic 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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doi:10.1016/j.eplepsyres.2011.05.007

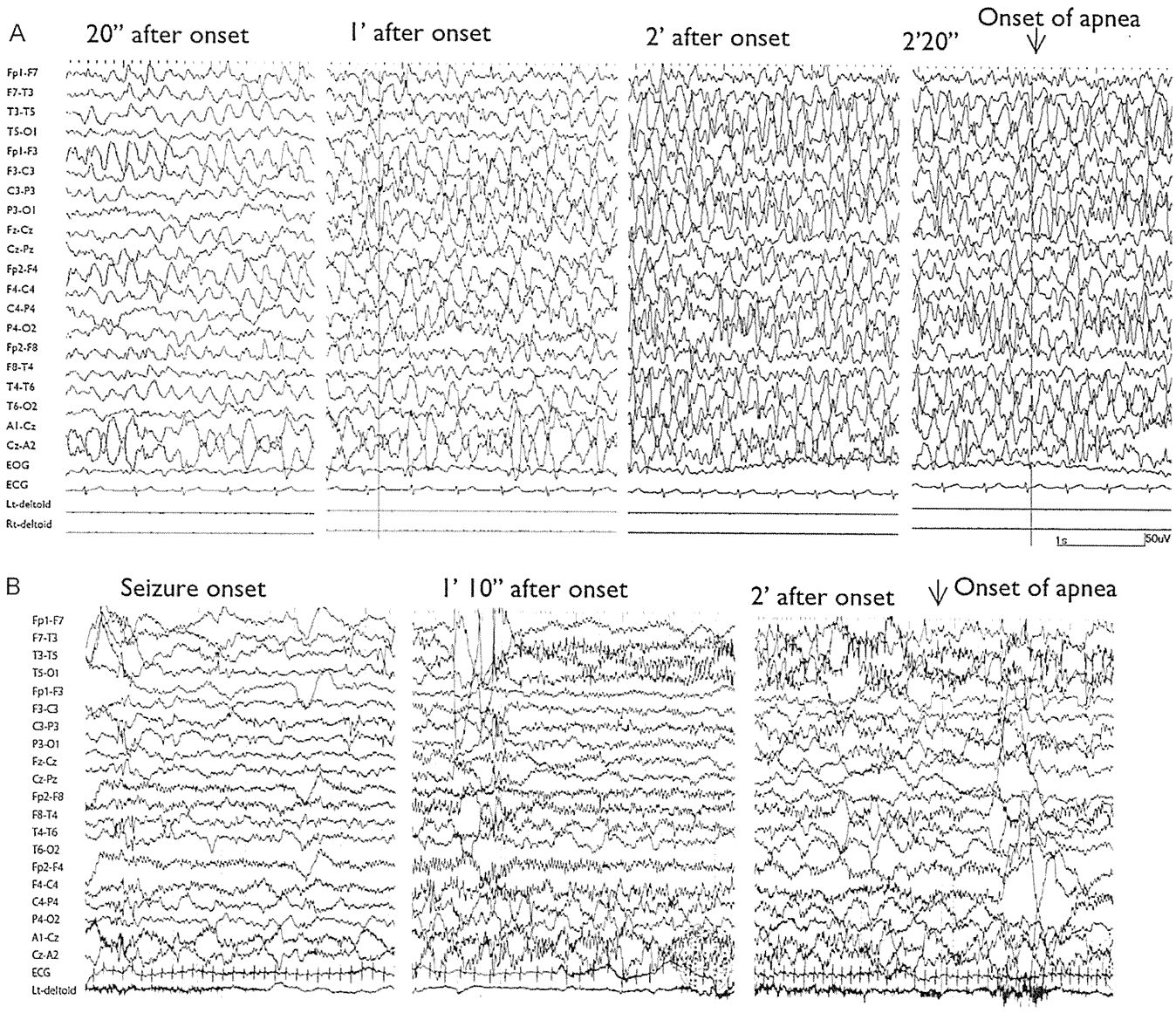

Figure 1 Ictal electroencephalography (EEG) for epileptic apnea. (A) Patient 1. At seizure onset with motion arrest, theta activities appeared in the right frontopolar area. These theta activities spread to the ipsilateral temporal and contralateral frontal regions within 20 s of the onset. One minute 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 centrotemporal 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

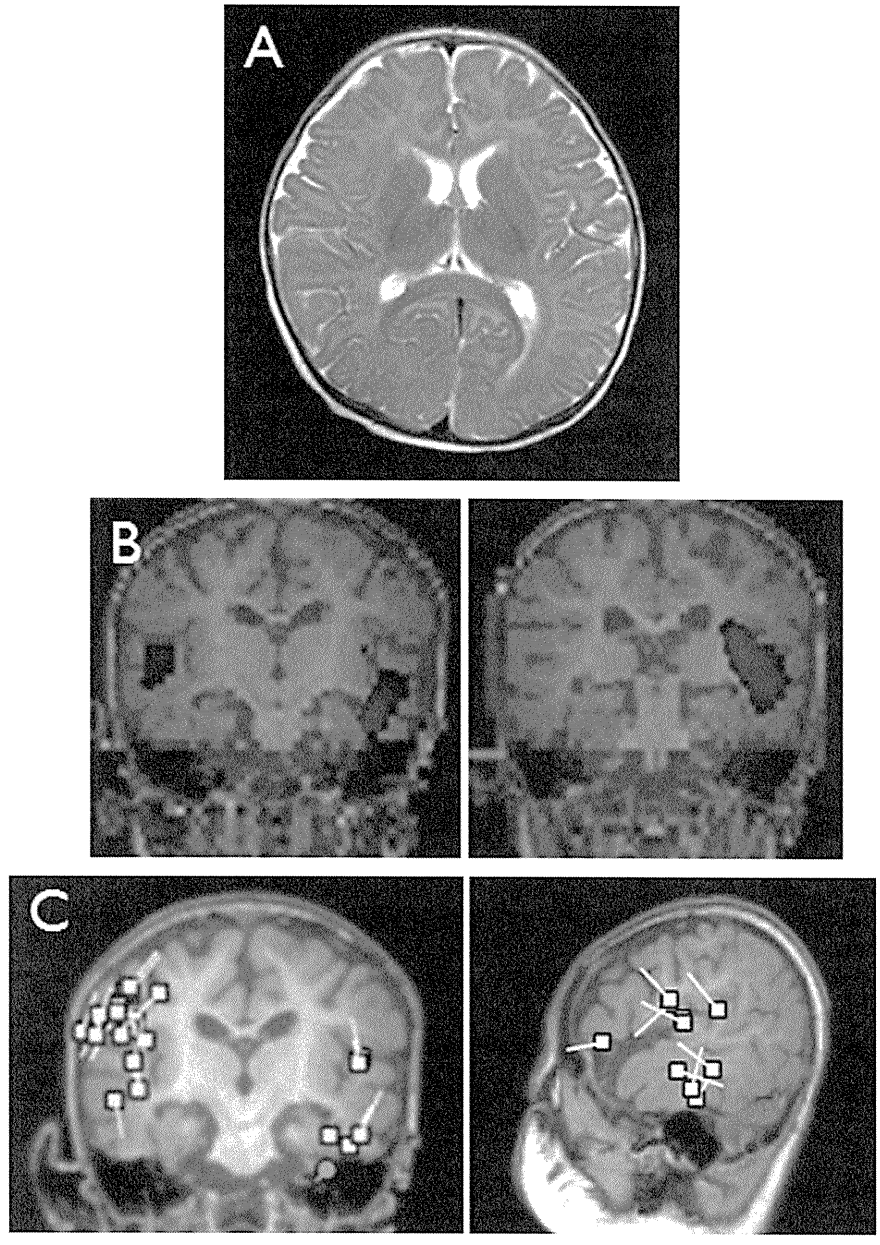

Figure 2 Neuroimaging of patient 1 during admission (A) magnetic resonance imaging, (B) subtraction ictal single-photon emission computed tomography coregistered with magnetic resonance imaging, and (C) magnetoencephalography. (C) Interictal EEG at this period showed periodic appearance with bursts of 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_2 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

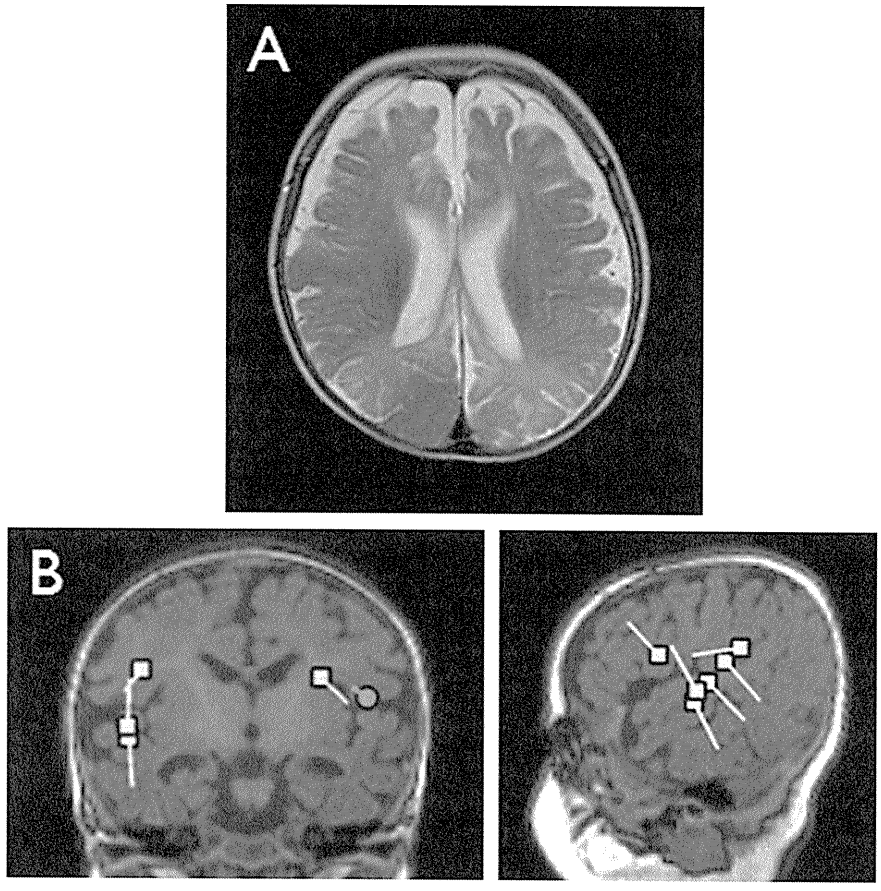

Figure 3 Neuroimaging of patient 2 (A) magnetic resonance imaging and (B) magnetoencephalography. In (A), high signal change on T2-weighted magnetic resonance imaging, involving both gray and white matter and accompanied by regional atrophy, is noted in the parieto-occipital areas bilaterally. Less severe 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 dysrythmic 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 symptomology 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-occpital 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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frontiers in NEUROLOGY

MINI REVIEW ARTICLE
published: 03 January 2012
doi: 10.3389/fneur.2011.00086

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% (Otten 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 (*CCM*1), was mapped in the long arm of chromosome 7 (7*q*11 to *tq*12), 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 (Revencu and Vikkula, 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 Brelie and Schramm, 2011). Spin echo and gradient echo sequences using T1 and T2-weighed 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 transsylvian 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). 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 Brelie 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, transoperatory 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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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 18 August 2011; paper pending published: 29 September 2011; accepted: 07 December 2011; published online: 03 January 2012.

Citation: Alonso-Vanegas MA, Cisneros-Franco JM and Otsuki T (2012) Surgical management of cavernous malformations presenting with drug-resistant epilepsy. Front. Neur. 2:86. doi: 10.3389/fneur.2011.00086
This article was submitted to Frontiers in Epilepsy, a specialty of Frontiers in Neurology.

Epileptic Disord 2011; 13 (3): 340-4

Dravet syndrome with an exceptionally good seizure outcome in two adolescents

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Received March 23, 2011; Accepted July 4, 2011

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

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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

doi: 10.1684/epd.2011.0453

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

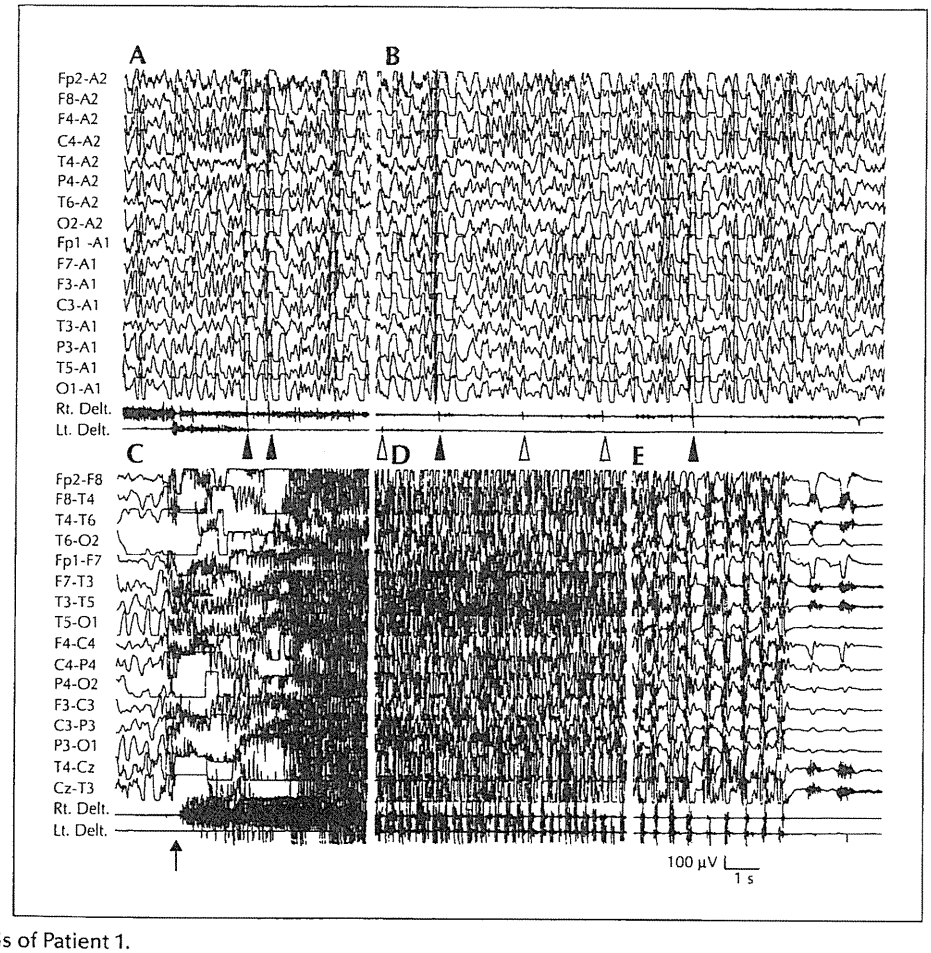

Figure 1. Ictal EEGs of Patient 1.
A-E) EEGs recorded at five years of age. Diffuse high-voltage slow waves continued on EEG during an obtundation status with persistent impairment of consciousness (**A, B**). Myoclonic seizures occurred in association with generalised spike-and-wave complexes (closed 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).

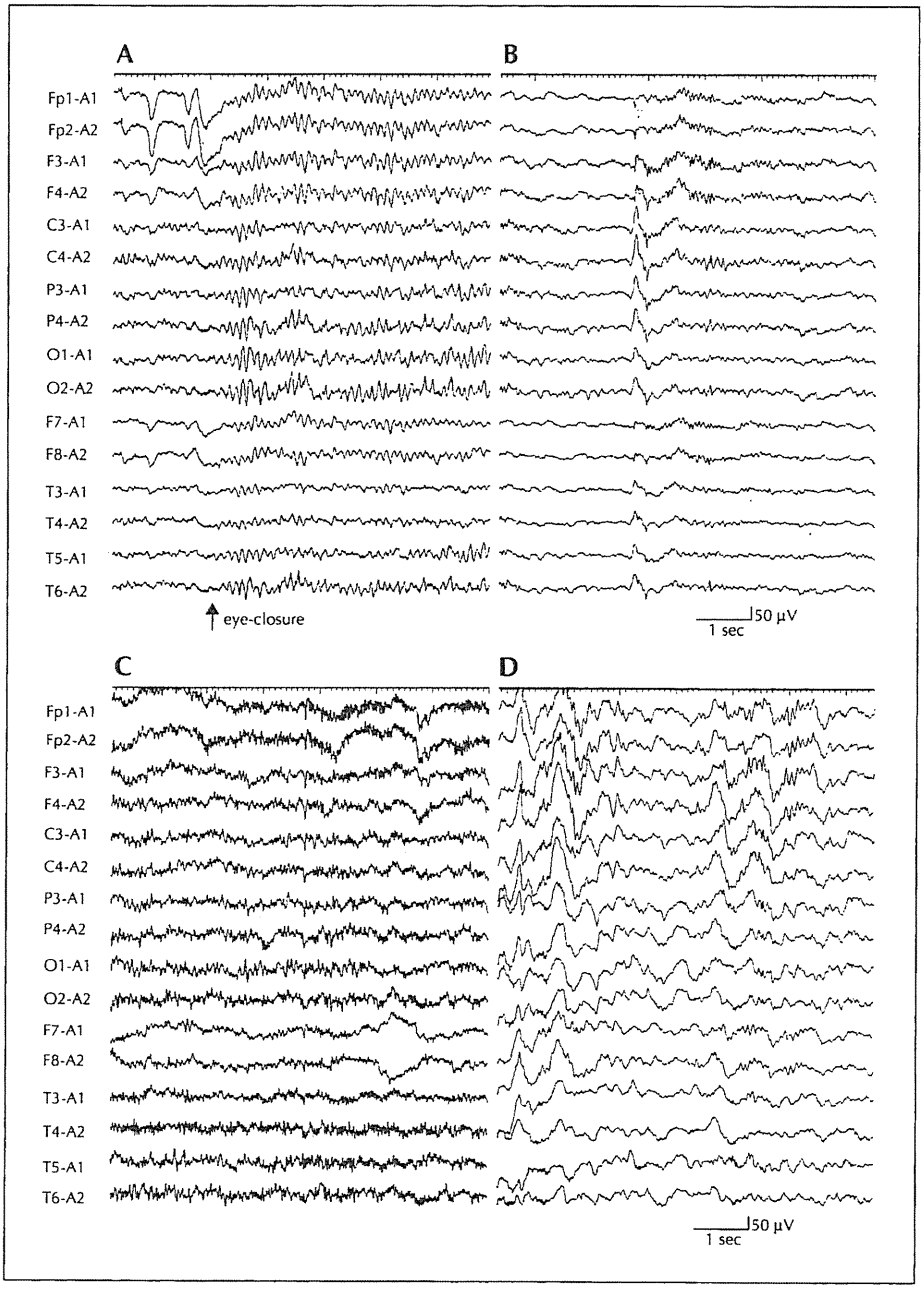

Figure 2. Interictal EEGs during seizure remission.
In Patient 1, waking EEG (**A**) and sleep EEG (**B**) at 15 years of age were normal with no epileptic discharges.
In Patient 2, waking EEG (**C**) at 11 years of age showed an increase in fast waves, but no epileptic discharges were observed during 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

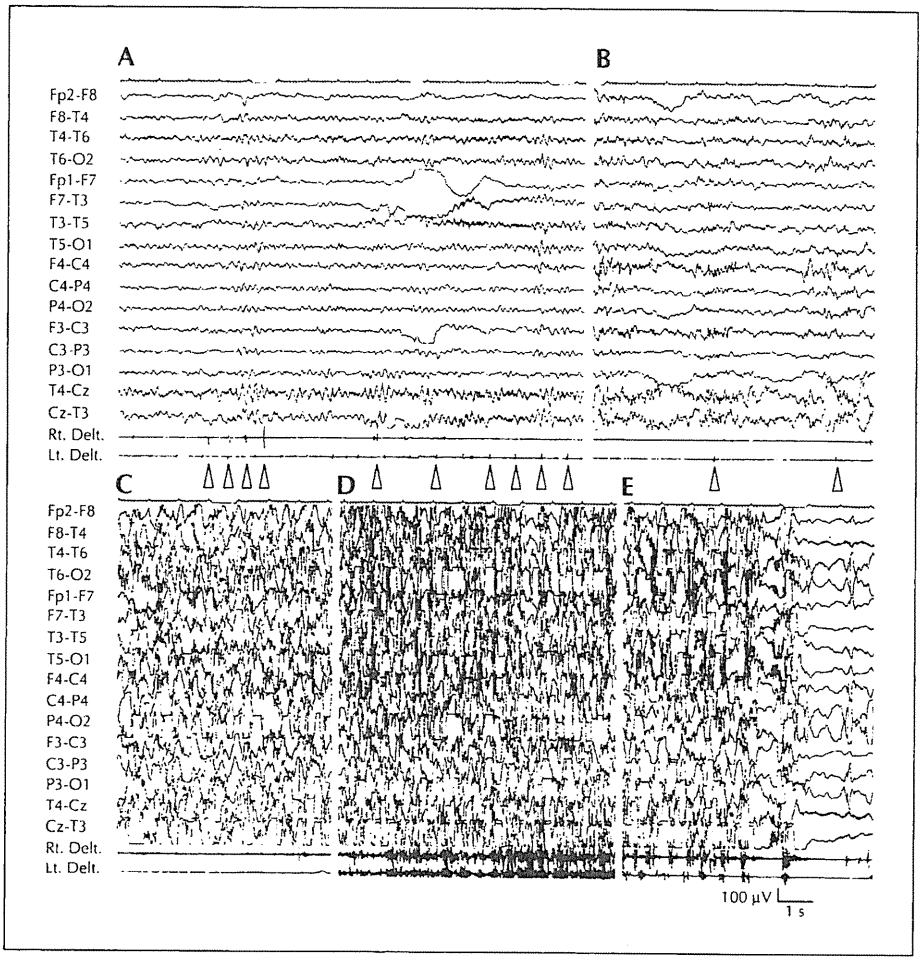

Figure 3. Ictal EEGs of Patient 2.
A-E) EEGs recorded at three years of age. Erratic segmental myoclonus was observed with no associated ictal epileptic EEG changes (open arrowhead) during wakefulness (**A**) and sleep (**B**). A 10-minute-long generalised tonic-clonic seizure occurred with corresponding EEG discharges (**C**, beginning; **D**, middle; **E**, end).

with VPA and ZNS at local hospitals; the development of status epilepticus was avoided by treatment including DZP rectal suppository, although detailed information is lacking.

The patient was admitted to Okayama University Hospital at three years of age. His development was mildly retarded, with a developmental quotient of 63 (Enjoji Developmental Scale). He showed erratic segmental myoclonus *(figure 3A, B)* and had almost monthly GTCS *(figure 3C, D, E)*, and had experienced one episode of obtundation status. No myoclonic seizures associated with the ictal EEG discharges were observed. The interictal EEG showed rare bifrontal spikes on the background with predominant theta activity. EEG revealed no photosensitive seizures or photoparoxysmal responses. The patient experienced several febrile GTCS per year, from six to eight years of age, but had no seizures since seven years and five months of age as of the last follow-up at 12 years; his medication includes VPA, KBr and clonazepam. EEG spikes disappeared at seven years of age *(figure 2C, D)*.

MRI was normal. His intelligence was retarded at 11 years of age with an IQ of 33 (Tanaka-Binet V). He showed no neurological abnormalities. Genetic analysis disclosed a frameshift *SCN1A* mutation (A1419fsX1433) in the patient but not in the mother. The parents were divorced and the father and sister could not be analyzed.

Discussion

The presented patients had clinical characteristics compatible with the diagnosis of Dravet syndrome during early childhood, including very intractable generalised and unilateral seizures precipitated by fevers, segmental myoclonus, obtundation status and the *SCN1A* mutation (Hattori *et al.*, 2008). Patient 1 also

had myoclonic seizures indicating typical Dravet syndrome and Patient 2, who lacked myoclonic seizures, was accordingly diagnosed with borderline Dravet syndrome. Seizures were suppressed for four years in both patients; this outcome is exceptional in Dravet syndrome, although one other patient with only febrile seizures (FS) during adolescence has been reported (Buoni *et al.*, 2006).

The patients had no episodes of convulsive status epilepticus with a duration of more than 30 minutes, which may be related to their overall good seizure outcome. In a report by Akiyama *et al.* (2010), the prevention of convulsive status epilepticus was suggested to be associated with a favourable effect on the prognosis of Dravet syndrome. In this previous report, patients with a seizure-free period lasting for at least one year experienced significantly fewer episodes of convulsive status epilepticus than patients with persistent seizures. It was indicated that the latter group's seizures had become intractable as a sequela of repeated convulsive status epilepticus, although it is also possible that patients who are genetically destined to have a poor prognosis might tend to experience more episodes of convulsive status epilepticus. In addition, there may be other unknown factors influencing the outcome. For the selection of an appropriate treatment regimen, it is essential not only to choose effective drugs but also to avoid drugs that are potentially harmful under certain conditions, such as CBZ and lamotrigine, which can aggravate seizures in Dravet syndrome (Chiron and Dulac, 2011); it was fortunate for Patient 1 that CBZ was discontinued because of exanthema.

Cognitive outcome may be affected not only by seizures but also by various other factors, as demonstrated by the deterioration of Patient 2's intelligence, in spite of relatively good seizure control. Some of the other factors in his case were premature birth, a protracted seizure with a duration close to 30 minutes, and a truncating mutation. Further study will help clarify the factors that contribute to mental prognosis.

A spectrum of epilepsies is purportedly associated with *SCN1A* mutation, ranging from genetic epilepsy with FS plus (GEFS+) to Dravet syndrome (Singh *et al.*, 2001; Harkin *et al.*, 2007). In addition, not only the types of *SCN1A* mutations but also other modifying factors are suggested to be involved in the expression of epilepsy (Zuberi *et al.*, 2011). The clinical courses of our patients appear to be initially similar to that of the patient cited above (Buoni *et al.*, 2006), but later progress further to seizure freedom in adolescence. It has already been confirmed that the spectrum of typical and borderline Dravet syndrome cases constitutes a single syndromic entity (Dravet *et al.*, 2005; Akiyama *et al.*, 2010). The elucidation of factors associated with a less severe form of Dravet syndrome may yield information relevant for the development of rational treatment for Dravet syndrome; one of these factors may be the early cessation of prolonged seizures before their development into status epilepticus (Akiyama *et al.*, 2010). □

Acknowledgments.

We thank Mr. Tomoyuki Nakahori for his contribution to the genetic analysis.

Disclosure.

K. Kobayashi was a recipient of the Health and Labour Sciences Research Grant: Research on catastrophic epilepsy in infancy and early childhood – epidemiology, diagnosis and treatment guide. I. Ohmori was supported by a Grant-in-Aid from the Ministry of Education, Culture, Sports, Science and Technology (Grant No. 21390312). M. Ouchida was supported by a Grant-in-Aid from the Ministry of Education, Culture, Sports, Science and Technology (Grant No. 15591110).

None of the authors has any conflict of interest to disclose.

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Epileptic Disord 2011; 13 (3): 326-30

Bilaterally independent epileptic spasms in a case of Aicardi syndrome

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Received April 4, 2011; Accepted July 25, 2011

ABSTRACT – A girl with Aicardi syndrome was observed to have two distinct types of asymmetric epileptic spasms, as detected by ictal video-EEG recording at three months of age. When the two types of spasm concurred, they showed no mutual interactions based on either clinical or EEG aspects. This observation does not support the hypothesis that the brainstem always plays an initiating role in generating spasms. *[Published with video sequences]*

Key words: Aicardi syndrome, ictal video-EEG recording, infantile spasms

The generation of epileptic spasms (ES), or infantile spasms, is traditionally considered to involve the brain subcortical structures, particularly the brainstem, as well as pathological interaction with the cortex (Dulac and Tuxhorn, 2005). Although a recent influx of reports on successful treatment of ES by cortical resection indicates that some ES originate from the cortex (Asano *et al.*, 2005), the question of whether the brainstem also affects the occurrence of ES in such situations remains unanswered. Data that may help answer this question are provided by the present case of Aicardi syndrome, exhibiting two different types of ES.

Case report

The female patient was born at 41 weeks gestation with a weight of 3468 g without asphyxia. There was no abnormality in her family history. Ventricular dilatation was suggested by foetal ultrasonography at six months of gestation. She started to have convulsive seizures on the fourth day of life, and her seizures changed into ES at around two months of age. The infant was admitted to Okayama University Hospital at three months of age; neurological examinations showed generalised hypotonia with no head control and no visual following. She did not smile. A fundoscopic examination

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doi:10.1684/epd.2011.0456

revealed bilateral chorioretinal lacunae. MRI demonstrated complete agenesis of the corpus callosum along with cortical dysplasia of the bilateral frontal lobes and a cystic lesion in the third ventricle *(figure 1)*. Thus, the diagnosis of Aicardi syndrome was made (Ohtsuka *et al.*, 1993). She had no defects in either the vertebrae or the spinal cord. No abnormality was detected by a battery of examinations, including blood biochemistry, blood gas analysis, cerebrospinal fluid, plasma amino acid analysis, urinary organic acid analysis, abdominal ultrasonography, or cardiac ultrasonography.

The infant was found to have two distinct types of ES which occurred in series but independently, as well as hypsarrhythmia with bilaterally independent periodicity on EEG. Analysis of part of the ictal EEG data has been published previously (Kobayashi *et al.*, 2004). One type of spasm (hereafter denoted as type A), characterised by downward forceful extension of the right arm, extension of the right leg, mild extension of the left leg and foot, and flexion of the left arm, was associated with left-hemispheric high-voltage slow waves (HVS) on EEG *(figure 2A; see video sequence 1)*. The other type of spasm (denoted as type B), characterised by upward extension of the bilateral upper extremities and flexion of the lower ones with rightward deviation, was associated with right-hemispheric HVS *(figure 2B; see video sequence 2)*.

The patient experienced 5 to 10 clusters of ES per day, with the total number of spasms per day ranging from around 100 to 300. We recorded ictal video-EEG of two different types of spasm occurring simultaneously, and observed that each type maintained an independent pace and ictal symptomatology. The two types of ES showed no mutual interaction based on either clinical or EEG aspects *(figure 3; see video sequence 3)*. Thirty percent of the patient's seizures were type A spasms, 60% were type B spasms, and 10% consisted of both types simultaneously. No focal seizures were observed and we found no focal discharges at the onset of series of ES.

Regarding treatment of ES, the patient did not respond to synthetic ACTH therapy, ketogenic diet, or thyrotropin-releasing hormone (TRH), or to various antiepileptic drugs, including sodium valproate, clonazepam, zonisamide, nitrazepam, lorazepam, and pyridoxal phosphate.

The patient exhibited rigidospastic tetraplegia with severe sclerosis but no signs of development such as head control or visual following, as of her last follow-up visit at nine years of age. The two types of ES persist, although the motor symptoms of spasms have become milder and the frequency of spasms has decreased to several clusters per week. Isolated tonic spasms are also sporadically observed.

Discussion

It has been demonstrated that ES can have a focal cortical onset, based on the reports of successful suppression of ES by cortical resection in many patients with brain tumours, cortical malformation, or tuberous sclerosis (Mimaki *et al.*, 1983; Asano *et al.*, 2005), as well as the detection of ictal high-frequency oscillations through cortical electrodes (Akiyama *et al.*, 2005; RamachandranNair *et al.*, 2008). It is also known that asymmetric behavioural manifestations of ES,

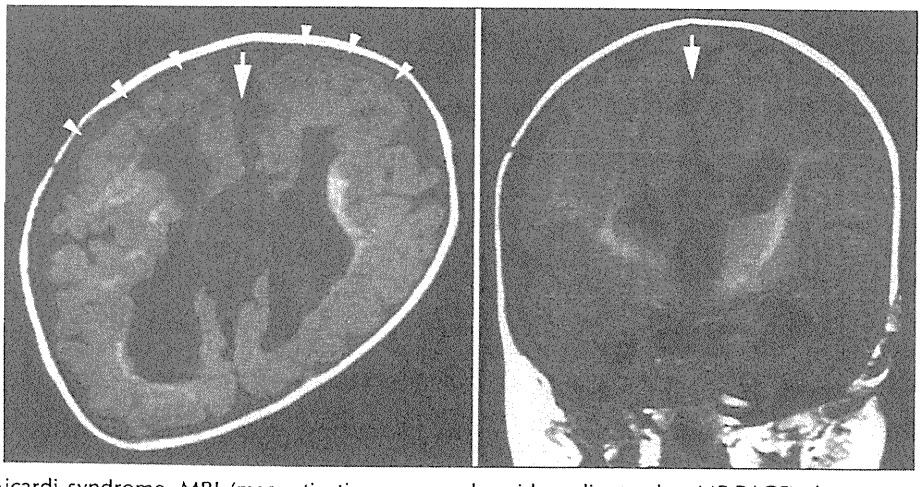

Figure 1. MRI of Aicardi syndrome. MRI (magnetization prepared rapid gradient-echo, MP-RAGE) shows agenesis of the corpus callosum (arrow) and associated cortical malformation in the bilateral frontal lobes (arrowhead).

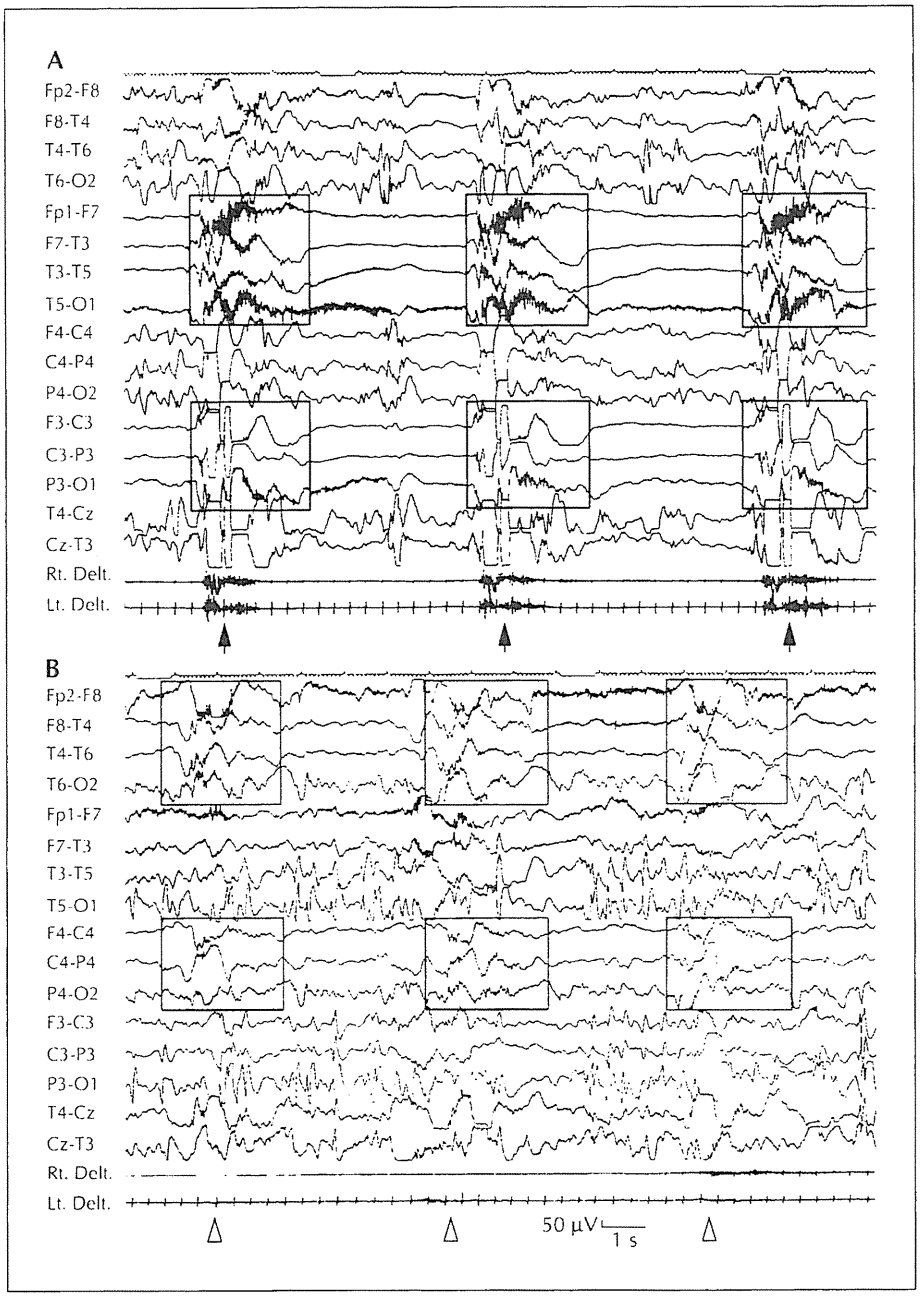

Figure 2. Ictal EEGs of two different types of epileptic spasm. Type A spasms were associated with left-hemispheric HVS (**A**: closed arrow, rectangle), and type B spasms with right-hemispheric HVS (**B**: open arrowhead, rectangle). In each type of spasm, the contralateral hemisphere showed interictal hypsarrhythmia with periodicity.

similar to those observed in the current patient, indicate a link between the behaviourally more involved side and the contralateral EEG discharges (Gaily *et al.*, 1995). The present patient had malformation involving the bilateral frontal lobes, and therefore it is possible that her cortical dysplastic lesion played a role in the generation of ES with such complex asymmetric manifestations. Her brain malformation may not be exactly symmetric because the two types of ES had considerably different semiology. However, this is not to say that

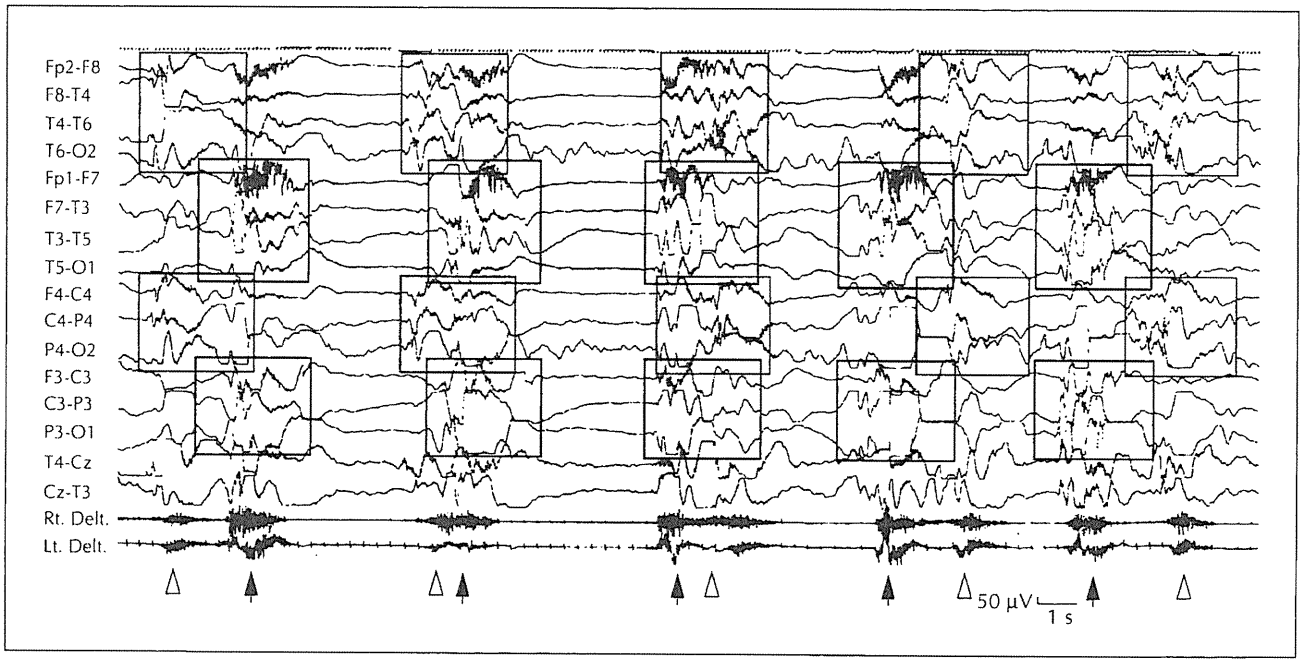

Figure 3. Concurrence of two different types of epileptic spasm. Left-hemispheric HVS associated with type A spasms (closed arrow, black rectangle) and right-hemispheric HVS associated with type B spasms (open arrowhead, grey rectangle) appear independently, each type maintaining an independent intrinsic interval.

the subcortical structures play no role at all, as there are reports of activation of the brainstem in West syndrome (Chugani *et al.*, 1992; Siniatchkin *et al.*, 2007). In this context, it is worth noting that the concurrence of two different types of spasm with no mutual interaction was successfully recorded. This fact demonstrates that the brainstem can be stimulated by each hemisphere independently. This observation failed to support the hypothesis that the brainstem always plays an initiating role in generating spasms. Although it may be impossible to generalise this notion of absolute secondary involvement of the brainstem to all infants with ES, the current case provides an important clue concerning the pathogenesis of ES confined within the cortex. □

Acknowledgments.
We thank Mr. Tomoyuki Nakahori for editing the video files.

Disclosure.
K. Kobayashi was a recipient of the Health and Labour Sciences Research Grant: research on catastrophic epilepsy in infancy and early childhood – epidemiology, diagnosis and treatment guide, and was also supported, in part, by a research grant (21B-5) for Nervous and Mental Disorders from the Ministry of Health, Labour and Welfare. Y. Ohtsuka was supported by a research grant (19A-6) for Nervous and Mental Disorders from the Ministry of Health, Labour and Welfare.
The authors have no conflict of interest to disclose.

Legends for video sequences

Video sequence 1

Type A spasms in series with simultaneous EEG recording (indicated as "A" in red).

Video sequence 2

Type B spasms in series with simultaneous EEG recording (indicated as "B" in blue).

Video sequence 3

Concurrence of type A spasms (indicated as "A" in red) and type B spasms (indicated as "B" in blue) with simultaneous EEG recording. When the two types of spasm concurred, each type maintained independent pace and ictal symptomatology with no apparent mutual interaction.

Key words for video research on www.epilepticdisorders.com
Etiology: Aicardi syndrome
Phenomenology: spasm (epileptic)
Localization: hemispheric, multifocal
Syndrome: epileptic encephalopathy not otherwise classified