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ILAE focal cortical dysplasia type IIIc in the ictal onset zone in epileptic patients with solitary meningioangiomatosis

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ABSTRACT – "Solitary" meningioangiomatosis (MA) is a rare, benign, hamartomatous lesion of the cerebral cortex and frequently leads to epilepsy. However, the source of the epileptogenicity in meningioangiomatosis remains controversial. We report two surgically-treated meningioangiomatosis cases with medically intractable epilepsy. In both cases, chronic subdural electrocorticogram (ECoG) recordings identified the ictal onset zone on apparently normal cortex, adjacent to and/or above the meningioangiomatosis lesion, not on the meningioangiomatosis lesion itself. The ictal onset zone was resected, along with the MA lesion, and good seizure outcome was achieved. Histological examination of the ictal onset zone revealed the presence of ILAE focal cortical dysplasia (FCD) type IIIc. Our case studies suggest that in the surgical management of epilepsy with meningioangiomatosis, it is important to identify undetected, but epileptogenic, ILAE FCD Type IIIc, using preoperative multimodal examinations, including chronic ECoG recordings.

Key words: meningioangiomatosis, focal cortical dysplasia, electrocorticogram, ictal onset zone

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"Solitary" meningioangiomatosis (MA) is a rare hamartomatous or vascular malformative lesion, usually affecting the leptomeninges and underlying cortex. Seizures occur frequently in patients with MA (Wiebe *et al*., 1999; Jallo *et al*., 2005) but the location of the epileptogenicity of MA is controversial. In some cases, intrinsic epileptogenicity of MA lesions has been documented (Jallo *et al*., 2005),

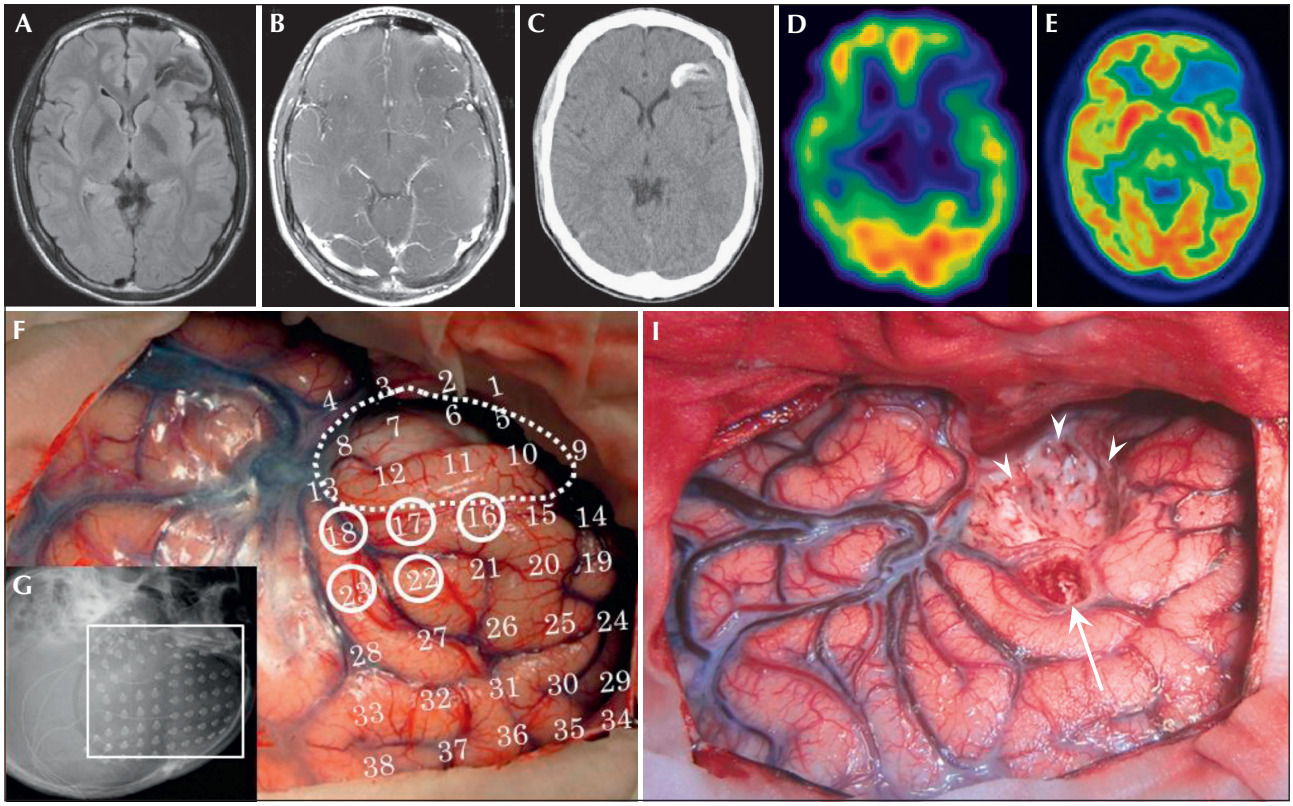

Figure 1. Case 1. (A) FLAIR MRI demonstrates hypointensity at the site of lesion in the left frontal lobe. (B) The lesion has no contrast enhancement on GdT1WI. (C) The lesion has a calcified area on CT. (D) IMZ SPECT demonstrates reduced IMZ uptake in the lesion. (E) 18-FDG-PET shows focal hypometabolism of the lesion and mild hypometabolism of the cortex around the lesion in the frontal lobe. (F) An intraoperative photograph indicating the position and number of subdural electrodes on the surface of the frontal lobe. The location of the structural lesion, which was identified with neuronavigation, is marked with a dotted circle. Electrodes located within the ictal onset zones (IOZ) are marked with white circles. (G) Postoperative X-ray photography (X-P), shown in an orientation match with (F), demonstrates the position of the chronic subdural electrodes. The white square indicates the extent of the craniotomy. (I) An intraoperative photograph after the resection of the structural lesion (white arrow heads) and the IOZ (white arrow).

whilst in other cases epileptogenicity was confined to the peri- or extra-lesional cortex (Kobayashi *et al.*, 2006), and even multifocal or generalized lesions are reported elsewhere (Wiebe *et al.*, 1999). One group recently reported the histopathological association of MA and ILAE focal cortical dysplasia (FCD) type IIIc in a single patient with MA (Batra and Prayson, 2013). However, electrophysiological evidence from the diseased area in the patient was not clearly described.

In this study, we report two cases of intractable frontal lobe epilepsy associated with MA, which was surgically treated. Chronic subdural electrocorticographic (ECoG) recording was used to locate the electrophysiologically-confirmed ictal onset zone (IOZ), revealing the existence of histopathologically-confirmed ILAE FCD type IIIc (Blümcke *et al.*, 2011) at this location. The study reported here may be the basis of a new approach to plan epileptic MA surgery.

Case studies

Between 2000 and 2012, our institution performed 98 resection surgeries for intractable epilepsy. These included 75 patients with medial temporal lobe epilepsy, 21 patients with neocortical epilepsy, and the two patients with MA included in this case report.

Clinical courses and radiological/electrophysiological work-up

Case 1

A 17-year-old boy with no evidence of neurofibromatosis type 2 (NF2) suffered with intractable seizures. He experienced weekly complex partial seizures, causing his neck to turn to the left, and biannual generalized, tonic-clonic seizures since the age of 12.

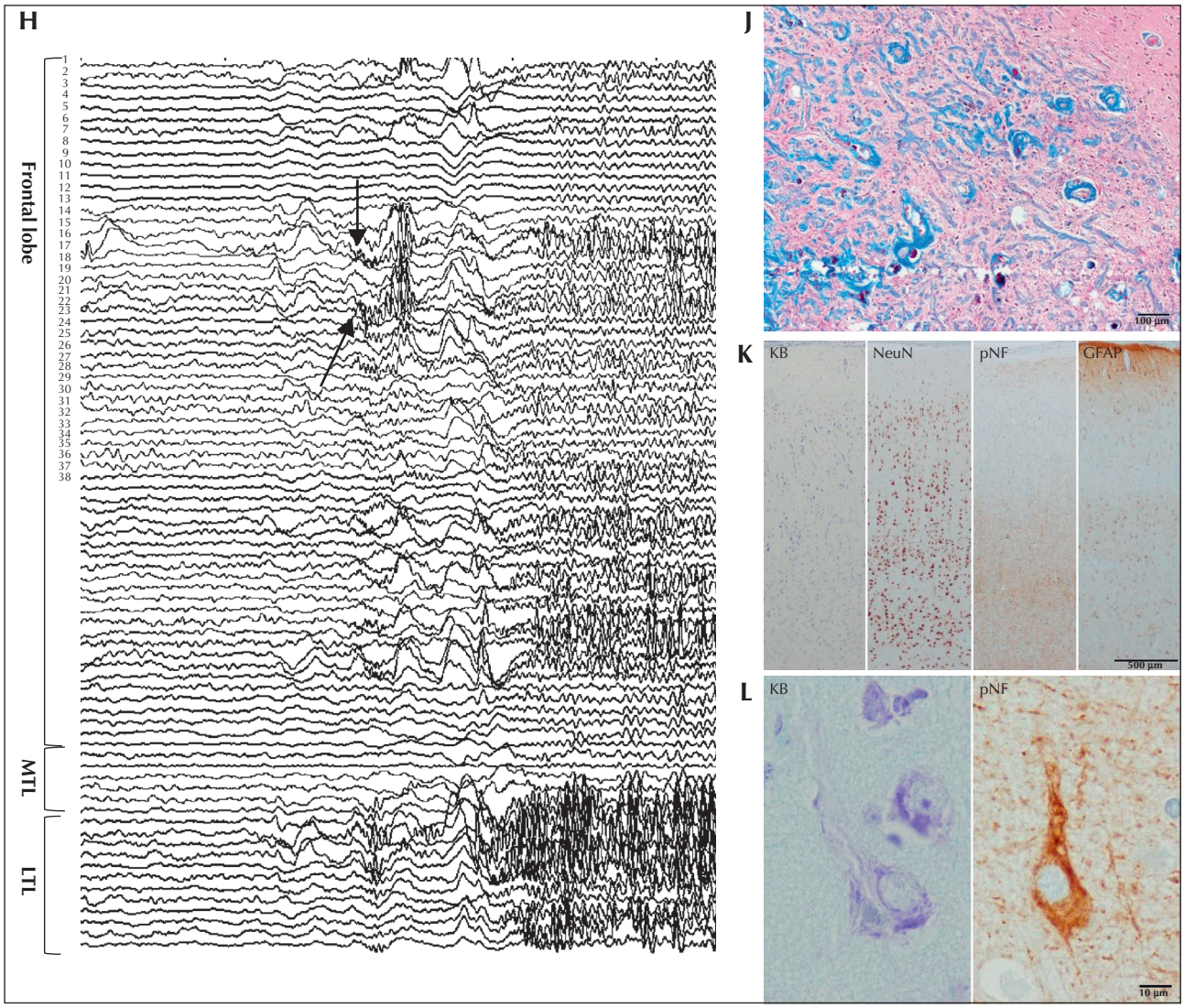

Figure 1. (H) Ictal ECoG demonstrates that the ictal discharges begin at the electrodes on the cortex adjacent to the lesion (electrodes 16-18 and 22-23 indicated with black arrows).
(J) Masson's Trichrome staining of the lesion shows a highly desmoplastic lesion consisting of proliferation of blood vessels and meningeal cells within the cerebral cortex. (K) Photomicrographs of the cerebral cortex of the IOZ (from left to right: Klüver-Barrera [KB] staining, and immunostaining for NeuN, phosphorylated neurofilament [pNF], and GFAP). KB staining and NeuN-immunostaining show normal cortical lamination. Immunopositivity for phosphorylated neurofilament (pNF) is restricted to the layers 3-6. GFAP-immunostaining reveals gliosis in the IOZ cortex. (L) KB staining (left panel) shows large hypertrophic neurons with clumped Nissl bodies in layer 3 of the IOZ cortex. Hypertrophic neurons occasionally show pNF-immunopositivity in the dendrites and perikarya (right panel).
Bar: 100 µm (J); 500 µm (K); 10 µm (L).

A variety of scanning techniques were used to investigate the lesion. Fluid-attenuated inversion recovery (FLAIR) magnetic resonance imaging (MRI) revealed hypointensity at the site of lesion in the left frontal lobe but no cortical or subcortical abnormalities around the lesion (*figure 1A*). There was no contrast enhancement on gadolinium-enhanced T1-weighted images (Gd-T1WI; *figure 1B*). Computed tomography (CT) scanning revealed calcification of the lesion (*figure 1C*). ^{123}Iomazenil (IMZ) single-photon emission computed tomography (SPECT) demonstrated reduced IMZ uptake in the lesion (*figure 1D*). ^{18}Fluorodeoxyglucose positron emission tomography (FDG-PET) showed focal hypometabolism of the lesion and mild hypometabolism of the cortex of the frontal lobe around the lesion (*figure 1E*). Ictal electroencephalogram (EEG) suggested that the IOZ was located in the left frontal region.

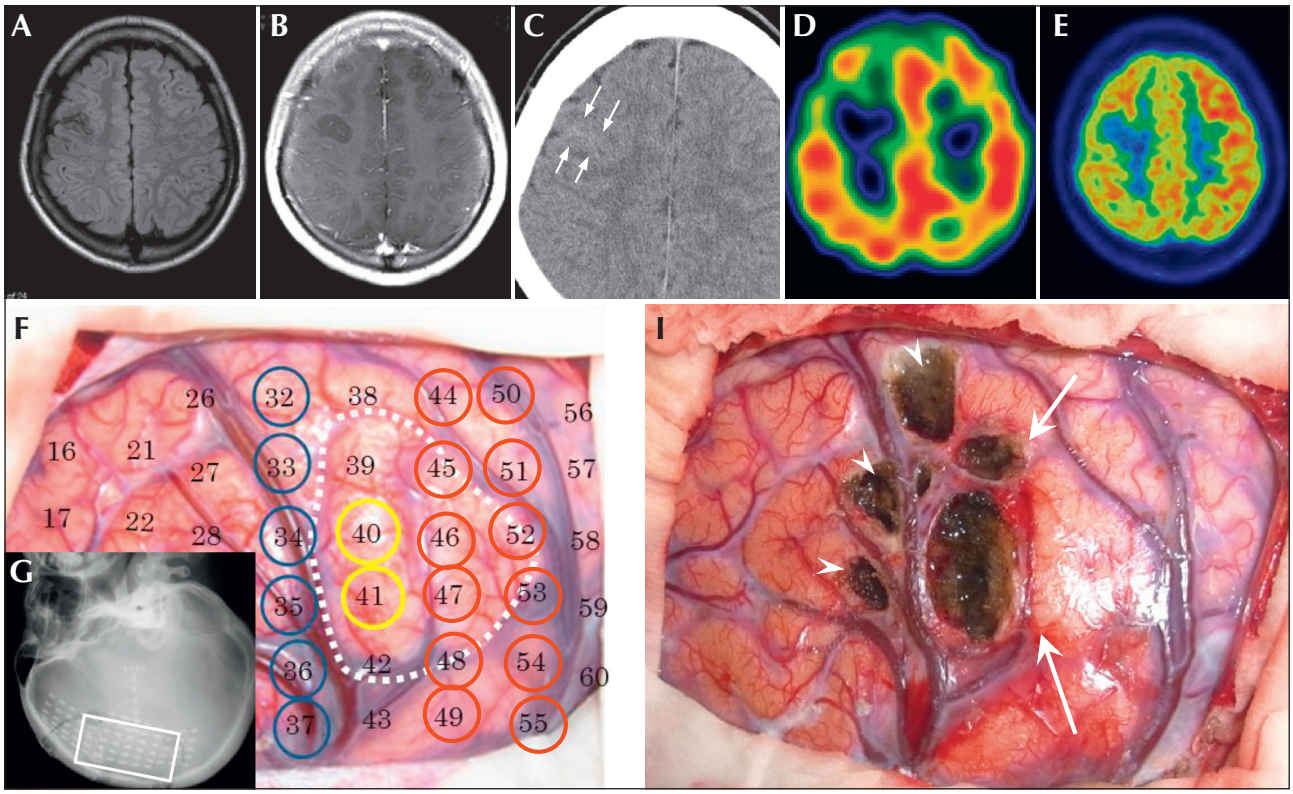

Figure 2. (A) FLAIR MRI demonstrates hypointensity at the site of lesion in the right frontal lobe and a slight hyperintensity of the cortex. (B) The lesion has no contrast enhancement on Gd-T1WI. (C) CT scan demonstrates a potential high-density lesion in the right frontal lobe. (D) ^{123}IMZ-SPECT shows decreased accumulation of IMZ around the lesion. (E) 18-FDG-PET shows focal hypometabolism of the lesion. (F) An intraoperative photograph indicating the position and number of subdural electrodes on the surface of the frontal and parietal lobes. The location of the structural lesion, which was identified with neuronavigation, is marked with a dotted circle. Electrodes located within the IOZ are marked with yellow and blue circles. The motor-related area is indicated with red circles. (G) Postoperative X-P, shown in an orientation matched with (F), demonstrates the position of the chronic subdural electrodes. The white square indicates the extent of the craniotomy. (I) An intraoperative photograph after the resection of the structural lesion including the IOZ (white arrows), and the IOZ just posterior to the lesion (white arrow heads).

Consequently, chronic subdural electrodes were placed on the convex surfaces of the frontal and temporal lobes (*figure 1F,G*) and as the lesion was not visible, it was identified by neuronavigation (*figure 1F*). Four habitual seizures were observed during continuous video-ECoG monitoring. During this procedure, the ictal discharges began at the electrodes placed on the apparently normal cortex adjacent to the lesion, rather than those on the lesion itself (*figure 1H*). Functional cortical mapping with direct cortical stimulation revealed that the language- and motor-related areas were not located on the IOZ and so total resection of the lesion, as well as the IOZ, was performed (*figure 1I*).

Case 2

A 16-year-old boy with no evidence of NF2 had suffered from intractable epilepsy since he was 13 years old. His symptoms started with simple paresis of the left hand followed by the development of secondary generalized seizures.

FLAIR MRI revealed hypointensity at the site of lesion without contrast enhancement, and a slight hyperintensity of the affected cortex was also found (*figure 2A,B*). A CT scan revealed possible calcification (*figure 2C*). IMZ-SPECT demonstrated decreased uptake of IMZ of the peri-lesional cortex in the frontal lobe, in addition to in the lesion (*figure 2D*). ^{18}FDG-PET showed focal hypometabolism of the lesion (*figure 2E*). Ictal EEG showed rhythmic discharges of 6 to 7 Hz, beginning in the bilateral frontal region, predominantly on the right.

Chronic subdural electrodes were placed on the right frontal and parietal lobes (*figure 2F*). As the lesion was not visible, it was identified using neuronavigation (*figure 2F*). Four habitual seizures were observed during continuous ECoG monitoring. The ictal

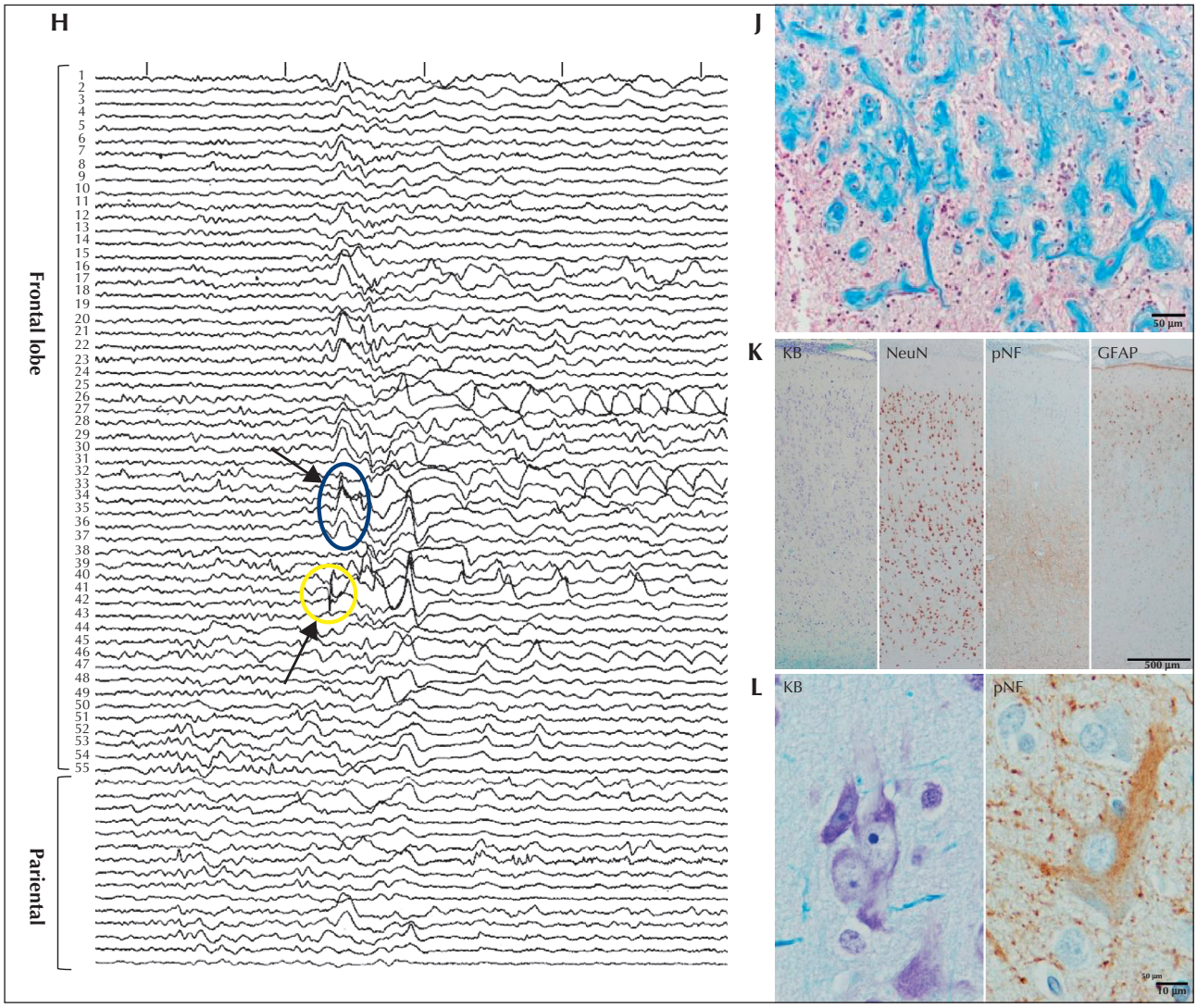

Figure 2. (H) ECoG demonstrates that the ictal discharges begin at the electrodes on the apparently normal cerebral cortex above the structural lesion (electrodes 40, 41; yellow circle), and they immediately propagate to the cortex just posterior to the structural lesion (electrodes 32-37; blue circle).
(J) MT staining of the lesion shows a highly desmoplastic lesion consisting of proliferation of blood vessels and meningeal cells within the cerebral cortex.
(K) Photomicrographs of the cerebral cortex of the IOZ (from left to right: Klüver-Barrera [KB] staining, and immunostaining for NeuN, phosphorylated neurofilament [pNF], and GFAP). KB staining and NeuN-immunostaining show somewhat indistinct, but still discernible cortical lamination. Immunopositivity for phosphorylated neurofilament (pNF) is restricted to layers 3-6. GFAP-immunostaining reveals gliosis in the IOZ cortex. (L) KB staining (left panel) shows large hypertrophic neurons with clumped Nissl bodies in layer 3 of the IOZ cortex. Hypertrophic neurons occasionally show pNF-immunopositivity in the dendrites and perikarya (right panel).
Bar: 50 µm (J); 50 0µm (K); 10 µm (L).

discharges began at the electrodes over the apparently normal cortex above the lesion and immediately propagated to the cortex just anterior to the lesion (*figure 2H*). Direct cortical stimulation identified the motor-related area just posterior to the lesion (*figure 2F*). Therefore, partial removal of the lesion, as well as the complete resection of the IOZ, was performed, as presented in *figure 2I*.

Histopathology

Histopathologically, the two cases showed very similar findings. The highly desmoplastic lesions consisted of marked proliferation of hyalinized blood vessels, and spindle-shaped or meningothelial meningeal cells within the cerebral cortex (*figures 1J, 2J*). Numerous calcospherites were also noted in Case 1 (*figure 1J*).

Degenerative neurons with granulovacuolar change or neurofibrillary tangles, and reactive astrocytes were entrapped in the lesion (not shown). The findings were compatible with MA. In Case 1, small nests of meningothelial meningioma were noted at the surface of the lesion, which is a known feature of MA (not shown). The IOZ of each case showed almost normal lamination, although Case 2 showed a decreased number of granular neurons in layers 2 and 4. Both cases showed hypertrophic neurons with enlarged nuclei, prominent nucleoli, clumped Nissl bodies, and accumulation of phosphorylated neurofilament in the dendrites and perikarya (detected with 2F11 antibody) in layers 3-6 (*figures 1K, 1L, 2K, 2L*). These features were compatible with FCD type IIIc associated with MA (Blümcke *et al*., 2011). Postoperatively, both patients have been seizure-free for two years.

Discussion

Although the literature mentions intractable epilepsy as a clinical feature of solitary MA (Wiebe *et al*., 1999; Jallo *et al*., 2005), its epileptogenicity is not fully understood. Jallo *et al*. (2005) reported that the total resection of the MA lesion is key to controlling the seizures. Conversely, some have reported the involvement of peri- or extra-lesional cortex in epileptogenicity (Wiebe *et al*., 1999; Kobayashi *et al*., 2006). Wiebe *et al*. (1999) reported on total resection of both the MA lesion and the surrounding epileptogenic area (detected using "intraoperative" ECoG), and emphasized the importance of considering extra-lesional epileptogenesis when planning surgery.

In the present study, the IOZ was located using chronic ECoG recording in regions of apparently normal cortex adjacent to and/or above the lesion. Moreover, during histopathological investigation, we found ILAE FCD type IIIc in the IOZ. There is only one previous report of the coexistence of MA with FCD, which lacks a description of the topographical relationship between the epileptogenic cortex and the location of the FCD (Batra and Prayson, 2013).

FCD type II is well-known to be highly epileptogenic and the complete resection of FCD type II is considered as a key prognostic factor for the outcome of epilepsy surgery (Morioka *et al*., 1999). We have previously reported FCD type II as epileptogenic in patients where it is associated with longstanding lesions, such as glioneuronal tumours and leptomeningeal angiomatosis in Sturge-Weber syndrome (Murakami *et al*., 2012). On the contrary, ILAE FCD type IIIc is likely an acquired process and should not be considered as "double pathology" (Blümcke *et al*., 2011). However, seizure activities may arise from altered networks in the ILAE FCD type IIIc area (Ferrier *et al*., 2007; Blümcke *et al*., 2011). Our report is the first to present MA cases with a clearly documented topographical relationship between the IOZ and ILAE FCD type IIIc.

It has been reported that the most common MRI findings in MA are hypointensity in T1WI, hyperintensity in T2WI, and Gd-enhancement in T1W MRI, however, various patterns have been demonstrated (Kashlan *et al*., 2011). Typically, for FCD type II, T2WI FLAIR shows cortical thickening, blurring of the grey-white matter junction, and hyperintensity of white matter (Colombo *et al*., 2003). Although MRI features of ILAE FCD type IIIc have not been fully reported (Kim *et al*., 2012), it is postulated that, as shown in our cases, microscopic alterations in architectural composition (cortical lamination, hypoplasia) or cytoarchitectural composition (hypertrophic neurons) adjacent to MA are relatively difficult to detect before surgery, even with currently available high-resolution MRI techniques, as is the case for FCD type II (Kim *et al*., 2012). Considering these facts, it might be difficult to identify the presence of ILAE FCD type IIIc associated with MA using only preoperative imaging studies. Thus, chronic ECoG monitoring will be useful to detect ILAE FCD type IIIc which although may be initially undetected, is epileptogenic.

MA is occasionally associated with meningioma. However, no essential difference between MA with and without meningioma is noted in clinical presentations, especially in the development of seizures (Perry *et al*., 2005). Meningioma has also been considered as simply the spread of MA along perivascular Virchow-Robin spaces, without arising via transformation from MA (Perry *et al*., 2005). In Case 1, meningioma was present but was not located in the IOZ. Rather, it was located at the surface of the MA lesion. As such, the meningioma component of MA did not directly contribute to the epileptogenesis. □

Disclosures.
The authors have no conflicts of interest to declare.

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