Efficacy of Surgical Treatment of De Novo, Adult-Onset, Cryptogenic, Refractory Focal Status Epilepticus

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Background: There have been few published reports of successful surgical treatment of focal status epilepticus. Surgical intervention is considered a last resort after medical strategies have been exhausted.

Objective: To report a case of an adult who was initially seen with de novo, medically refractory, cryptogenic focal status epilepticus and underwent resection of an electrographically defined portion of the left middle frontal gyrus with multiple subpial transections of the adjacent cortex resulting in termination of the electroclinical seizure activity.

Design: Report of a case of successful surgical treatment of cryptogenic focal status epilepticus.

Intervention: After an initial 35 days of oral antiepileptic drug therapy and subsequent 16 days of continuous electroencephalography-guided intravenous antiepileptic drug therapy in an intensive care unit setting, and after extensive preoperative and intraoperative characterization of the epileptogenic zone, a tailored resection of the left middle frontal gyrus with multiple subpial transections of the surrounding cortex was performed.

Results: The restricted surgical resection and multiple subpial transections terminated the seizure activity. Neuropathological examination of the resected tissue revealed moderate inflammatory changes and a few abnormally located neurons without any definitive evidence of dysplasia, which was suspected preoperatively.

Conclusions: We suggest that focal cortical resection may be an appropriate intervention in medically refractory focal status epilepticus even when an overt structural etiology is not evident preoperatively and should be considered as an option at the onset of intractability.

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FOCAL STATUS EPILEPTICUS IS typically treated in the same manner as generalized status epilepticus with the exception of lesional epilepsy where a candidate structural lesion is potentially resectable. Treatment of refractory focal status epilepticus with suppressive therapy in an intensive care unit (ICU) setting remains the current standard of care for these difficult cases, albeit with high associated morbidity and mortality. Despite the theoretical plausibility of surgical intervention in refractory focal status epilepticus, this is rarely undertaken except in later stages of case management when medical intervention has proven ineffective. Frequently, by the time surgery is undertaken, the cumulative morbidity of prolonged status epilepticus and prolonged medical management renders surgical intervention a high-risk procedure with limited utility and poor long-term outcome. Reported cases of emergent surgery for refractory focal status epilepticus generally describe patients with documented lesions with a recrudescence of seizures.[1-9] We report a case of cryptogenic, adult-onset, refractory focal status epilepticus where medical management proved ineffective and where relatively early (before ICU day 30) surgical intervention successfully terminated the focal status epilepticus.

REPORT OF A CASE

A previously healthy, 36-year-old, right-handed woman was transferred to the Massachusetts General Hospital for further evaluation and treatment of complex partial status epilepticus. There were no reported risk factors for epilepsy, either remote or recent.

One month prior to transfer, the patient had her first seizure, characterized by flexed dystonic posturing of her right upper limb, right hemifacial tonic activity, and dystonic head turning to the right associated with altered awareness. This event
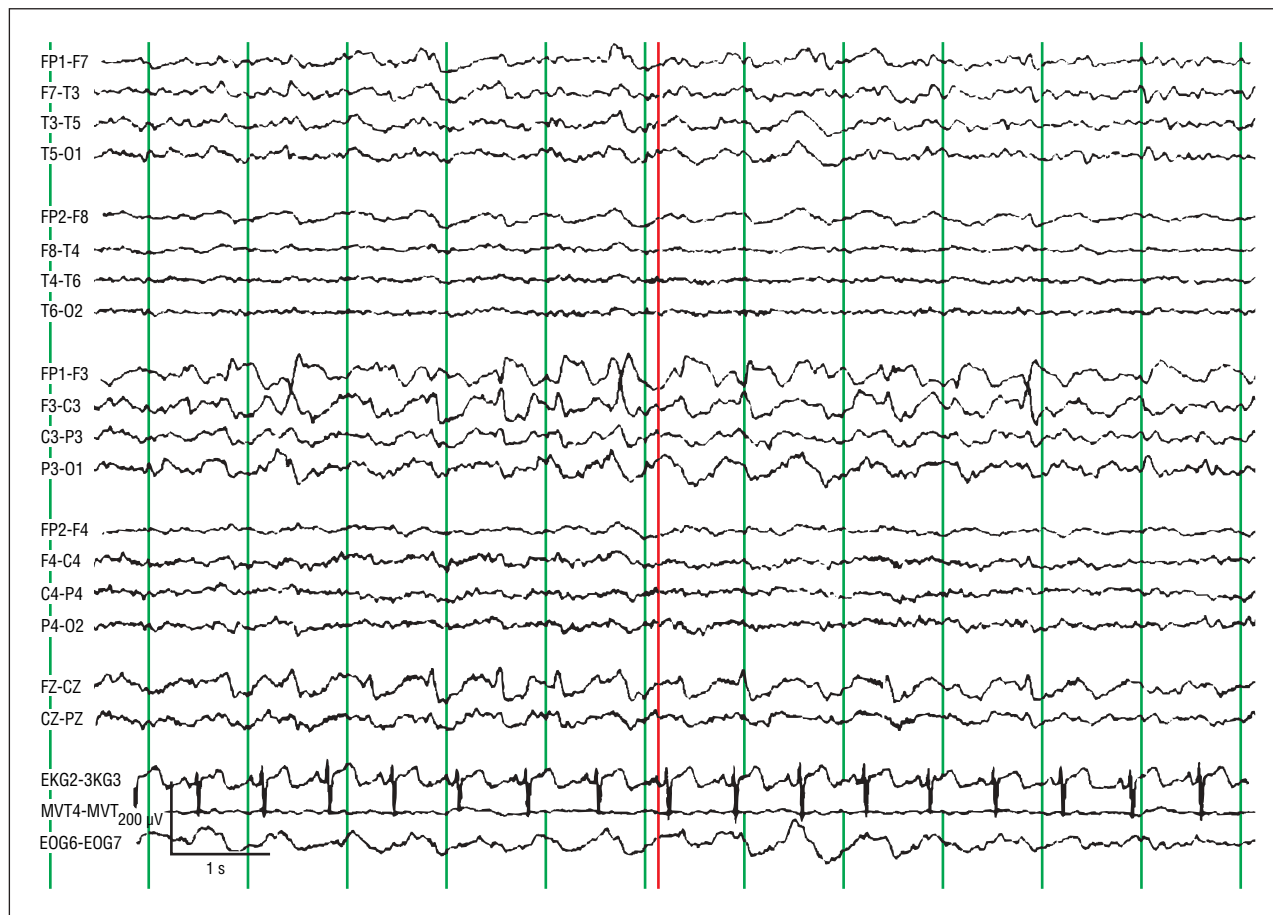
Figure 1. Baseline electroencephalogram during a relatively quiescent clinical period on hospital admission before intravenous therapy.

was followed by postictal word-finding difficulties for 30 minutes. One week later, another seizure of similar clinical evolution occurred with a more prolonged postictal phase. Over the subsequent 2 weeks, the patient experienced a marked increase in the previously described seizures. During this time, the postictal state became gradually more prolonged and increasingly characterized by language difficulties and behavioral disturbances. A trial of oral valproate sodium administration produced no change in seizure frequency or severity.

The patient was admitted to another hospital 9 days prior to transfer to the Massachusetts General Hospital where an electroencephalogram (EEG) revealed frequent sharp waves centered over the left frontotemporal region, maximal at F3. Initial investigations demonstrated a modest cerebrospinal fluid lymphocytic pleocytosis of 17/mm³ cubed (with no red blood cells, normal cerebrospinal fluid protein and glucose levels), blurring of the gray-white matter junction over the left frontal lobe on magnetic resonance imaging (MRI), and negative herpes simplex virus polymerase chain reaction study results. She was empirically treated with acyclovir and increasing doses of valproate and phenytoin sodium. Over the next week, although the seizures became less prominent, the patient became progressively encephalopathic with bizarre, combative, disinhibited behavior associated with language difficulties and occasional right hemibody clonic movements. Throughout

this time, intermittent EEG recording showed frequent sharp transients over the left frontotemporal region.

On transfer to the Massachusetts General Hospital, the principal clinical signs were behavioral with pronounced dyscontrol, emotional lability, and disinhibition. Her behavioral changes fluctuated, and at times, she appeared relatively lucid, insightful, and cooperative, following basic commands appropriately. She exhibited expressive language difficulties with nonfluent, perseverative speech and frequent literal paraphasic errors. Ictal motor manifestations were rarely evident, manifesting as subtle right hemifacial clonic activity. There were no systemic clinical signs and the patient was afebrile.

Initial continuous EEG monitoring demonstrated frequent, often repetitive, sharp and slow wave discharges over the left frontotemporal region with maximal activity over F3 (**Figure 1**). This focal electrographic activity frequently had an organized appearance highly suggestive of focal electrographic seizures (**Figure 2**).

On hospital admission, the patient received a loading dose of intravenous phenobarbital and the oral phenytoin dose was increased. An MRI of the brain demonstrated, in the left midfrontal region, apparent thickening of the cortical mantle over the left midfrontal region associated with a subtle increase in T2 signal intensity and modestly restricted diffusion without evidence of underlying structural abnormality (**Figure 3**). These findings were felt to be peri-ictal in nature, correlating with
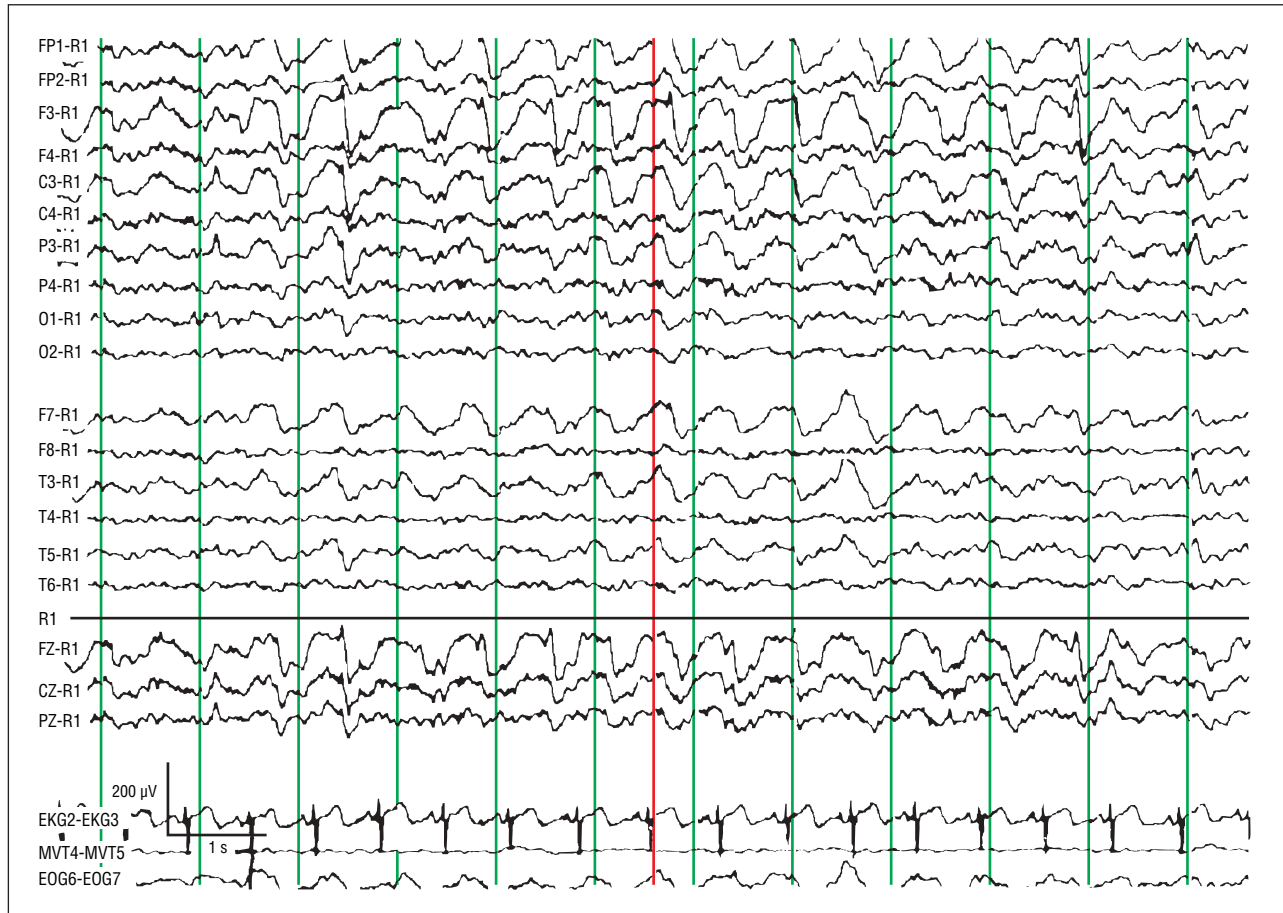
Figure 2. "Active" electroencephalogram demonstrating focal electrographic seizure activity on hospital admission before intravenous therapy, R1 over second cervical vertebra.
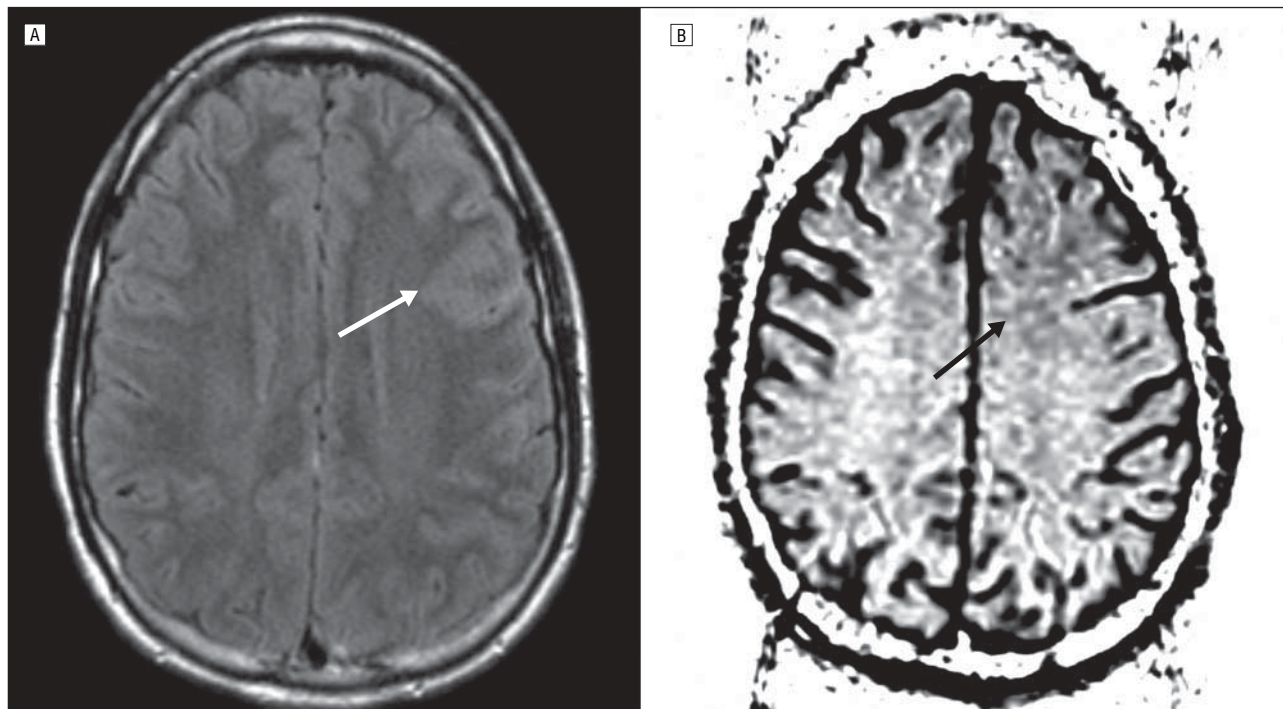

Figure 3. Brain magnetic resonance images demonstrating blurred, indistinct cortex in the left frontal convexity (arrow) on a fluid-attenuated inversion recovery sequence (A), with subtle restricted diffusion on an apparent diffusion coefficient map (B).
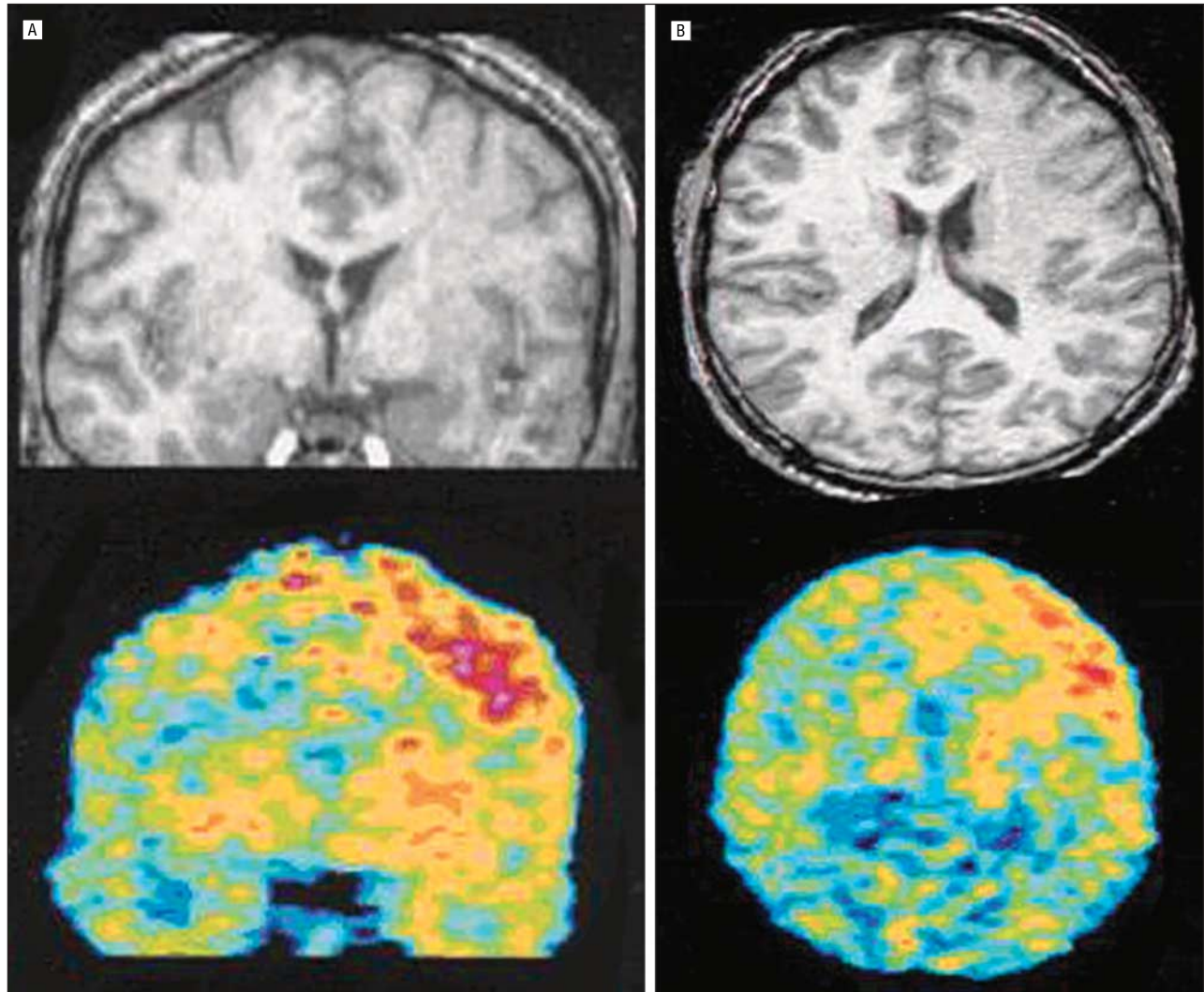
Figure 4. Coregistered, subtracted (interictal study subtracted from ictal study) fluorodeoxyglucose F18–positron emission tomography and T1-weighted magnetic resonance images of the brain. A, Coronal view. B, Axial view.
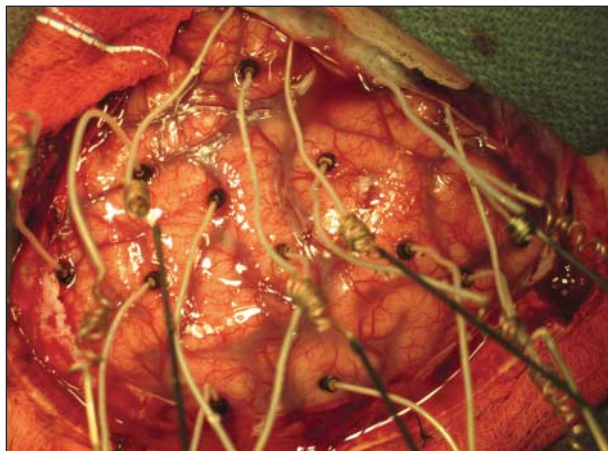

Figure 5. Direct visualization of the left frontal convexity intraoperatively with a Montreal frame in situ.

the region of maximal electrographic epileptiform activity. Cerebrospinal fluid analysis again revealed a lymphocytic pleocytosis of 31 per millimeter cubed with normal protein and glucose concentrations. An exhaustive

search for an underlying cause of the patient's de novo focal status epilepticus was negative for infectious, immunological, neoplastic, and paraneoplastic processes.

After it was evident that dual therapy with high doses of oral phenytoin and phenobarbital was ineffective, the patient was electively paralyzed, ventilated, and commenced on an infusion of propofol. Over the course of 2 weeks, the patient received trials of propofol, midazolam, and ketamine hydrochloride in varying combinations titrated to produce a burst-suppression EEG pattern, all of which were ultimately ineffective in controlling the electrographic seizure activity. Maintenance oral antiepileptic agents included combined phenytoin, phenobarbital, levetiracetam, and topiramate, all at high doses. Four sessions of electroconvulsive therapy produced no clinical or EEG changes.

Though the electrographic seizure activity largely remained maximal over the left frontocentral region, a wider distribution of epileptiform ictal activity became increasingly evident. To further clarify the ictal nidus, a fluorodeoxyglucose F18–positron emission tomography brain study was performed during a period when focal sei-
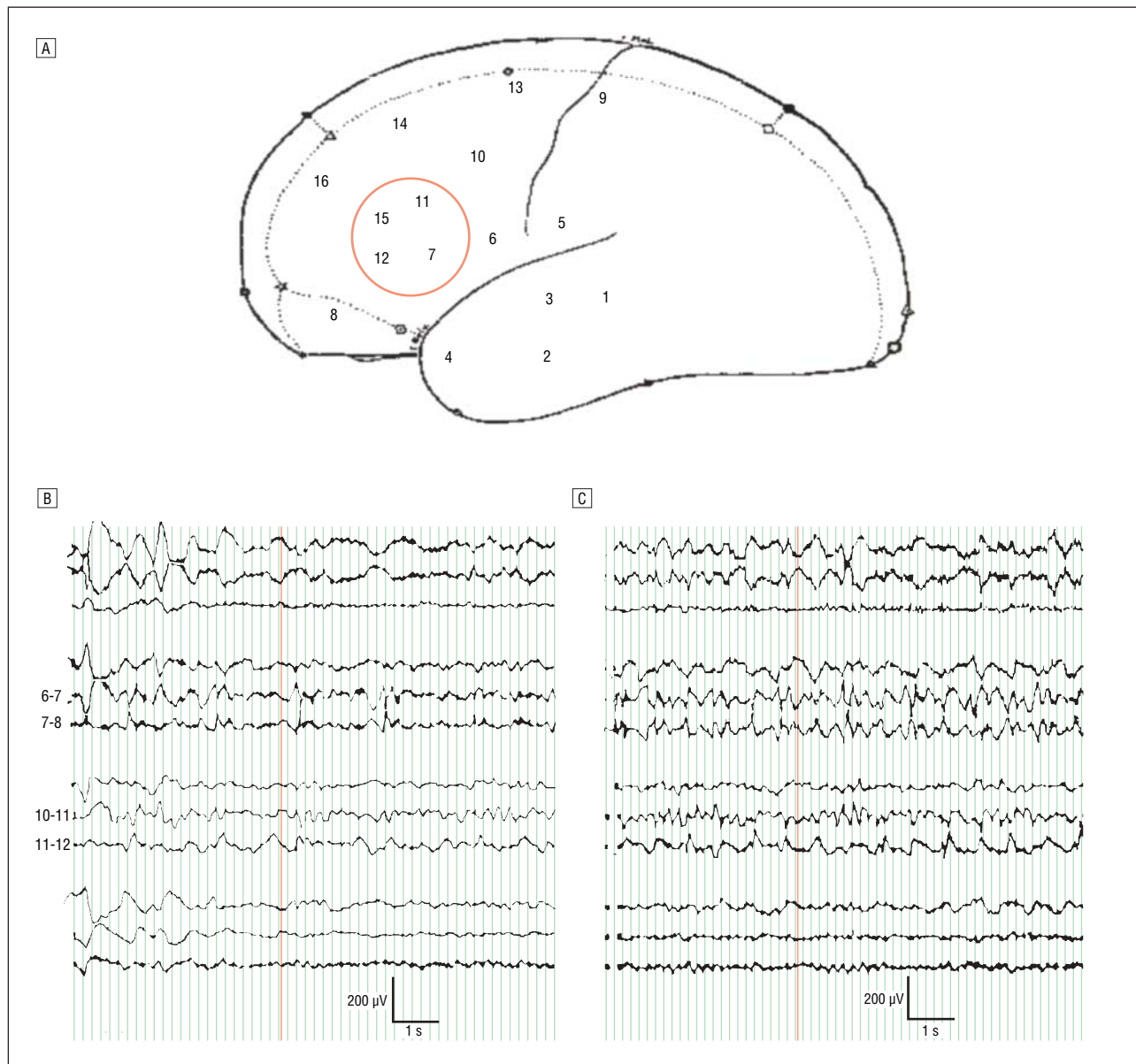
Figure 6. Electrocorticography (ECoG) of the left frontal convexity using a Montreal frame. A, Schematic representation of maximal ECoG activity with electrodes in the final position. B, Spontaneous ECoG recordings at baseline. C, Electrocorticography recordings after administration of intravenous alfentanil hydrochloride.

zure activity was allowed to manifest electrographically. Coregistration of the positron emission tomographic findings with T1-weighted MRI confirmed a focal area of ictal hypermetabolism, the location of which was concordant with the ictal EEG localization (**Figure 4**).

Ongoing medical management was complicated by iatrogenic hypotension, iatrogenic fever, upper limb deep venous thrombosis, and hypostatic pneumonia. Twenty-one days after transfer to the hospital (day 51 after first seizure), based on the failure of medical management, increasing complications and hemodynamic instability, worsening but still focal EEG findings, and the focal features on imaging studies, the patient was electively taken to surgery. A left frontal craniotomy was performed. Intraoperative visual inspection of the left frontal lobe was unremarkable (**Figure 5**).

Electrocorticography was performed to define the epileptogenic zone, using activation with intravenous alfen-

tanil hydrochloride (**Figure 6**). This confirmed an area of maximal epileptogenic activity over the left middle frontal gyrus approximately midway between the left frontal polar region and the central sulcus. Functional cortical mapping was attempted but not completed because of the presence of spontaneous limb movements when the anesthetic was lightened. The primary motor cortex was identified visually before proceeding to a tailored 3×2-cm resection of the left middle frontal gyrus cortex and multiple subpial transections of the surrounding cortex.

Immediate, postoperative, continuous EEG monitoring revealed an area of focal slowing over the left frontocentral region. Over the subsequent week, intravenous antiepileptic agents were withdrawn gradually without return of epileptiform EEG activity or clinical ictal manifestations. The postoperative course was complicated by transient intention tremor (resolved after a

Figure 7. Electroencephalogram 1 month after resective surgery, displayed at 7 uV/mm sensitivity.

month), pulmonary sepsis, phenytoin-associated rash, and right foot drop.

The patient continued to improve without any return of clinical seizure activity or preoperative behavioral difficulties. At 4 weeks, the EEG remained static without evidence of epileptiform activity (**Figure 7**).

Findings from neuropathological examination of the resected tissue revealed microglial activation and a few abnormally located subcortical neuN(+) neurons. While the resected cortex had some dysplastic features, the small specimen was insufficient to support a definitive diagnosis of focal cortical dysplasia. The inflammatory changes seemed consistent with the history of ongoing prolonged seizure activity. No viral inclusions or vasculitic changes were evident.

Four months postoperatively, the patient had not had any clinical seizures or distinct periods of encephalopathic behavior. She was ambulant (with a recovering right foot drop) and articulate but had difficulties with multistep tasks (eg, cooking a meal), where she became frustrated and upset. Her speech was fluent with intact naming, comprehension, and repetition. She read, wrote, and performed simple arithmetic with difficulty. Her spouse reported personality changes with blunted affect ("no sense of humor anymore," "no spark"), occasional tearfulness, impulsivity, and impatience with her children. Overall, he reported a gradual but slow improvement in

her abilities to carry out daily activities but recognized that she had not reached her baseline state.

At the time of publication, the patient is 16 months after surgery. She has not had any further seizures since her admission. She remains well. Her EEG does not demonstrate any epileptiform activity. She is independent in activities of daily living and plans to return to work in the near future.

COMMENT

This case report shows the efficacy of relatively early (before ICU day 30) surgical intervention in refractory focal status epilepticus, even when a definitive preoperative diagnosis is not established. While guidelines exist for the initial management of status epilepticus, the optimal management of refractory status epilepticus is less clear, and individual cases are managed according to physician experience and preferences. Conventional treatment approaches include intravenous antiepileptic agents and anesthetics, and dosing is typically guided by suppression of epileptiform EEG manifestations. In the majority of cases, the ongoing electroclinical seizure activity is terminated by antiepileptic agents in conjunction with treatment of the underlying etiological process.

This case report shows de novo focal status epilepticus occurring in an adult where no definite etiology was

evident preoperatively and where pharmacological intervention was ineffective. The relatively restricted and refractory nature of the electrographic seizure activity raised the possibility of a radiologically occult focal cortical dysplasia, not evident on 1.5-T MRI with phased-array surface coils, possibly because of obscuration by peri-ictal MRI changes such as cortical edema with blurring of the gray-white matter junction. Focal cortical dysplasia is a recognized but sometimes elusive cause of de novo, refractory focal status epilepticus in adults.[2] In the current case, surgery abolished the electroclinical seizures. Hence, one can be reasonably confident that the resected and/or disconnected (by multiple subpial transections) cortex represented the epileptogenic region. Despite careful analysis of the resected cortex by an experienced neuropathologist, definite dysplastic features were not evident. Rather, the neuropathological features were nonspecific and could have been accounted for by the prolonged ictal activity. This apparent clinicopathological mismatch could be explained either by inadequate tissue sampling or the possibility that the status epilepticus was not due to structural disease but due to disorder of function, ostensibly "idiopathic" status epilepticus.

Ultimately, this patient was operated on relatively early in the treatment course because (1) multimodal investigations were concordant in localization of the active epileptiform focus and (2) the distribution of the epileptiform activity appeared to be involving progressively more cortex and because of (3) the morbidity accrued by the patient from ongoing medical therapy in an ICU setting, (4) recognition that no reversible etiology was evident, and lastly, (5) recognition that conventional pharmacological approaches were proving ineffective.

Successful surgical intervention has been reported in the setting of medically refractory status epilepticus.[1-9] These selected cases all describe an acute (or subacute) worsening of seizure control in patients with known or suspected structural lesion. Even in the setting of a known epileptogenic structural lesion, the decision for surgical intervention is traditionally viewed as a "last resort" or life-saving measure. This case focuses attention on the optimal timing of surgical intervention in refractory focal status epilepticus. Traditionally, in the absence of a gross structural lesion, exhaustive efforts at medical management, often pursued for many weeks or even months, are undertaken prior to consideration of surgical intervention. In this context, we are not aware of reliable early markers of eventual success with medical treatment, and numerous studies indicate that longer duration of refractory focal status epilepticus is associated with poorer outcome.[10-15] When surgery is considered, late outcome may be compromised by accumulated medical complications and by the spread of epileptic activity to adjacent or more distant structures. While poorly studied, the short-term mortality from refractory focal status epilepticus is very significant, on the order of 10% to 30%.[10-15] In our experience, the outcome of late (after >30 ICU days) surgical treatment has been disappointing. Advances in neuroimaging, including anatomical and functional techniques, in combination with improved and more widely available continuous EEG recording, now allow a greater degree of certainty with regard to the localization of epileptogenic cortex, even if a causative lesion cannot be identified with certainty, as in the present case. A multistep algorithmic approach to refractory focal status epilepticus is needed, where intervention and diagnostic workup go hand in hand and, where appropriate, arrive at early surgical intervention. While a multicenter study of surgical treatment for refractory focal status epilepticus would be required to fully define its utility, our case, in combination with published reports, suggests that surgical treatment relatively early in the course of refractory focal status epilepticus may lead to improved outcome in well-selected patients.

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