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Anatomo-electro-clinical correlations: the Cleveland Case Report (March 2008)

Temporal lobe neoplasm and seizures: how deep does the story go? *

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ABSTRACT – [March 2008 - Cleveland Case Report]. There is a well-described association between the occurrence of developmental tumors and the presence of cortical dysplasia in the neighboring brain tissue. The main surgical approaches in the treatment of medically refractory epilepsy related to such developmental tumors include a lesionectomy *versus* a tailored cortical resection, often guided by an invasive evaluation. This case report describes the surgical management of a 26-year-old female with olfactory auras evolving into automotor seizures and convulsions, occurring in the context of a right temporo-parietal developmental lesion. It illustrates the pros and cons of various surgical approaches, and discusses some pathophysiological aspects of developmental tumors, dysplasia and epilepsy. *[Published with video sequences]*

Key words: temporal lobe epilepsy, neoplasm, cortical dysplasia

Presentation of the "March 2008 Cleveland case"

A 26-year-old, right handed woman was seen in the outpatient epilepsy clinic for the evaluation of recurrent seizures. Her first spell was a generalized tonic-clonic (GTC) convulsion that occurred while awake, at 10 years of age. Subsequently, she remained seizure-free and off antiepileptic drugs, until 17 years of age, when she had her second convulsion. Phenytoin was then initiated. The GTC resolved, however, a new type of event began. These would start with an unusual "sweet smell" or a feeling of "butterflies in her stomach" followed by loss of awareness, during which observers described her as "staring", "chewing", and "talking out of context". These seizures lasted 1-3 minutes, and occurred twice per week, despite treatment with phenytoin and levetiracetam, and prior treatment with carbamazepine and oxcarbazepine. The patient had no prior history of CNS infections, head trauma, or febrile seizures. Her past medical and surgical history and her physical examination were unremarkable. She had an uncle with a

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history of seizures. She had no mental health problems, but was not driving or working for fear of recurrent seizures. Neuropsychological testing revealed that she was generally functioning in the low average to average range with some mild difficulties in intellectual functioning and confrontation naming. Her brain MRI is shown in *(figure 1)*.

Radiological diagnosis

Dr Ruggieri: "This MRI shows an isolated, non-enhancing lesion in the dorsal aspect of the right temporal lobe at the junction of the middle and superior temporal gyri. This lesion is heterogeneous in intensity on FLAIR and T-2, and has a cystic component in the underlying white matter without significant mass effect. Hyperintensity seen on unenhanced T-1 suggests a component of dystrophic calcification. The wedge shape of the lesion suggests a malformation of cortical development (MCD), yet its striking heterogeneity suggests a neoplasm.
The underlying mesial temporal structures appear normal and symmetric in signal intensity characteristics, size and morphology."

Further investigation

Dr Lüders: "Do you feel that any further investigations are needed, or should the patient be directly referred to surgery for removal of the lesion? "

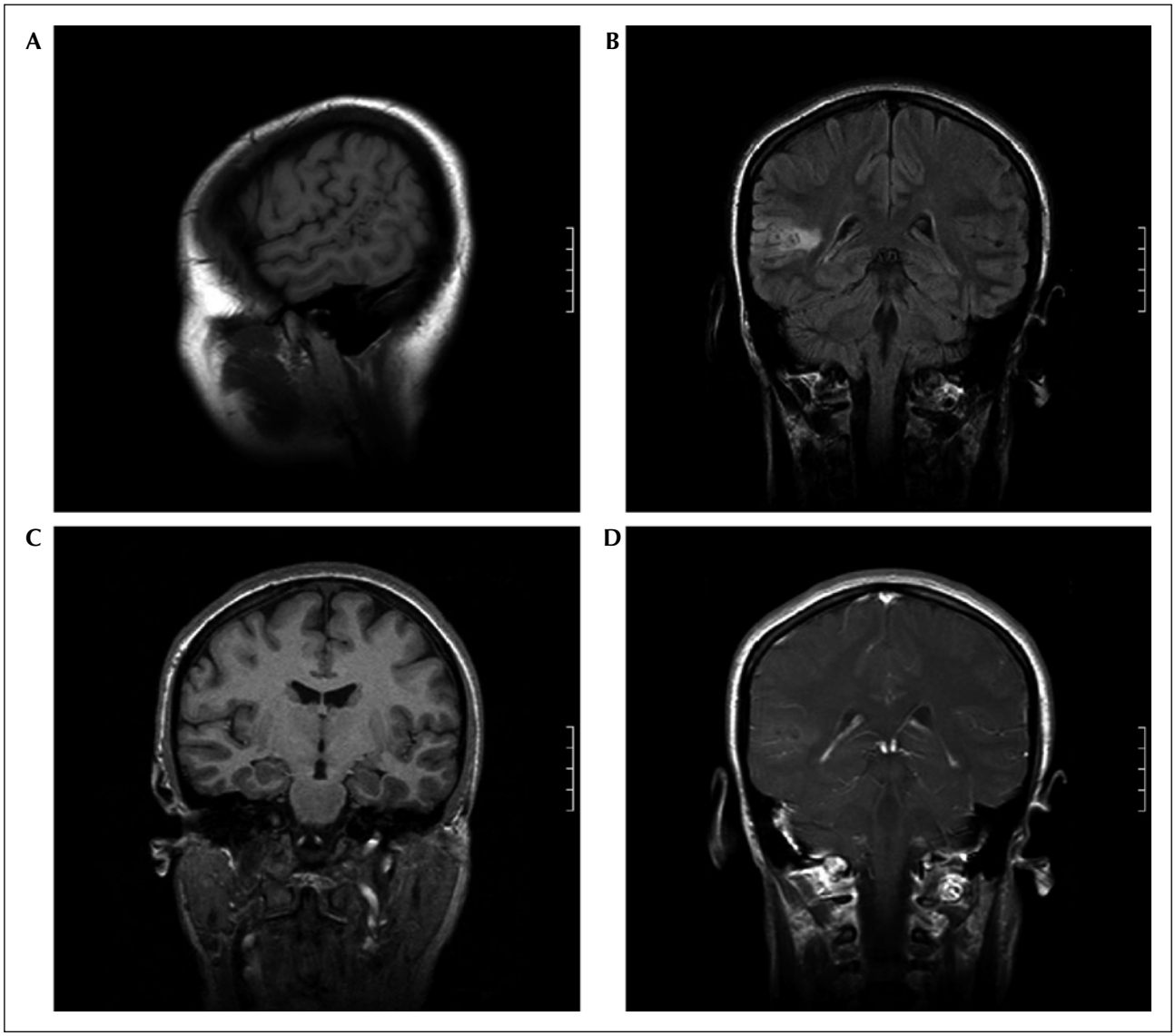


Figure 1. Selected T1 (**A, C**), FLAIR (**B**) and gadolinium enhanced (**D**) MRI brain showing cystic, non-enhancing, heterogeneous lesion at the junction of the right superior and middle temporal gyri.

Dr Morris: "She needs a video-EEG evaluation for several reasons. First, we need to confirm that the patient's episodes are indeed seizures, by recording the corresponding electrical abnormalities. Second, we need to decide what tissue to remove: obviously the neocortical lesion has to be resected because it appears to be a tumor, a ganglioglioma or more likely a dysembryoplastic neuroepithelial tumor (DNET), but her seizure semiology, specifically her olfactory aura suggests additional involvement of her mesial temporal structures raising concerns for dual pathology. A normal hippocampus on MRI does not exclude it being pathologically abnormal or epileptogenic. If her hippocampus is involved, removing the MRI lesion will not make her seizure-free. "

A noninvasive video-EEG evaluation was performed, using the 10-20 international system, with additional sphenoidal electrodes. Interictal sharp waves were seen in the right mesial temporal region, maximum at the SP2 electrode (frequency: 1 every 5-10 sec, 90% of her overall spikes). In addition, isolated sharp waves were seen in the left mesial temporal region, maximum at the SP1 electrode (10%). EEG source analysis of the interictal spiking corroborated a mesial temporal origin. One clinical seizure lasting 90 seconds was recorded. The patient pushed the seizure button to alert the nursing staff, but lost awareness before she could describe her exact aura. This was associated with manual and oral automatisms and followed by postictal confusion. Ictal EEG started with a rhythmic delta activity in the right mesial temporal region, which spread within three seconds to the left temporal region, and was obscured seven seconds later by muscle artifact *(figure 2).*

An intracarotid Amobarbital test was consistent with a left hemispheric dominance for speech, and bilateral memory representation (she had a 67% retention score and remained nonverbal for 59 sec following left internal carotid injection, while she never lost her speech and had a 75% retention score following right internal carotid injection).

Management

Invasive evaluation

Dr Foldvary: "She has right temporal lobe epilepsy (TLE). The question is whether it is neocortical or mesial. The answer to this question determines whether a lesionectomy alone is an adequate treatment option, or whether the mesial temporal structures should also be removed. Her MRI lesion is posterior temporal but her interictal spiking is right anterior temporal. She also has left temporal interictal abnormalities and an ictal pattern that appears early in the left mesial temporal region. Her epilepsy could then be originating from the surface or depths of the lesion with spread to involve mesial temporal structures bilaterally. A neocortical temporal lobe lesion can often be associated with ipsilateral mesial temporal spikes and we may not even see any posterior temporal spikes. I suppose if the duration of the epilepsy is long enough, as in this case, you could see some degree of bilaterality as with mesial TLE. However, the semiology of an olfactory and abdominal aura suggests that this could all be of mesial origin.

I would proceed with an invasive evaluation to study the relationship between her neocortical lesion and her mesial temporal structures. This could be designed in a number of ways: one way would be to just use subdural grids to cover as much as possible of the right temporal lobe, the lesion and getting close to the mesial structures. A better way would be to combine those grids with depths inserted in her right mesial temporal structures. Depending on how strongly you feel we need to investigate the left temporal abnormalities, you can go one step further and also implant depths and grids over the left temporal lobe.

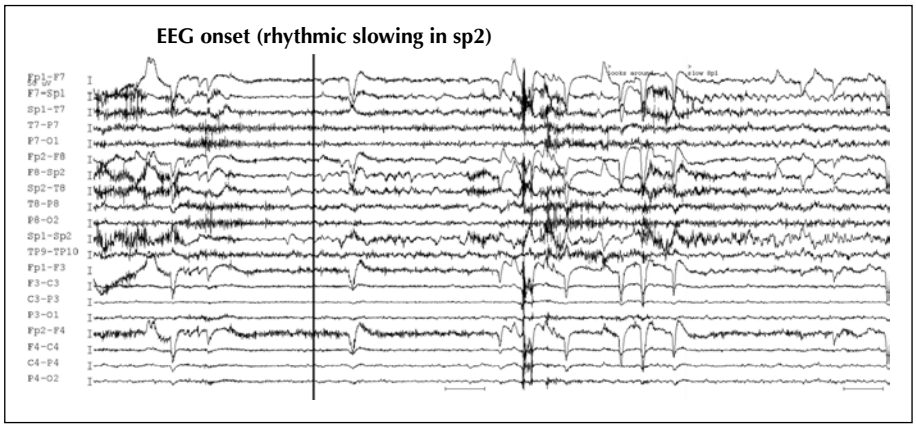


Figure 2. Automotor seizure recorded on scalp EEG showing a right temporal ictal onset.

The reality is though that we are not going to operate over the left side, so we could probably forego that."
Dr Wyllie: "I'd like to hear from our neuropsychologist about the risks of removing the hippocampus in this non-dominant temporal lobe?"
Dr Naugle: "She was able to achieve average scores in measures of her visuospatial abilities, which would suggest a risk of decline in those measures postoperatively. The issue though is that this correlation between preoperative abilities and postoperative changes is less strong in individuals undergoing a non-dominant temporal resection.
Even if she shows a decline in her testing scores, it is unlikely that she will complain of any memory change in her daily life."
Dr Wyllie: "Given the potential risk of neuropsychological changes associated with removing the hippocampus, an invasive evaluation would be additionally helpful as it may allow us to spare her mesial structures if they prove to be non-involved."
Dr Kotagal: "Even an invasive evaluation using a combination of grids and depths has its limitations though. One problem is that we don't know how to modify our surgical plans based on results of such evaluations in patients with dual pathology. We don't know if spread occurs to the mesial temporal region within for example 5 sec versus 10 sec; whether that means we have to remove the hippocampus or not."
Dr Dinner: "Even ictal patterns seemingly starting in the hippocampus could actually be originating from non-monitored regions within the depth of the lesion."
Dr Bingaman: "We also need to discuss the risk of having subdural electrodes and depths implanted. There is 20-30% chance of having some sort of a problem, including stroke and hemorrhage which could be devastating. It is also costly: $25 000 for a non-invasive video-EEG. Here with two surgeries, the cost may be up to $100 000. Although we don't always think about cost, it should be factored in."

Lesionectomy

Dr Morris: "Given the limitations of an invasive evaluation, and the 70% chance of seizure-freedom quoted in most papers following lesionectomies, we could make an argument for just doing a complete resection of the lesion at this point and hoping for the best. I previously looked at a series of failed DNETs that required reoperation, and in all of them, on reoperation, there was either residual tumor or dysplastic changes (Morris *et al.* 1993). If seizures recur in this patient after a lesionectomy, I would think they're more likely to originate from residual tissue around the lesion, than from her mesial temporal structures, but we would then need to evaluate both with an invasive evaluation."
Dr Bingaman: "An important question is what is this lesion? Is it neoplasm, or is it dysplasia? And if it is neoplasm, is there an associated dysplasia that extends perhaps throughout the temporal lobe, including the mesial structures. If dysplasia is involved, the chance of seizure-freedom would probably be less than the 70% quoted. Another issue is that lesionectomies can be tailored intraoperatively according to how the temporal lobe feels on palpation. A dysplastic tissue "feels" different. The problem here is that with a lesion that is so far posterior, we cannot feel the amygdala intraoperatively and tailor the lesionectomy accordingly. Intraoperative EcoG would not be very helpful because the mesial structures are not something you can sample easily in the operating room."

Right temporal lobectomy

Dr Wyllie: "Another possible approach, given that this is her non-dominant temporal lobe, might be to just do a large right anterior temporal lobectomy, removing both the lesion and the hippocampus. The problem with this approach in this case is that the lesion is located too far posteriorly. In cases where the neocortical lesion is closer to the hippocampus, the decision to remove both together is easier."
Dr Bingaman: "A temporal lobectomy could be presented to the patient as a method of removing the EEG abnormality, in addition to the MRI lesion. But the question is then: are you removing normal brain that can be spared? To answer that, you can do some form of a subdural and depth evaluation. This would be the most scientific option, to try to define the relationship of the lesion to the EEG. In view of how posterior the lesion is and how remote it is from the mesial structures, and how anterior and mesial the ictal EEG looks, I would probably favor an invasive evaluation."
Actual treatment: stereotcatically guided lesionectomy.

Pathological diagnosis

Dr Prayson: "The pathology of this lesion is interesting. It does not fit into any of the current classification systems used for either dysplasia or neoplasia. On the whole, I think it is best classified as a tumor *(figure 3)*.
It was multinodular, with sections containing roundish cells with perinuclear clearing and capillary vascular patterns, occasional larger neuronal or ganglion type cells without much atypia, features characteristic of a DNET rather than a ganglioglioma which tends to be more of a uninodular mass. Other sections showed very cellular, well circumscribed nodules, with a mixture of both atypical glial and neuronal cells in one region. Similar foci can be encountered in a low grade glioma or mixed astrocytoma, or in a ganglioglioma. Sections from adjacent gyri ranged from reasonably normal cortex to areas of very abnormal, very cellular, disturbed architecture, typical of Type Ia cortical dysplasia.

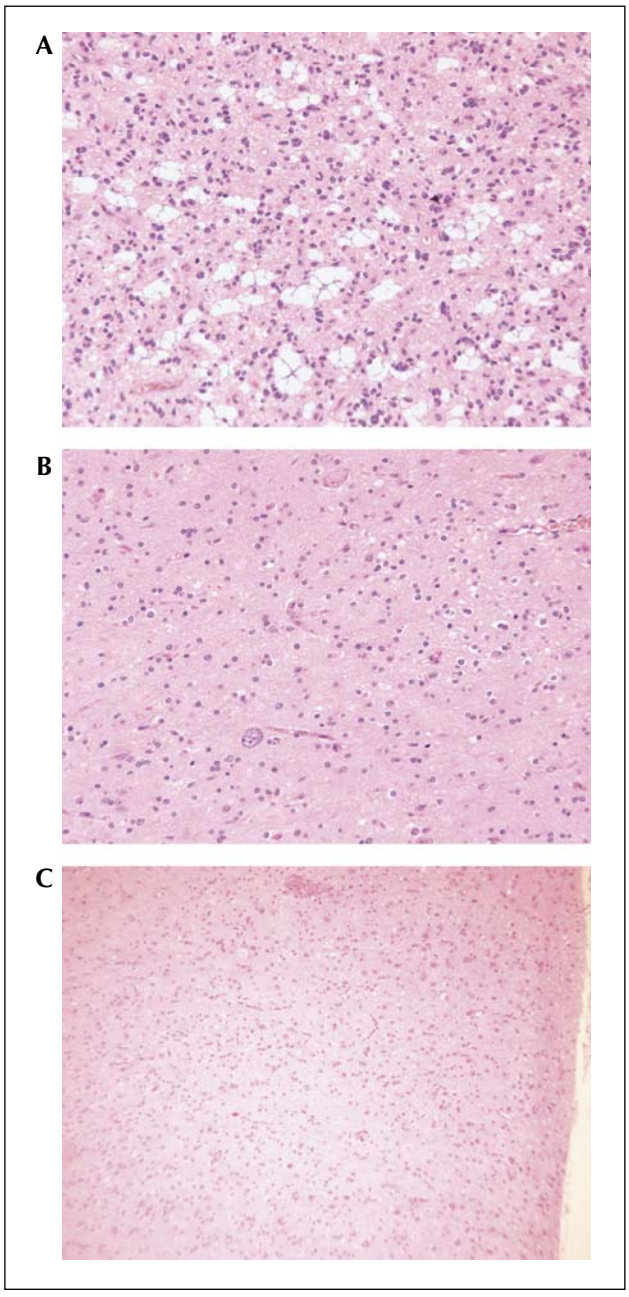


Figure 3. Pathological sections from lesionectomy showing sections of nodularity and marked cellular atypia (**A**), cells with perinuclear clearing (**B**) and surrounding cortex with mild cellular disorganization (**C**), features consistent with a developmental tumor.

I believe the lesion represents a tumor with a component of cortical dysplasia adjacent to it. We did a K67 immunostain as a marker of cell proliferation, there was little staining (< 1%), typical of DNETs or gangliogliomas. This particular tumor is multinodular with areas that look more like DNET and others more like a ganglioglioma. It appears to be a hybrid. Such cases have previously been documented in the literature.
I can not make comments on whether the margins of the resection were free from any cellular changes because we don't usually marginate those lesionectomies."

Postoperative MRI *(figure 4)*

Dr Ruggieri: "You can see a very focal resection in the dorsal aspect of that superior temporal gyrus. There is residual hyperintensity on FLAIR along the dorsal margins of the resection and along the mesial aspect of the lesion. It is, however, difficult to discern how much of this hyperintensity relates to surgical manipulation versus residual abnormal tissue. My guess is the mesial hyperintensity at least, is a portion of the underlying abnormal tissue seen preoperatively projecting towards the ventricle."
Postoperative course: typical seizures recurred five weeks after surgery, with an unchanged frequency, duration and semiology. Routine EEG showed right temporal spikes (Max FT10).
With neuropsychological testing, all scores were essentially unchanged when compared to preoperative values except for less efficient reading ability and problem solving, an unexpected finding given that she was previously tested using the same measures. This may have occurred because she was quite fatigued during the testing session.

Further management

Dr Bingaman: "There is residual dysplasia in the deep white matter underlying the lesion. Resection there puts her at risk for visual field loss. EEG still shows the same findings. The discussion of whether to do a large temporal lobectomy versus invasive evaluation still applies. Typically, after a first failed surgery we do invasives, so I think that's a reasonable course of action."
Dr Morris: "Based on my prior series, I am sure there is residual dysplasia. The problem is in defining the borders of the dysplasia: she has already had surgery there, so the margins will not feel normal to the surgeon, and they already removed what looked grossly abnormal on the MRI, so it will be harder to determine margins for a new lesionectomy. You don't have an option to define those margins except by doing an invasive evaluation, acknowledging that interictal spikes may just reflect neuronal irritation from the grids and do not necessarily have to come out."
Dr Wyllie: "I am more interested in the postoperative MRI. The hole is much smaller than I anticipated based on the preoperative evaluation. It seems there are issues related to visual field loss. Were there other elements that contributed to this rather small resection?"
Dr Bingaman: "The mass effect present in the preoperative study is resolved, so it contributes to the resection looking

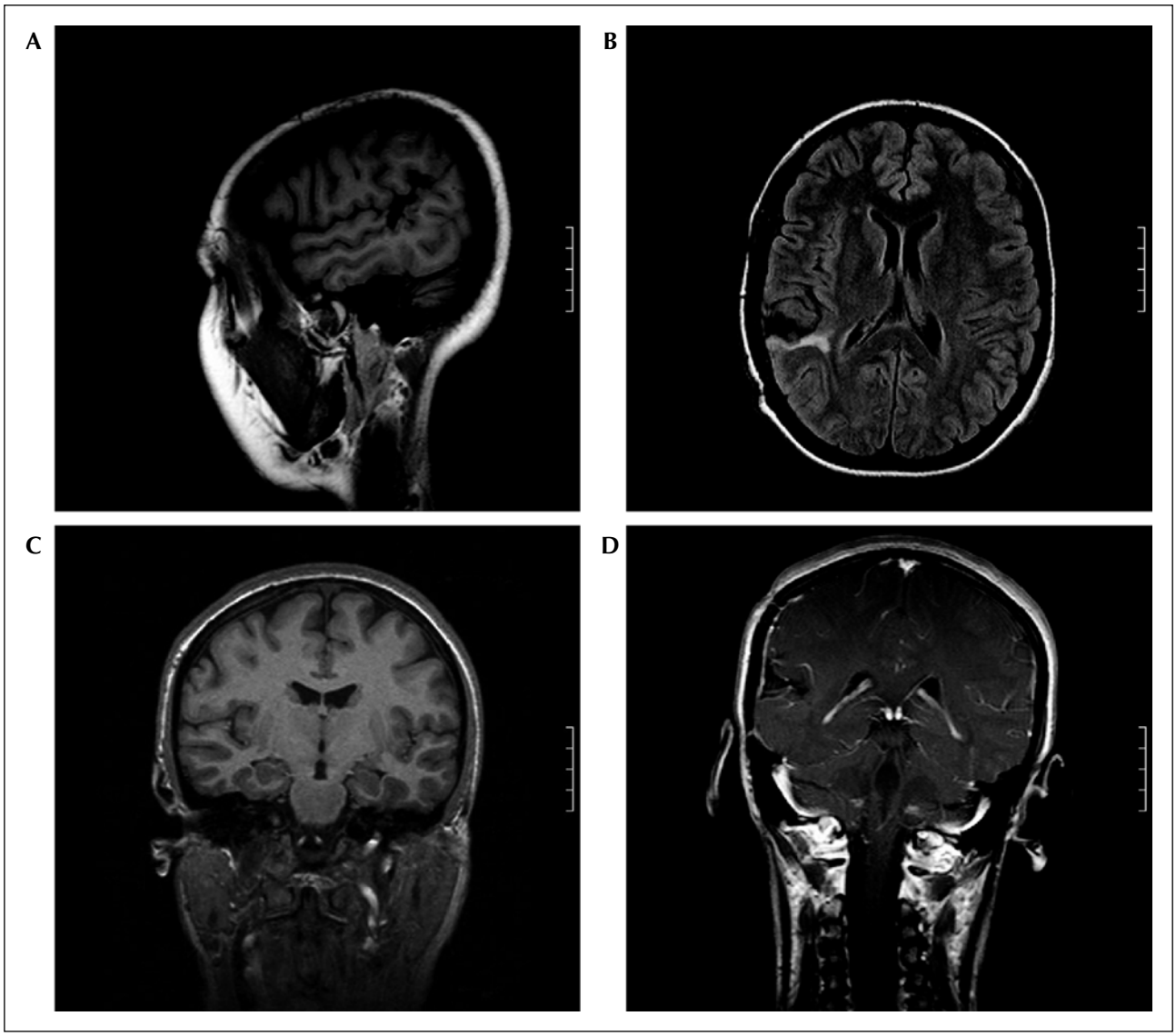


Figure 4. Sagittal T1, axial FLAIR, and coronal enhanced brain MRI showing limited lesionectomy.

smaller than it actually is. There is also the fear of injuring visual radiations in the deep white matter. The parietal extent of the lesion is around the sylvian fissure which is a highly vascularized structure, another potentially complicating factor."

Dr Bingaman: "How long do you wait in between evaluations?"

Dr Morris: "A period measured in weeks or months, but not years. I don't think there is an exact time."

Dr Bingaman: "According to Sperling's data, there was increased mortality risk in patients who failed a first surgery, especially when they their typical seizures recurred and at high frequency. So it might be useful not to wait too long."

Dr Lüders: "Usually we wait six months. If seizures recur like this, the chance of controlling them with medication is virtually zero."

Actual management

There was a six-month lag between the initial surgery and an invasive evaluation that consisted of subdural grids only *(figure 5)*. No depths were used.
Interictal spiking was predominantly anterior temporal *(figure 6)*.
A typical seizure was recorded. This started with an olfactory aura, followed by unresponsiveness, manual and oral automatisms, followed by postictal confusion.

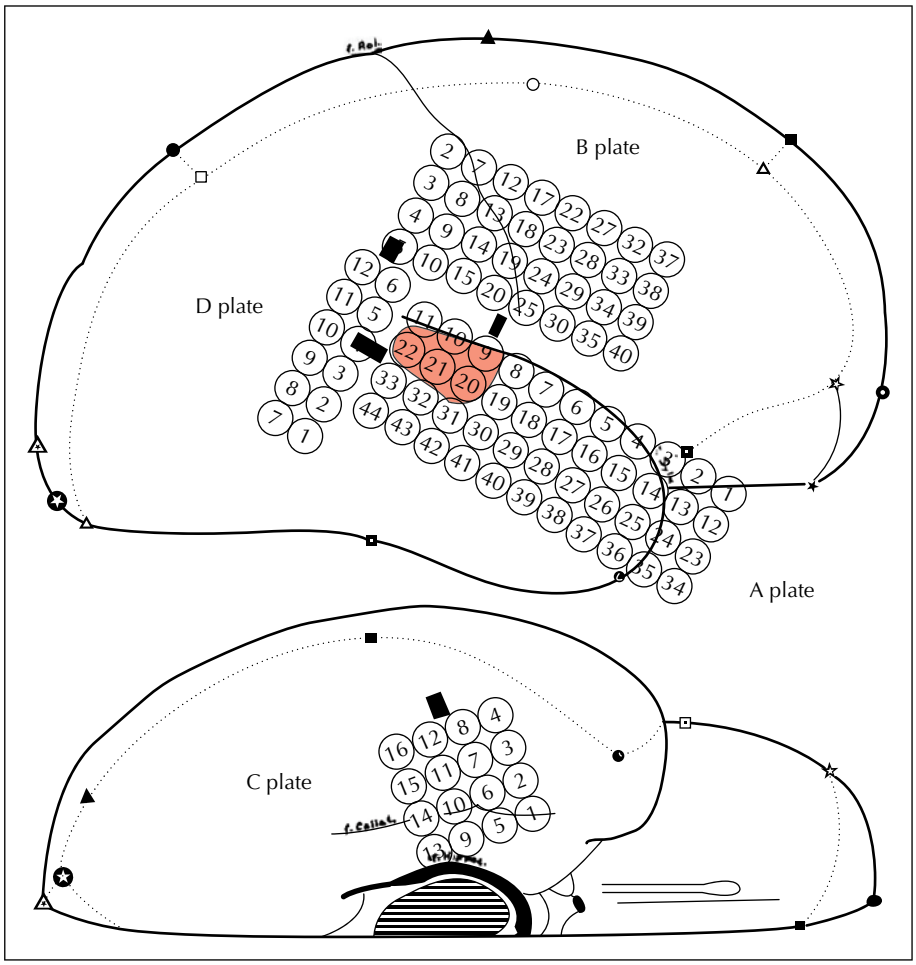


Figure 5. Cartoon showing lateral temporoparietal and basal temporal subdural grid coverage. Area of previous lesionectomy is highlighted in red.

The EEG onset was characterized by a rhythmic fast activity that evolved in amplitude over the lateral temporal contact SA17, followed by spread within 13 seconds to the anterior part of the lateral temporal A plate and the entire, subtemporal C plate. The frontoparietal and posterior temporoparietal plates remained electrically quiet *(figure 7)*. The electrode of ictal onset (SA17) was shown to be 3-4cm anterior to the margin of the lesionectomy by MRI reconstruction.

Proposed treatment

Extended lesionectomy

Dr Kotagal: "I am concerned because the ictal rhythm is starting 3-4cm anterior to the lesion in an area that appears normal on imaging. Is it then really starting from the depths of the lesion and just spreading to the apparent ictal onset? In that case, one might consider just performing a bigger resection of the tumor and surrounding gliosis while sparing the rest of the temporal lobe. This might also reduce the risk of a quadrantanopsia associated with a bigger resection."
Dr Bingaman: "If we remove all the white matter underneath the lesion and go deep to the ventricle, there is a risk of some visual field loss. Nowadays we would perform diffusion tensor imaging (DTI) to map the optic radiations, co-register it and follow it intraoperatively, although this might not necessarily help us avoid it."

Temporal lobectomy

Dr Morris: "We have to go with the results of the studies we ordered. We knew the limitations of grids, but we identified an active epileptogenic focus, so we can't ignore it. If we were going to ignore it, why put the electrodes in? Given what we have, I think she needs a large anterior temporal lobectomy, and then it will be interesting to see if, pathologically, she had or did not have hippocampal sclerosis. I would do a corticectomy around the lesion, but avoid all the deep white matter because I still think you will find dysplasia and or tumor back there. I think she will probably have some deficits on neuropsy-

chological measures upon retesting (chances about 20%), but she would probably not notice this."

Dr Bingaman: "The problem is that we still don't know whether the anterior temporal patterns we are seeing on the surface are originating from the depths of the lesion or from the mesial temporal structures. Nowadays, we would have put depth electrodes in the hippocampus and temporal pole to better assess those structures. But, given this information, I would also recommend a temporal lobectomy, going posteriorly to the previous lesionectomy margin together with some cleaning of the deep white matter."

Dr Diehl: "I agree with temporal lobectomy since all current evidence points to epileptogenicity anterior to the lesionectomy. Electrodes posterior to the lesion were quiet, suggest-

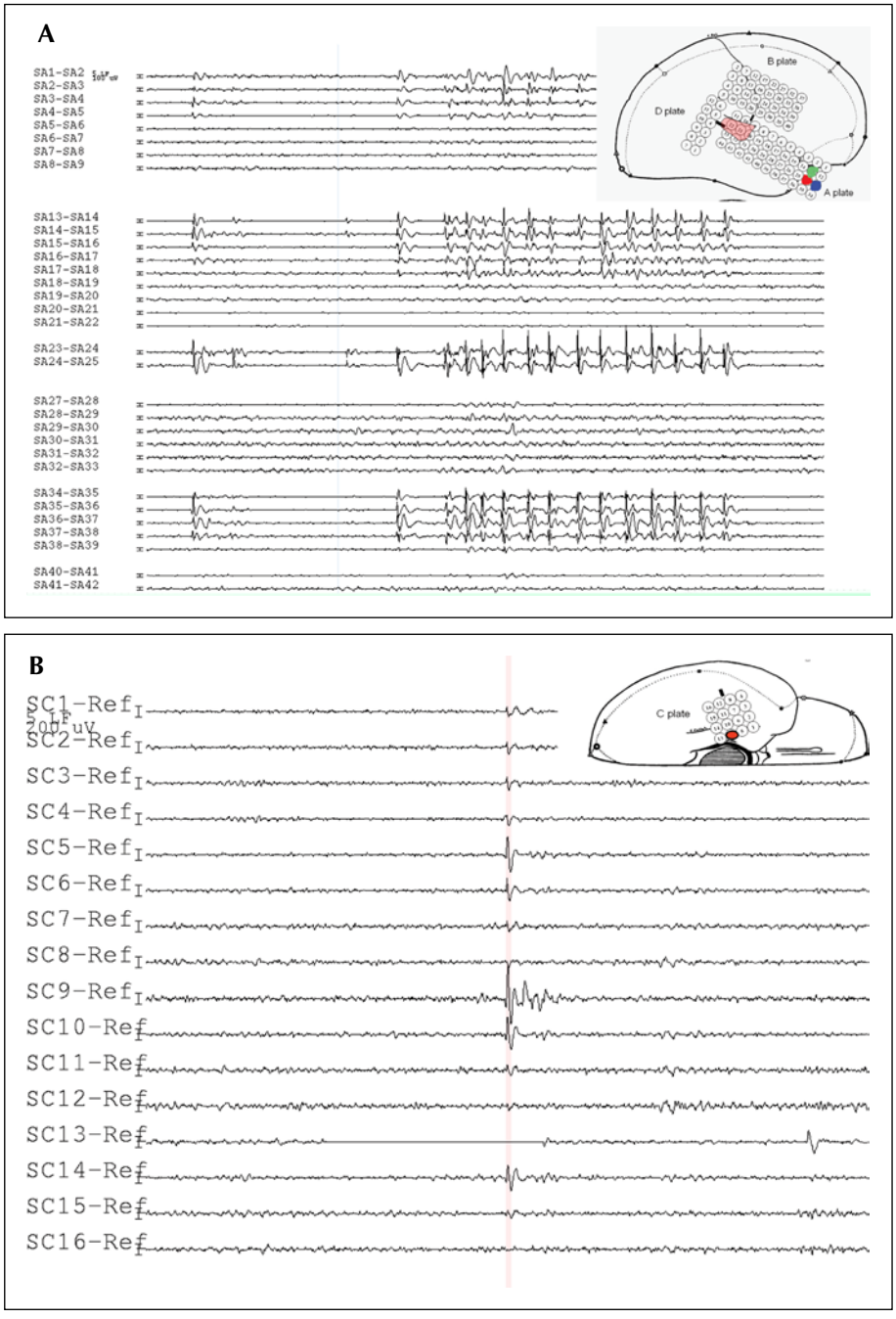
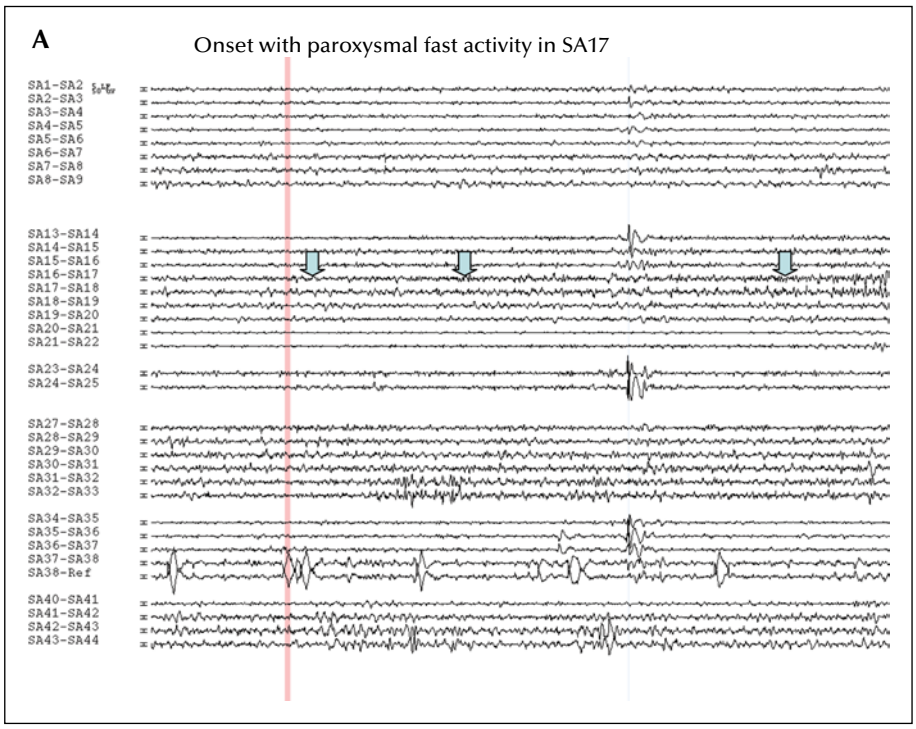
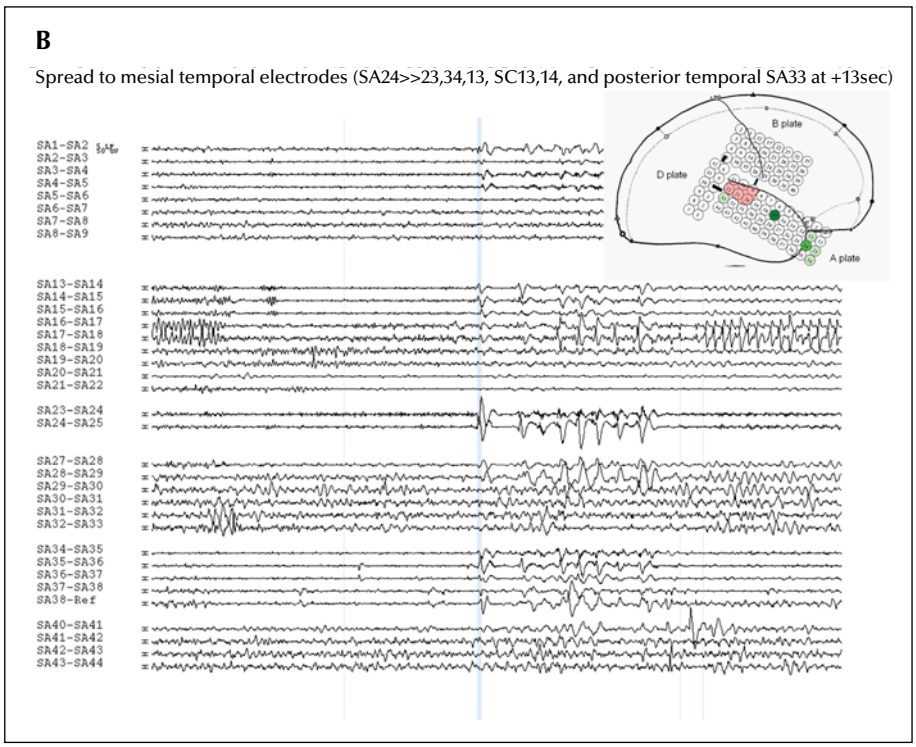


Figure 6. Interictal spiking seen predominantly in the right anterior temporal distribution (SA 24, and SC9, shown in red, 80% of spiking, followed by SA 13, green 15%, then SA24, shown in blue).

ing that that area does not need to be investigated further and that anterior resection is probably enough to treat the epilepsy. This would not compromise functions that Dr Bingaman is worried about if a new resection was to extend more superiorly in the parietal lobe."

Drs Alexopoulos, Bautista, and Lachwaani: "We agree on a temporal lobectomy. We can't give an exact chance of seizure-freedom, but we think it should be above 50% - probably around 60-70% - because we would have





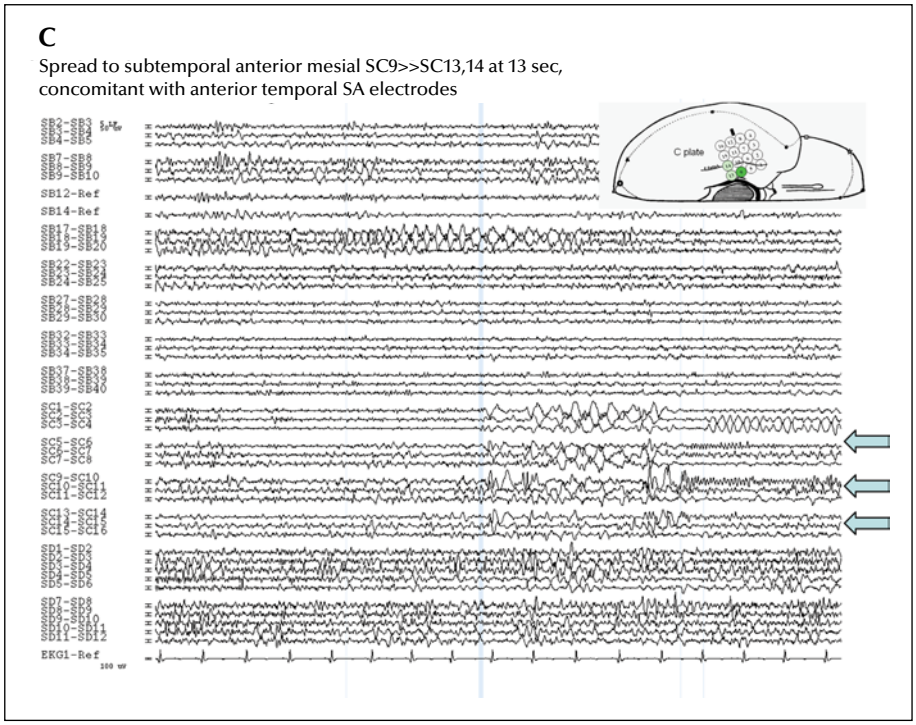


Figure 7. EEG seizure with onset manifesting as paroxysmal fast activity (solid arrows) in the right lateral temporal region (SA17, shown in dark green), with spread within 13 s to the anterior and basal temporal regions (electrodes shown in lighter green).

removed both imaging and electrical abnormalities recorded, and the mesial structures."
Dr Bingaman: "In general, the chances of a successful outcome following a first failed surgery and dysplasia are less than 50%. The nice thing about this case is that everything is anterior to the lesion, and it is non-eloquent brain so we can make a bigger hole."
Actual treatment: anterior temporal lobectomy and a separate temporoparietal resection around the previous lesionectomy.

Postoperative MRI *(figure 8)*

Dr Ruggieri: "We see a more extensive resection along the margins of the lesion itself superficially, and deeper in the white matter to include resection of the previous FLAIR hyperintensity that extended to the ependymal surface. Areas of hyperintensity on this study are probably related to postoperative changes. In addition, we see an anterior temporal lobectomy with volume studies showing complete resection of the amygdale, head and body of the hippocampus with some residual tissue from the body of the hippocampus mesially and posteriorly."
Dr Jeha: "Superimposing the preoperative and postoperative MRI reconstruction, we see the more extensive lesionectomy and the amount of brain tissue removed with the ATL, including SA17, the electrode of ictal onset."
Dr Wyllie: "What was the thought process behind leaving this island of tissue behind in between lesionectomy and ATL?"
Dr Bingaman: "Probably to avoid a field cut, a risk that is usually unacceptable to patients, especially if they're driving or want to drive."

Pathology *(figure 9)*

Dr Prayson: "Sections taken from the area around the previous lesionectomy show a cellular tissue populated mostly with CD68-(macrophage marker) positive cells, consistent with the reactive gliosis expected in an operative bed. Sections from the anterior temporal lobe show some chronic inflammation on the surface, likely related to the invasive monitoring, but no evidence of dysplasia and no evidence of tumor. The hippocampus looked normal. The section of amygdale had one aggregate of small neurons which we call hamartia, which probably represents a localized microscopic area of dysplasia of unkown significance."

Outcome

The patient has been seizure-free for five years now postoperatively, without any new neuropsychological deficits.

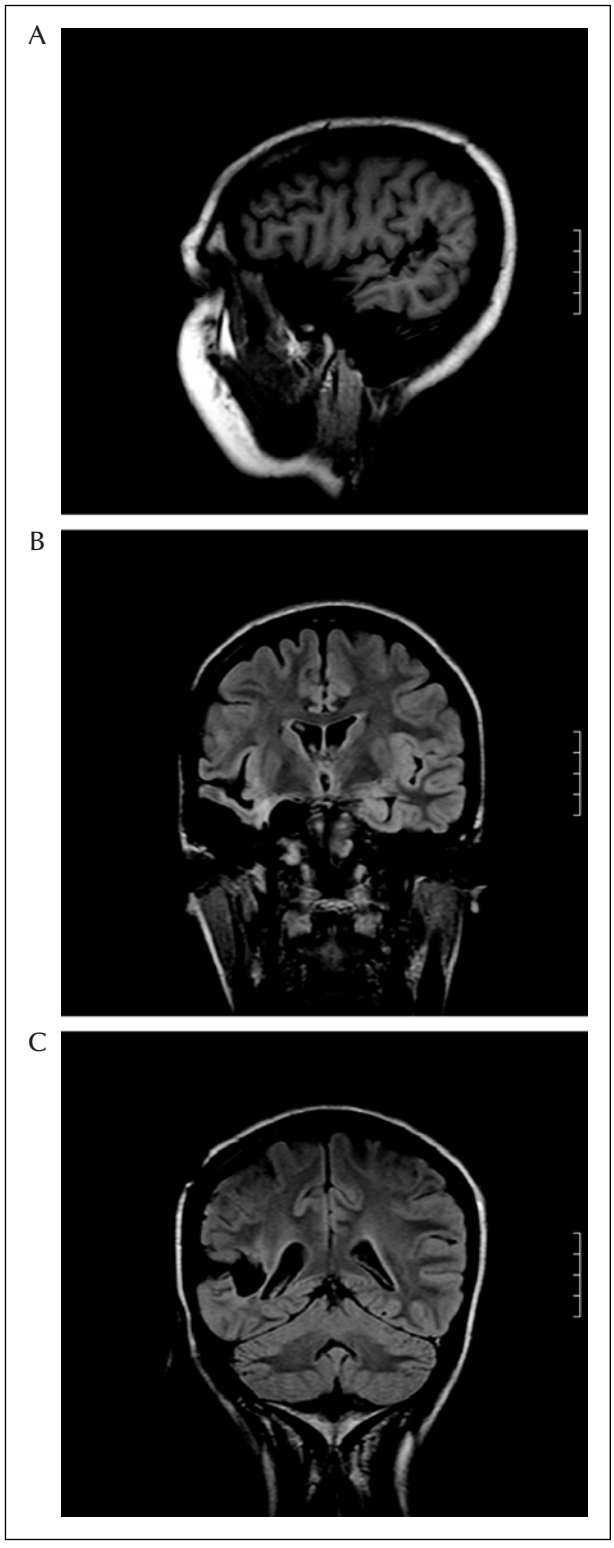


Figure 8. Postoperative MRI showing extension of lesionectomy and associated anterior right anterior temporal resection.

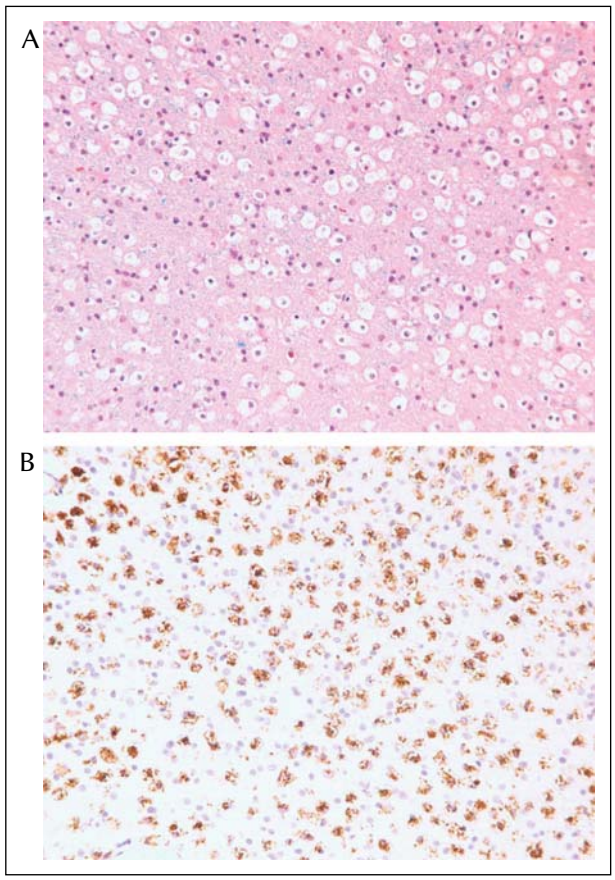


Figure 9. Pathological slides analyzed showing predominantly gliosis but no evidence of residual tumor.

Final outcome from the audience

Dr Dinner: "It is good that she had a seizure-free outcome, but it would have been tantalizing to see if the same result could have been achieved with a more extensive lesionectomy alone. I come back to Dr Kotagal's comments about inserting electrodes in the lesion to investigate the pathophysiology of the seizures in relation to the lesion."
Dr Kotagal: "This case illustrates the idea that if you have a lesion such as a DNET or a ganglioglioma, even in the non-dominant hemisphere, invasive evaluation might be helpful in defining the epileptogenic zone in relation to the lesion to produce a better outcome."
Dr Lüders: "I am not sure how helpful an invasive evaluation using grids alone would be. If the epileptogenic zone is within the depths of the lesion or in the tissue surrounding it, as in this case, ictal patterns recorded with surface grids may be somewhere else while actually representing a spread pattern. It could be different with depth electrodes."
Dr Bingaman: "I am still confused as to what cured this patient's epilepsy. Was it the more aggressive resection of the lesion? In that case, as Dr Wyllie suggested in the

beginning, a "bigger hole" might have resolved the issue to start with. Was it resection of the EEG abnormality? If so, could we have just biopsied the lesion and watched it, as we frequently do with those developmental lesions. One message is that these dysplasia cases are all unique with their metabolic and anatomic variations, and should be approached as such. But perhaps if we adopt a standardized approach for evaluation (such as the use of depths and grids) we will eventually learn enough about their pathophysiology to answer those questions."

Authors' conclusions

This case illustrates the frequent association seen between developmental tumors and cortical dysplasia (Prayson *et al.* 1993; Takahashi *et al.* 2005).

It is our impression that this patient's epileptogenic zone was in the tissue surrounding the lesion, likely in the deeper parts of the tumor, with the ictal temporal patterns recorded from the subdural plates representing spread rather than true ictal onset. This is supported by the normal histology of the resected temporal lobe and the absence of hippocampal sclerosis. We suggest that similar patients with developmental tumors should undergo extensive lesionectomies to avoid reoperation.

The invasive coverage in this case did not include depth electrodes within the lesion. This was therefore inadequate to answer the question of whether seizures started independently in the anterior temporal lobe or spread there from deeper parts of the tumor. We suggest that invasive evaluations of temporal lobe developmental tumors should include subdural electrodes and depth electrodes inserted in the depths of the lesion and in the hippocampus to evaluate appropriately the electrophysiological correlation between these structures.

Although multiple studies of patients with dual pathology have shown better outcomes with temporal lobectomy compared to lesionectomy (Li *et al.* 1999; Chan *et al.* 2006), an adequately designed invasive evaluation might allow sparing of the mesial temporal structures when the only "pathology" seen on imaging is the tumor itself. □

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