In the pursuit of the epileptogenic zone – listen carefully and look deeply

Fábio A. Nascimento¹, Visish M. Srinivasan², Sameer A. Sheth², Jay R. Gavvala¹

ABSTRACT – We report a 30-year-old right-handed man with a history of drug-resistant, non-lesional, childhood-onset focal epilepsy featuring (i) focal unaware seizures with left upper extremity automatisms and tonic posturing preceded by an aura of a ringing/beeping noise, and (ii) nocturnal hyperkinetic seizures. Non-invasive video-EEG, MEG, and PET were unable to delineate the epileptogenic zone (EZ) warranting an invasive investigation with bilateral depth electrodes (SEEG). SEEG data localized the EZ to the right superior temporal sulcus (STS) and right superior temporal gyrus (STG), wherein the auditory cortex lies, with subsequent ictal spread to anterior topography including the operculo-insular region. This hypothesis explained the patient’s semiology consisting of focal aware seizures featuring auditory phenomena and nocturnal hyperkinetic seizures. Our multi-disciplinary team elected to proceed with a resection of the posterior right STG guided by electrocorticography (ECoG). Prior to resection, ECoG identified seizures arising from the peri-sylvian region, seemingly discordant to previous SEEG data. Following resection of the posterior right STG, ECoG continued to show seizures from contacts overlying the parietal operculum. It was not until the cortex was resected, at the depth of the right STS, that ECoG no longer showed epileptiform abnormalities. Pathology revealed focal cortical dysplasia type 1A.

Key words: epilepsy; seizure semiology; stereo-electroencephalography; SEEG; electrocorticography; ECoG; epilepsy surgery

Case presentation

A 30-year-old right-handed man was referred to our center for evaluation of drug-resistant, childhood-onset focal epilepsy. His initial seizures started at the age of eight years and were characterized at onset by a ringing or beeping noise followed by impairment of awareness. Since his teenage years, he has had both nocturnal and diurnal seizures. The former were nightly and occurred primarily upon transitioning in and out of sleep; they were characterized by hyperkinetic movements without any preceding aura or warning. Diurnal seizures were characterized by a feeling that “everything feels distant” along with perceived loss of focus and a lifting sensation in his chest. Occasionally, these progressed to impairment of awareness and forceful picking movements with his left hand followed by stiffening of the left upper extremity. Progression to bilateral tonic-clonic activity occurred occasionally, and postictal symptoms included cognitive slowing for roughly 15 minutes. At presentation, his anti-seizure medications included lamotrigine 250 mg bid, carbamazepine 600 mg bid, and perampanel 10 mg daily. Neurological examination was normal.
**Hypothesis**

In terms of lateralization, tonic posturing in the left upper extremity reliably suggests right hemisphere seizure onset [1, 2]. In terms of localization, semiologic features suggest temporal, frontal, or operculo-insular onset. The former hypothesis is based on the presence of automatisms and auditory/cognitive manifestations [2]. Within the temporal lobe, gestural automatisms are indicative of medial origin [3] whereas auditory manifestations (especially when simple in nature, including “buzz” sounds and “noises”) are indicative of lateral neocortical origin [2]. The presence of nocturnal seizures with hyperkinetic behavior may represent frontal [4] or operculo-insular onset [5].

**Non-invasive workup**

Brain 3T MRI (seizure protocol) with and without contrast was unremarkable. Long-term video-EEG monitoring revealed interictal runs of semi-rhythmic sharp waves over the right posterior temporal region (T8, P8), rare left temporal sharp waves, and intermittent focal polymorphic slowing over the right temporo-parietal region. The patient’s habitual nocturnal seizures were captured; these were characterized by axial predominant hyperkinetic motor movements, primarily demonstrated as proximal stereotypies with left upper extremity tonic posturing. Electrographically, seizures had right hemispheric onset, however, due to EMG artifact, it was not possible to perform further localization.

Interictal FDG-PET evaluation was normal. Functional MRI lateralized language to the left hemisphere. Magnetoencephalography (MEG) identified a primary dipole cluster in the mid to posterior right superior temporal sulcus (STS) (figure 1A, B) with secondary clusters in the right insula, right inferior temporal sulcus, and right lateral occipito-temporal sulcus.

**Hypothesis**

Semiology broadly suggested a right frontal, operculo-insular, or temporal onset. While the earliest semiologic feature of Phase I evaluation (hyperkinetic movements) would suggest either a frontal or insulo-opercular onset, the prior history of an initial auditory aura would seem to suggest a temporal lobe onset, specifically the superior temporal gyrus (STG) or temporal operculum. Temporal epilepsies, especially the temporo-perisylvian subgroup of temporal epilepsies, are known to have a rich connectivity with extratemporal cortices including the frontal lobe - such as the frontal operculo-insular and orbitofrontal cortices [6]. Propagation from the temporal region to the frontal or operculo-insular region would potentially explain the semiology seen in our patient.

In summary, based on the semiology, EEG, MEG and the known connectivity common to the temporal region, the unifying hypothesis localized the EZ to the right temporal lobe with subsequent seizure propagation to the right frontal or operculo-insular region.

![Figure 1. MEG and SEEG data. MEG shows a primary dipole cluster in the mid (A) to posterior (B) right superior temporal sulcus. Brain MRI/reconstruction (C-F) shows the scheme of depth electrodes; selected electrodes are labeled. Pink depth electrode (D-F) represents RHP.](image-url)
Invasive workup

The prevailing hypothesis localized the EZ to the right temporal and/or frontal and/or operculo-insular region; left hemispheric onset could not be excluded due to interictal left temporal epileptiform discharges on scalp EEG. Subsequent investigation with intracranial EEG monitoring was warranted for further localization of the EZ. A stereotactic EEG (SEEG) approach rather than subdural grid electrodes (SDG) was chosen because of the need to sample deeper structures within the bilateral hemispheres over the right fronto-temporal and left temporal regions. The stereotactic electrodes placed are listed in table 1.

Near-constant repetitive spiking was seen over the deepest contacts of the depth electrode (RHP), sampling the right superior temporal sulcus (STS) (figure 2, upper panel). Seizures featured habitual nocturnal episodes of arousal and hyperkinetic manifestations associated with rhythmic slowing, followed by low-voltage fast activity at RHP (electrodes covering the right posterior STS) (video sequence and figure 2, lower panels), before spreading to adjacent electrodes – RIL, RT2, and RIA (video sequence). Notably, hyperkinetic movements were seen after ictal spread to RIL, RT2, and RIA electrodes, which sampled operculo-insular regions.

Interpretation of invasive workup

The additional SEEG data localized the EZ to the mesial, deep contacts of the right posterior STS and STG – wherein the auditory cortex lies [7]. It also revealed seizure propagation to anatomic regions that are intimately connected, specifically the operculo-insular regions (RIL, RT2 and RIA). This hypothesis explains the patient’s initial semiology with auditory manifestations followed by hyperkinetic seizures.

Treatment

The consensus recommendation from a multi-disciplinary surgical conference was for resection of the right posterior STG guided by intraoperative electrocorticography (ECoG). The interictal pattern seen on SEEG was felt to represent an underlying cortical dysplasia, however, the spatial extent of the dysplasia was not clearly defined. Intraoperative ECoG was favored in order to define the extent of the EZ and resection. Frameless stereotactic neuronavigation was used to plan the craniotomy in the posterior peri-sylvian region. Multimodal neuronavigation was utilized to identify the prior location of the SEEG depth electrodes. Prior to the resection, a subdural grid was arrayed over the right lateral temporal region. Three seizures were recorded arising from grid electrodes 8-9 and 12-17, which corresponded to the peri-sylvian region (including the supra and infra-sylvian regions) – seemingly discordant in comparison to previous SEEG data (figure 3A; middle panel). The right posterior STG was then resected. However, ECoG continued to show ictal patterns that arose from electrodes that seemed to correspond to the inferior parietal lobule at the parietal operculum. This area was spared but further

<table>
<thead>
<tr>
<th>Brain coverage</th>
<th>Entry</th>
<th>Target</th>
<th>Depth electrodes</th>
<th>Jackbox name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right temporal</td>
<td>Right MTG</td>
<td>Hippocampal head</td>
<td>RMTG-HCH</td>
<td>RAM</td>
</tr>
<tr>
<td></td>
<td>Right MTG</td>
<td>Hippocampal body</td>
<td>RMTG-HCB</td>
<td>RHB</td>
</tr>
<tr>
<td></td>
<td>Right STS</td>
<td>Posterior STS</td>
<td>RpMTG</td>
<td>RHP</td>
</tr>
<tr>
<td></td>
<td>Right ITG</td>
<td>Basal temporal</td>
<td>RTG-BT</td>
<td>RF3</td>
</tr>
<tr>
<td>Right frontal</td>
<td>Right IFG</td>
<td>Orbitofrontal</td>
<td>RIFG-OFC</td>
<td>ROF</td>
</tr>
<tr>
<td></td>
<td>Right MFG</td>
<td>Anterior Insula</td>
<td>RMFG-aINS</td>
<td>RIA</td>
</tr>
<tr>
<td></td>
<td>Right MTG</td>
<td>Anterior Insula</td>
<td>RaMTG-aINS</td>
<td>RT2</td>
</tr>
<tr>
<td>Right insula</td>
<td>Right STG</td>
<td>Middle Insula</td>
<td>RpSTG-mINS</td>
<td>RIL</td>
</tr>
<tr>
<td></td>
<td>Right SFG</td>
<td>Posterior Insula</td>
<td>RSFG-pINS</td>
<td>RPI</td>
</tr>
<tr>
<td></td>
<td>Right SFG</td>
<td>Anterior Cingulate</td>
<td>RSFG-ACC</td>
<td>RF1</td>
</tr>
<tr>
<td>Right cingulate</td>
<td>Right IPL</td>
<td>Posterior Cingulate</td>
<td>RIPL-PRFCC</td>
<td>RIP</td>
</tr>
<tr>
<td>Left temporal</td>
<td>Left MTG</td>
<td>Hippocampal head</td>
<td>LMTG-HCH</td>
<td>LHA</td>
</tr>
<tr>
<td>Left insula</td>
<td>Left MFG</td>
<td>Insula</td>
<td>LMGF-INS</td>
<td>LF2</td>
</tr>
</tbody>
</table>

STS: superior temporal sulcus; MTG: middle temporal gyrus; STG: superior temporal gyrus; ITG: inferior temporal gyrus; IFG: inferior frontal gyrus; MFG: middle frontal gyrus; SFG: superior frontal gyrus; IPL: inferior parietal lobule.
**Figure 2.** Interictal and ictal SEEG. Upper panel: interictal bipolar montage showing RHP:1-3 spiking (red box) at 2-3 Hz. Middle and lower panels: ictal bipolar montage showing low-voltage fast activity at RHP:1-2 (onset at red arrow, evolution at purple arrow). Sensitivity: 75 μV/mm; LF: 0.5-1 Hz; HFF: 600 Hz.
Figure 3. (A, B) Intraoperative images prior to (A) and after (B) resection; depth electrode RHP entry point is indicated by the star. Middle panel: Ictal ECoG prior to resection shows repetitive spiking at electrodes 12-17 and 8-9, and less prominently at 10-11. Lower panel: ECoG following resection without any epileptiform abnormalities. Note that the temporo-occipital-parietal junction was not entirely sampled on ECoG. STG: superior temporal gyrus; SF: Sylvian fissure; IPL: inferior parietal lobule; ANT: anterior; POST: posterior.
ECoG revealed seizures arising from the superficial cortex at the bottom of the STS was performed (figure 3B). Resection of the parenchyma at the depth of the sulcus resulted in resolution of the previously described epileptiform activity (figure 3; lower panel). Pathology identified focal cortical dysplasia (FCD) type 1A. The patient did not report any functional deficit postoperatively and at the last follow-up visit.

**Discussion**

This complex focal epilepsy case teaches us invaluable concepts related to epilepsy. From a clinical standpoint, we learn the importance of carefully obtaining seizure semiology data and interpreting it in the context of seizure propagation networks. The former is illustrated by how our patient's ictal auditory manifestations identified the auditory cortex (hence the posterior STG) as a likely EZ location, whereas the latter by how his hyperkinetic seizures suggested ictal spread to frontal networks including the operculo-insular region. Notably, seizure propagation to anterior structures (including the orbitofrontal and operculo-insular regions) is mostly remarkable in temporal seizures in which the EZ lies either in mesio-lateral or temporoperisylvian topographies [6]. We are also reminded that every patient with drug-resistant epilepsy [8] should be promptly referred to an epilepsy center for evaluation.

From a diagnostic standpoint, we learned that invasive EEG monitoring should be pursued in patients with drug-resistant epilepsy whose EZ cannot be delineated by semiology and non-invasive diagnostics (including video, scalp EEG, and neuroimaging). Moreover, it is important to reinforce the distinct ability of SEEG to record electrical activity from deeper sources of the brain, including the depths of sulci, and sample large (and bilateral, if needed) cortical regions thereby revealing underlying seizure networks.

With the increased utilization of SEEG, the pre-implantation planning increasingly becomes more important. This SEEG evaluation was performed shortly after our institution adopted SEEG. While it was effective in localizing the EZ, it was not as informative in defining its extent. Several electrodes in the STG as well as the suprasylvian cortex would have provided optimal assessment of the extent of the EZ. As a result of the limited SEEG coverage, we had to rely on intraoperative ECoG to define the implicated cortex. As shown in the ECoG, ictal patterns can reflect falsely localizing propagation to superficial cortex, and it is not without monitoring of the deeper cortex that the true epileptogenic cortex is revealed. In our case, ECoG revealed seizures arising from the superficial cortex (grid electrodes 8-9 and 12-17) although we knew, based on SEEG data, that the seizure source was located deep in the posterior STS topography (mesial contacts of depth electrode RHP). Lastly, by showing our patient's SEEG pattern over the posterior STS, characterized by near-continuous 2-to-5-Hz spike-wave discharges, we reviewed this EEG pattern typically associated with FCD [9].

This case illustrates the systematic approach used when caring for patients with drug-resistant epilepsy. The ability to retrospectively analyze this patient's diagnostic odyssey and therapeutic intervention gives us an opportunity to review key concepts related to epilepsy care and, hopefully, improve seizure outcomes in these patients.

**Disclosures.**

FAN is a member of the Epileptic Disorders Editorial Board. VMS, SAS, and JRG report no disclosures relevant to the manuscript.

**References**

In the pursuit of the epileptogenic zone

Legend for video sequence

A habitual seizure during Phase 2 characterized by awakening followed by axial hyperkinetic movements and left upper extremity tonic posturing. SEEG shows initial interictal RHP:1-3 spiking, followed by RHP:1-3 rhythmic 3-4 Hz slowing, RHP:1-3 low-voltage fast activity, and ictal spread to RIL:1-6, RT2:3-8, and RIA:1-4.

Key words for video research on www.epilepticdisorders.com

Phenomenology: aura (auditory), hypermotor, motor seizure (complex)
Localization: temporal lateral, temporal (right), non-dominant hemisphere
Syndrome: focal non-idiopathic temporal lobe epilepsy
Aetiology: focal cortical dysplasia type 1

TEST YOURSELF

(1) Where is the auditory cortex located?
   A. In the superior temporal gyrus.
   B. In the middle temporal gyrus.
   C. In the inferior temporal gyrus.
   D. In the uncinate gyrus.
   E. In the fusiform gyrus.

(2) Which of the following may be associated with repetitive, high-amplitude, fast spikes followed by high-amplitude slow waves on stereo-EEG?
   A. Subarachnoid hemorrhage.
   B. Hypoxic-ischemic brain injury.
   C. Hypothalamic hamartoma.
   D. Hippocampal sclerosis.
   E. Focal cortical dysplasia.

(3) Which of the following associated with stereo-EEG is of benefit?
   A. Ability to sample bilateral locations in the brain.
   B. Ability to record electrical activity from deeper sources in the brain.
   C. Ability to sample large locations in the brain.
   D. Ability to identify seizure networks.
   E. All the above.

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section “The EpiCentre”.