Clinical impact of a high-frequency seizure onset zone in a case of bitemporal epilepsy

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Received February 12, 2008; Accepted July 3, 2008

ABSTRACT – High-frequency activity has been described as having a role in the initiation of epileptic seizures. The case of a patient with refractory bitemporal epilepsy is presented. Extraoperative monitoring with depth and subdural electrodes revealed an ictal pattern with a build-up of high-frequency (> 80 Hz) activity originating in the cortex, with spread to both hippocampi. This observation was only revealed with the use of high-pass filtering, and represented crucial information that significantly influenced the decision about the side, localization and extent of resection. Removal of the cortex generating high-frequency activity, led to cessation of seizures in this patient. Current knowledge about the role of high-frequency activity and the case presented here support the importance of recording with equipment capable of detecting fast activity during the presurgical invasive monitoring. An active search for a high-frequency seizure onset zone in patients with structurally-unaffected hippocampi may improve the outcome beyond that possible with conventional bandwidth, invasive EEG recordings. [Published with video sequences]

Key words: bitemporal epilepsy, ictal high-frequency activity, seizure onset zone, ictogenesis

Several recent human studies have described the presence of high-frequency activity at the onset of seizures or preceding them (Allen et al. 1992, Fisher et al. 1992, Jirsch et al. 2006, Worrell et al. 2004). Experimental studies both in vivo (Bragin et al. 1999b) and in vitro (Bikson et al. 2003, Dzhala and Staley 2003) have also demonstrated that high-frequency activity occurs specifically in epileptic foci. However, high-frequency recording during invasive clinical investigation, and the assess-
vent of wide-band data, are still not routine practice. A case in which identification of high-frequency activity significantly influenced the decision about selection of the appropriate surgical approach is presented, with an analysis of the characteristics of this activity.

Case presentation

The patient is a 49-year-old woman whose seizures started at the age of 32 years. The seizures occurred with a frequency of 5-10 per month and were refractory to four antiepileptic drugs. No history of any possible initial precipitating injury or risk factors for epilepsy was present. Her medical history was unremarkable, except for cholecdocholithiasis with pancreatitis, followed by cholecystectomy at the age of 35 years. Habitual seizures were recorded during video-EEG monitoring and were classified as complex partial seizures with early oroalimentary automatisms without an aura. Interictal EEG was characterized by frequent spikes over the right fronto-temporal region and independent discharges over the left fronto-temporal region. Seizures started with attenuation of background activity lasting three to six seconds, followed by rhythmic discharges with a frequency of 4 Hz and reaching maximum amplitude in both fronto-temporal regions (electrodes F9, F10, T9, T10). In one seizure, this pattern first occurred over the right fronto-temporal area, with involvement of the contralateral side within one second. MRI demonstrated multiple, small, non-specific lesions in the white matter of both hemispheres and a small cystic lesion in the pole of the left temporal lobe (figure 2). The lesions were suspected to have had a vascular origin. Both hippocampi were assessed as normal in volume and signal on MRI, however, single-voxel MR spectroscopy revealed metabolic abnormalities in both hippocampi, with right-side predominance. FDG-PET was normal (figure 3). Neuropsychological examination revealed impairment of non-verbal intellect, pathological occipital screening and mild, immediate verbal memory impairment. The intracarotid amobarbital procedure demonstrated left hemisphere speech dominance and asymmetry in memory performance in favour of the left temporal lobe. Based on these examinations, the diagnosis of possible bitemporal epilepsy was concluded and invasive exploration suggested. After obtaining informed consent, the patient was implanted with bilateral, hippocampal depth electrodes from the occipital approach and with subdural strips over the right and left temporopolar cortex (figure 4). Data were low-pass filtered < 300 Hz and digitized with a sampling frequency of 1 kHz. Invasive recordings were characterized by the presence of independent, interictal epilepti-

![Figure 1](ictal scalp EEG - initial attenuation of background activity followed by rhythmic discharges with a frequency of 4 Hz and reaching a maximum of amplitude in both fronto-temporal regions (electrodes F9, F10, T9, T10).)
form discharges in all the areas covered, bilateral synchronous discharges were less frequently observed. At the left temporal pole, repetitive epileptiform discharges were present.

Following drug withdrawal, a typical seizure was recorded (figure 5A) that started in the left hippocampus, and was characterized by isolated epileptiform discharge followed by a build-up of low-amplitude rhythmic activity at 33 Hz, which gradually slowed down and increased in amplitude until it transformed into rhythmic activity at 13 Hz. Three seconds after the onset in the left hippocampus, rhythmic activity started in the contralateral hippocampus, and one second later spread to both temporopolar regions. However, thorough examination of the recording using a high-pass filter with a cut-off frequency of 80 Hz and higher gain, revealed that left hippocampal onset was preceded by a build-up of high-frequency activity (from 85 to 140 Hz) lasting 24 s in contacts adjacent to the cystic lesion in the left temporal pole (figures 5B, 6). There was no aura reported by the patient. The initial ictal semiology

**Figure 2.** Preoperative MRI - small cystic lesion in the pole of the left temporal lobe (white arrow). A) Coronal section. T1-weighted image. B) Coronal section. T2-weighted image. C) Transversal section. T2-weighted image. D) Transversal section. FLAIR image (Department of Radiological Techniques, Motol Hospital, Prague).
was oroalimentary automatisms that appeared only when the seizure activity spread to the hippocampus (see video sequence). Visual review of all the recordings using a high-pass filter later revealed another high-frequency build-up over the left temporal pole that did not spread to the hippocampus and was not accompanied by a clinical seizure. Because of these findings, and of preserved verbal memory, the patient underwent a very restricted resection in the left temporal pole that included the cortex generating the high-frequency activity and the adjacent small cystic lesion (figure 7). Histopathological examination of the lesion suggested a possible postmalacic pseudocyst; no features of malformation of cortical development were identified in adjacent cortex. At one year follow-up, the patient was seizure-free.

Data from the invasive recordings were retrospectively analyzed by Morlet wavelet analysis (Li et al. 2007) to obtain power spectra and spectrograms. Summated power over the frequency band 80-250 Hz was calculated for individual channels. These data showed that both seizures started with a build-up of fast activity localized only to the left temporopolar electrode No. 4 (figure 8) and later spread to adjacent electrodes No. 3 and 2. Interictal high-frequency activity summated power (80-250 Hz) was maximal in the left hippocampus and in the left temporal pole electrode adjacent to the cystic lesion.

Figure 3. Interictal FDG PET - no region of significant hypometabolism was found. A) Transversal section. B) Coronal section (PET Center, Na Homolce Hospital, Prague).

Figure 4. Position of subdural strip contacts in relation to the cystic lesion. A) MRI coronal section. Build-up of high-frequency activity started in Tpolsin4 electrode and later spread to Tpolsin3 electrode, covering the temporo-polar neocortex adjacent to the cystic lesion. B) Transversal section. T1-weighted images (Radiology Department, Central Military Hospital, Prague).
Interictal, high-frequency activity was also observed in the right hippocampus. In contrast, summated power was low in the right temporal cortex. Interictal high-frequency activity occurred superimposed on the interictal discharges. A spatial map of summated power and an analysis of synchrony (linear cross-correlation) demonstrated that the ictal high-frequency activity is a very localized process that does not extend over large distances (figure 8).

Figure 5. A) Raw data from invasive electrodes. The seizures start with discharge in the left hippocampal electrode (AHsin3) followed by a build-up of low-amplitude fast activity (33 Hz), which then transforms into high-amplitude rhythmic activity with rapid spread to the right hippocampus and right and left temporal cortex. An asterix marks the onset of clinical symptoms characterized by orofacial and bilateral hand automatisms. B) Band-pass (80-250 Hz) filtered signal – identical time period as in A. The figure shows that left hippocampal onset is preceded by a long-lasting build-up of high-frequency activity in the left temporopolar electrodes (Tpolsin4 and Tpolsin3), not obvious in the raw data.
Discussion

Several clinical studies demonstrating the important role of high-frequency activity in epilepsy and seizure genesis have been published (Allen et al. 1992, Bragin et al. 1999a, Fisher et al. 1992, Traub et al. 2001, Worrell et al. 2004). However, the majority of these studies are retrospective. In our patient, the presence of long-lasting, high-frequency build-up was used as crucial diagnostic information that influenced the selection of the surgical procedure. The resection focused mainly on the removal of the high-frequency (> 80 Hz) seizure-onset zone adjacent to a small cyst, which was initially not considered as the epileptogenic lesion. This approach led to seizure-freedom and confirmed the leading role of the temporopolar cortex in the initiation of hippocampal seizures (Chabardes et al. 2005), which were responsible here for the ictal symptomatology. Removing mainly the cortical region generating the high-frequency activity is in accordance with the observation that fast activity is highly specific for the epileptic foci and, including such areas into the resection, is associated with a more favourable outcome. However, more work is needed to define which high frequencies should be accepted as specific for the seizure-onset zone and which may be neglected. Bragin et al. (1999a) stressed that frequencies of 250-500 Hz are highly specific for the epileptogenic region but lower frequencies, around 100 Hz, have also been described in

Successful treatment in this case depended on two main factors. The first was optimal placement of the recording contacts close to seizure onset zone. High-frequency seizure onset was a very focal process localized only in one...
or two electrodes, unlike the subsequent high-amplitude potentials that spread over several electrodes and involved large brain areas. Minor changes in electrode position would possibly prevent detection of the high-frequency onset. The second important factor was the ability to record high-frequency signals. Jirsch et al. demonstrated that the invasive macroelectrodes used routinely are capable of recording high-frequency activity up to 500 Hz at the onset of seizures (Jirsch et al. 2006). However, smaller electrodes may improve detection of the higher frequencies (Worrell et al. 2006). Therefore, the main issue is availability of equipment to record wide-band activity at high sampling frequencies. Using narrow-band filters and low sampling frequency setups may prevent high-frequencies being recorded. Then it can manifest as local attenuation of background activity. The failure to detect the high-frequency seizure onset in our patient could have led to the selection of an inappropriate surgical resection targeting mainly the left hippocampus, with the risk of verbal memory decline, or to the denial of the surgical treatment because of this risk. In our opinion this case, together with the work of others, should encourage greater use of invasive recordings using wide-band setups and higher sampling frequency. Thorough analysis of the recorded data and an active search for the presence of high-frequency activity (by visual inspection using digital filters or with help of signal processing techniques) should be regular part of assessment of intracranial recordings.

Acknowledgments. This work was supported by the Epilepsy Research Foundation UK and grant IGA MZ CR NR/8843-4. The authors would like to thank all physicians participating in the preoperative evaluation and postoperative care of the patient.

Legend for the video sequence
Video of the seizure that was captured during invasive recording.

References


