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Withdrawal seizures *vs* on-medication seizures: an intracranial EEG recording case report

Mohamed Khateb[1], Anat Grinfeld[2,3], Michal Weiler-Sagie[4,5] and Moshe Herskovitz[1,5*]

Abstract

Background: It has long been an interesting question of whether withdrawal seizures in epileptic patients differ from habitual seizures in terms of semiology and electrophysiology.

Case presentation: Here, we addressed this issue in a 40 year-old woman with drug-resistant focal epilepsy monitored by presurgical intracranial EEG. As a part of this routine pre-operative investigation, anti-seizure medications (ASMs) were halted; as a result, multiple withdrawal seizures were recorded before ASM readministration. During 4 days of invasive monitoring, we noticed three different phases in seizure organization: *Acute withdrawal seizure (AWS):* The first recorded seizure 10h after the implantation; the *stabilized withdrawal seizures (SWS)*: seven habitual seizures recorded from 24h post implantation to readministration of ASMs; and the *Non-withdrawal seizures (NWS)*: ten seizures recorded 24h after readministration of ASMs. AWS and SWS had the same semiology and same epileptic network, but the propagation time from the temporal pole to the para-hippocampal gyrus (PHG) and hippocampus ranged from no latency in AWS to up to 50 s in SWS. NWS were electrographic seizures, without any apparent clinical manifestation. Seizure onset in this type of seizure, as in the first two types, was in the temporal pole. However, NWS could last up to 3 min without involving the PHG or hippocampus.

Conclusions: We concluded that in acute withdrawal seizures the propagation time of epileptic activity is significantly reduced without affecting ictal organization network or semiology. Furthermore, ASM in this case had a remarkable influence on propagation rather than initiation of epileptic activity.

Keywords: Withdrawal seizures, Intracranial EEG monitoring, Anti-seizure medication

Background

Withdrawal of anti-seizure medications (ASMs) is a widely accepted practice during pre-surgical assessment of epileptic patients, especially under long-term video-EEG monitoring (LTVEM). Rapid withdrawal of ASMs is used to enhance the yield of LTVEM. On the other hand, previous studies demonstrated that the rapid withdrawal of ASMs during pre-surgical LTVEM could be problematic and may impair the EEG validity and possibly lead to unnecessary risks and investigations during workup [1, 2]. Previous small studies have addressed the important issue of possible changes induced by the rapid ASM withdrawal. ASM withdrawal has been suggested to largely affect semiology as well as electrophysiological features of seizures such as propagation, ictal and inter-ictal findings [3–5]. For example, false localization was reported in a woman with epilepsy originating from the left frontal region because of ASM withdrawal due to contralateral and bitemporal spread of frontal epileptic activity [1]. On the other hand, other studies claimed only a minor influence, if any, on electrographic features or semiology [6, 7].

*Correspondence: m_herskovitz@rmc.gov.il
[1] Department of Neurology, Rambam Health Care Campus, Haifa, Israel
Full list of author information is available at the end of the article

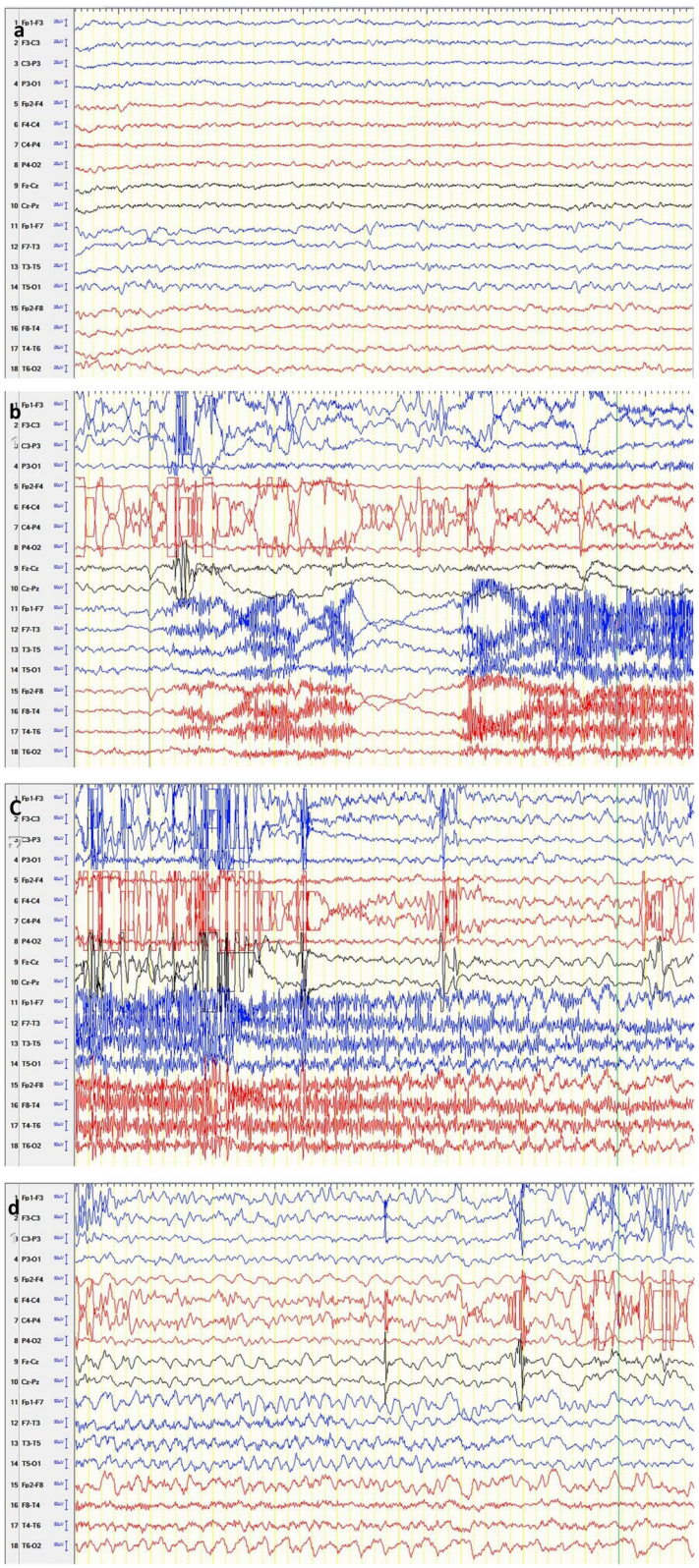

Fig. 1 Presurgical phase 1 EEG results. **a**. Interictal EEG showing sharp waves in the left anterior temporal region. **b**-**d**. Ictal EEG showing rhythmic discharges over the left anterior temporal region. Bipolar montage, page=10 s, sensitivity 7 µv/mm, filter band pass 0.5-30 Hz

Case presentation

A 40-year-old right-handed woman with drug-resistant epilepsy was admitted for an invasive presurgical evaluation.

Seizures' semiology included: loss of contact, right hand dystonic posturing, head turning to the left and oral automatism. Scalp LTVEM showed interictal sharp waves in the left anterior temporal region (Fig. 1a) and rhythmic ictal activity, maximal over the left anterior temporal region (Fig. 1a-b). MRI was unrevealing. PET scan showed left anterior temporal hypo metabolism and fMRI showed left hemispherical dominance (Fig. 2).

She was implanted with a 64-contact subdural grid over the left temporal lobe, 8-contact subdural strip over the temporal pole, 8-contact subdural strip over the left parahippocampal gyrus (PHG) and two depth electrodes: one to the left anterior hippocampus and one to the left posterior hippocampus.

Unfortunately, during this procedure, she had a left cortical intracerebral hemorrhage that was controlled, resulting in mild motor aphasia and right hemiparesis (Fig. 3). The patient had an almost complete recovery after one month of rehabilitation.

Since in our center, the subdural electrodes implantation was performed on Sunday and electrodes removal with final resection on Thursday, we withdrew ASM before the implantation to ensure an adequate number of seizures registration. Hence two days before implantation, the patient was admitted to our LTVEM unit and was fully withdrawn from all ASMs including levetiracetam (LEV), lacosamide (LCM), carbamazepine (CBZ) and phenobarbital (PB). After implantation the patient was admitted to the ICU and was monitored continuously with a 128-channel video EEG system (Natus, Quantum).

The inter-ictal invasive EEG showed continuous inter-ictal spiking over the left anterior temporal pole. Seizure onset was characterized by cessation of inter-ictal activity and discharges of low voltage fast activity over the left anterior temporal pole, with sequential involvement of the PHG, left anterior and posterior hippocampus. She underwent a left anterior temporal lobe resection. The excised lesion was compatible with a type 1A cortical dysplasia.

She was completely seizure free for more than a year and treatment with PB was withdrawn. Upon withdrawal

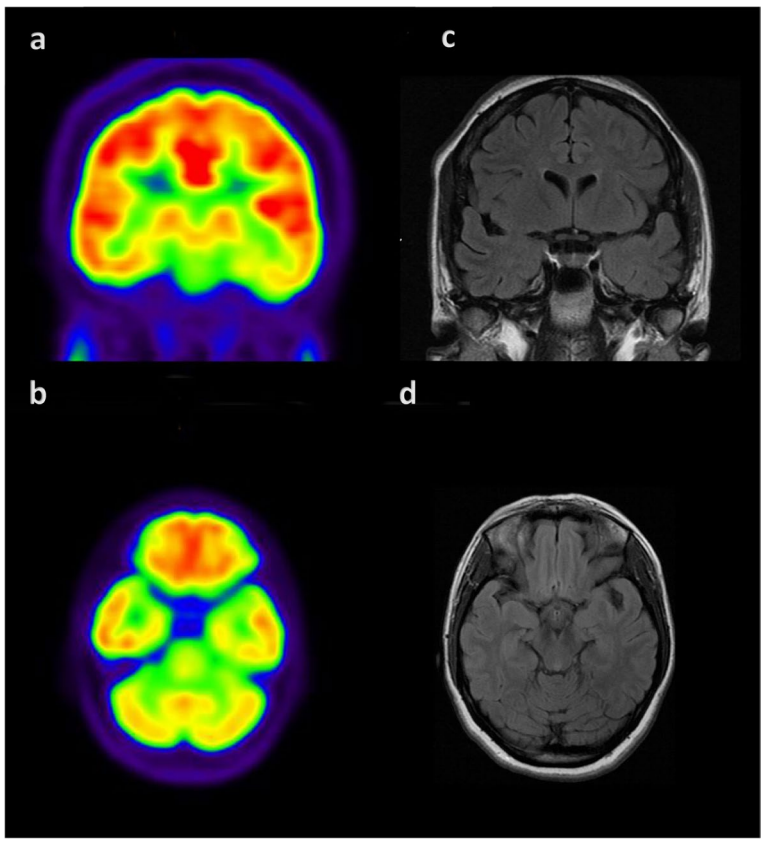

Fig. 2 Presurgical phase 1 imaging results. **a**. A coronal slice of brain FDG-PET/CT imaging, in high-contrast color scale, demonstrating reduced uptake in the left temporal lobe. **b**. An axial slice at the level of the temporal pole showing reduced uptake in the left temporal lobe. **c**, **d**. Coronal and axial T2 flair images

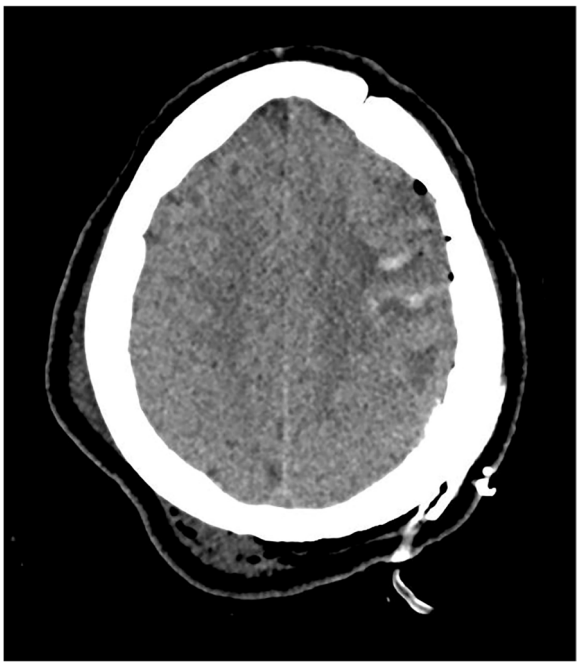

Fig. 3 Left cortical intracerebral hemorrhage. Non-contrast CT showing left cortical intracerebral hemorrhage

of LCM she suffered from several focal onset seizures with loss of awareness.

During her 4 days of invasive monitoring, we noticed three different phases in organization of seizures: *Acute withdrawal seizure (AWS),* the first recorded seizure 10h after the implantation; the *stabilized withdrawal seizures (SWS),* seven habitual seizures recorded between 24h post implantation and before readministration of ASMs; and the *Non-withdrawal seizures (NWS)*, ten seizures recorded 24h after readministration of ASMs. AWS and SWS had the same semiology and same epileptic network, but propagation time from the temporal pole to the PHG and hippocampus ranged from no latency in AWS, to up to 50 s of propagation latency in SWS. NWS were electrographic seizures, without any apparent clinical manifestation. Seizure onset in this type, as in the first two types, was in the temporal pole. However, NWS could last up to 3 minutes without involving the PHG or hippocampus.

The intracranial ictal EEG recordings of the 3 different types of seizures are summarized in Fig. 4.

Discussion

Withdrawal of ASMs is thought to affect epileptic activities in various aspects. We describe a 40-year-old patient with drug-resistant focal epilepsy originating from the left temporal pole. During intracranial LTVEM, the ASMs were paused, thus provoking multiple withdrawal seizures. Careful analysis of these seizures demonstrated no differences in the seizure organization network. However, prominent shortening of activity propagation or spread was observed. This claim was supported by fMRI studies suggesting that the resting-state functional connectivity was higher in patients after ASM withdrawal [8].

Previous studies suggested that atypical seizures observed in epileptic patients during ASM withdrawal were associated with diffuse or multifocal ictal onset [2, 9], thereby introducing confusing findings in the crucial pre-surgical evaluation. Nevertheless, most studies did not share this concern as they demonstrated that withdrawal seizures presented typical semiology and ictal EEG [2]. According to these studies, a possible increase in secondary generalization is expected. Our results partially support these claims since our recordings did not show multi-focal diffuse initiation or a change in the epileptic network. On the other hand, our intra-cranial ictal EEG did show significant changes mainly in the propagation times.

A possible mechanism underlying this drastic shortening of ictal propagation time without affecting other features like initiation, is the enhancement of excitatory synaptic transmission because of ASM withdrawal. This explanation may easily fit drugs acting on delaying synaptic neurotransmission such as LEV, valporic acid, perampanel, and others. However, seizures triggered by withdrawal from medications activating the GABA receptors, like benzodiazepines, or suppressing the activity of voltage-gated sodium channels such as CBZ, Phenytoin, LCM cannot be easily explained by this claim. In the latter group of medications, differences in ictal initiation is expected, which we did not observe. Notably, our patients had ASMs of both types. An additional possible mechanism is the rapid perturbation of the excitatory-inhibitory balance shifting the overall network's state towards hyper-excitation, thus creating a state of hyper-excitability on top of previously hypersynchronized networks yielding shorter propagation and longer termination times.

It is important to note that upon readministration of ASM, we saw the third type of seizure in which habitual initiation was seen without further propagation and without apparent clinical manifestation.

This relates to the effect of ASM on propagation. In this case, PB and LEV are probably responsible for this effect as LCM and CBZ are more influential on seizure initiation [10].

Our case report faced several limitations. First, it is difficult to determine the effect of each of the ASMs because the cessation of the drugs was global and abrupt. Second, during the intracranial EEG monitoring, we had

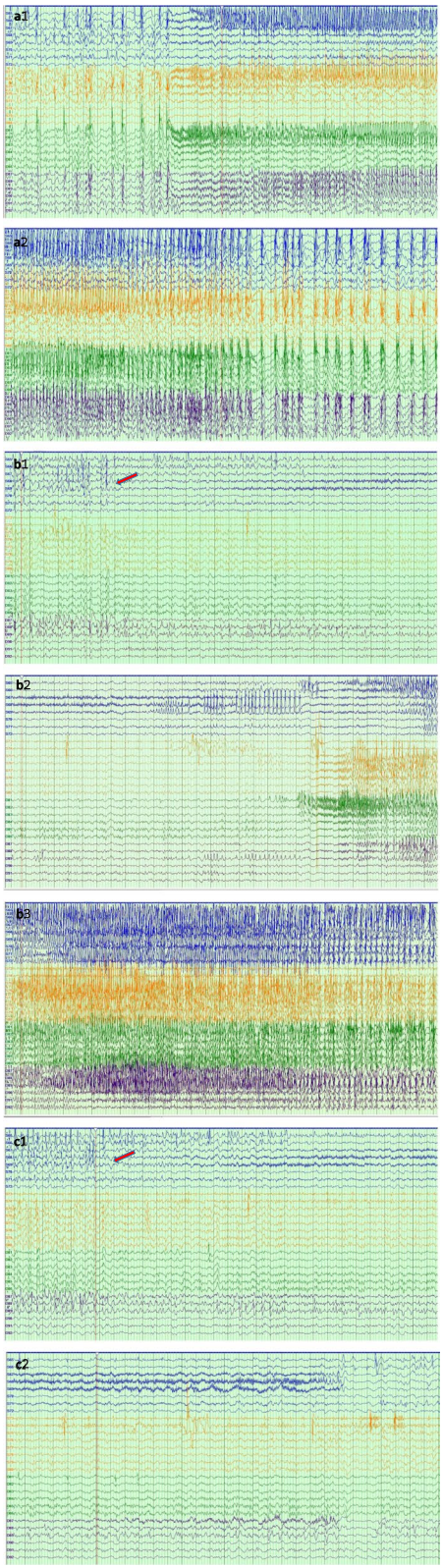

Fig. 4 Intracranial EEG monitoring. **a** 1+2.- Seizure occurring 10 h after implantation. Cessation of interictal activity and a burst of LVFA evolving into rhythmic high voltage spike activity. Note the simultaneous onset of seizure in all regions involved. **b** 1-3. Seizure occurring from 24 h after impanation before readministration of ASM. Cessation of interictal activity, seizure onset of LVFA in the temporal pole (arrow) occurring 45 s before involvement of the PHG, and Hippocampus. **c** 1-2. Seizures occurring after readministration of ASM- Habitual seizure onset with LVFA in the temporal pole (arrow) - last for 47 s without involving other regions and without apparent clinical signs. Referential montage: S65-S72, Temporal pole strip; S73-S80, PHG strip; D81-D83, AH electrodes; D84-D86, MTG electrodes; D87-D89, PH electrodes; D90-D92, Posterior MTG. Time scale, 15 mm/s; sensitivity, 50 µv/mm; filter band pass, 0.5-70 Hz. LVFA low voltage fast activity, TP temporal pole, PHG parahippocampal gyrus, AH anterior hippocampus, MTG middle temporal gyrus, PH posterior hippocampus

only one AWS compared to the other two types of seizures. The third limitation relates to the role of general anesthesia, since it may affect the network synchronization and possibly contribute to the hyper-synchronized state of the recorded withdrawal seizure during the first hours after the procedure. Furthermore, our patient suffered from iatrogenic cortical bleeding during the intracranial implantation. However, we believe this bleeding had minimal effect on the epileptic activity of the patient because of the relatively large distance from the epileptic zone.

Conclusions

The main conclusion from our case is that during withdrawal seizures, the propagation time of epileptic activity is significantly reduced without largely affecting the epileptic organization network or semiology. This implies a crucial role of ASM in suppressing the spread of epileptiform activity from the initiation zone to other brain regions.

Future studies using surface and intracranial EEG and functional imaging techniques like fMRI are needed to establish this observation and to further explore its exact mechanisms.

Abbreviations

AWS: Acute withdrawal seizures; SWS: Stabilized withdrawal seizures; NWS: Non-withdrawal seizures; ASM: Anti-seizure medications; LTVEM: Long term video-EEG monitoring; LEV: Levetiracetam, LCM – lacosamide, CBZ carbamazepine, PB phenobarbital; LVFA: Low voltage fast activity; TP: Temporal pole, PHG- parahippocampal gyrus AH- anterior hippocampus, MTG- middle temporal gyrus, PH - posterior hippocampus.

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Availability of supporting data

Not applicable.

Authors' contributions
Mohamed Khateb MD - Conceptualization of the study, Analysis and interpretation of data, and revision of the manuscript. Anat Grinfeld PHD - Analysis and interpretation of data, and revision of the manuscript. Michal Weiler-Sagie- Analysis and interpretation of data, and revision of the manuscript. Moshe Herskovitz MD – Conceptualization of the study, Analysis and interpretation of data, and revision of the manuscript. The authors read and approved the final manuscript.

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Declarations

Ethics approval and consent to participate
The study was approved by our local institutional ethical committee at Rambam health care campus (0175-21-RMB).
The patient signed a written informed consent for participating in the study

Consent for publication
The patient signed a written informed consent for the publication of the study.

Competing interests
The authors have no disclosures or conflict of interests to report.

Author details
[1]Department of Neurology, Rambam Health Care Campus, Haifa, Israel. [2]Radiology Department Rambam Health Care Campus, Haifa, Israel. [3]Faculty of Biomedical Engineering, Technion - Israel Institute of Technology, Haifa, Israel. [4]Nuclear Medicine Department, Rambam Health Care Campus, Haifa, Israel. [5]Rappaport Faculty of Medicine, Technion Institute of Technology, Haifa, Israel.

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References

1. Novitskaya Y, Hintz M, Schulze-Bonhage A. Rapid antiepileptic drug withdrawal may obscure localizing information obtained during presurgical EEG recordings. Epileptic Disord. 2018;20(2):151–7.
2. Skidmore CT, Sperling MR. Effect of anticonvulsant withdrawal on seizure semiology and ictal electroencephalography. In: Textbook of Epilepsy Surgery. London: CRC Press; 2008. p. 742–5.
3. Zhou D, Wang Y, Hopp P, Kerling F, Kirchner A, Pauli E, et al. Influence on ictal seizure semiology of rapid withdrawal of carbamazepine and valproate in monotherapy. Epilepsia. 2002;43(4):386–93.
4. Ludwig BI, Marsan CA. EEG changes after withdrawal of medication in epileptic patients. Electroencephalogr Clin Neurophysiol. 1975;39(2):173–81.
5. Engel J Jr, Crandall PH. Falsely localizing ictal onsets with depth EEG telemetry during anticonvulsant withdrawal. Epilepsia. 1983;24(3):344–55.
6. Wang-Tilz Y, Tilz C, Wang B, Pauli E, Koebnick C, Stefan H. Changes of seizures activity during rapid withdrawal of lamotrigine. Eur J Neurol. 2005;12(4):280–8.
7. Gotman J, Koffler DJ. Interictal spiking increases after seizures but does not after decrease in medication. Electroencephalogr Clin Neurophysiol. 1989;72(1):7–15.
8. Hermans K, Ossenblok P, Van Houdt P, Geerts L, Verdaasdonk R, Boon P, et al. Network analysis of EEG related functional MRI changes due to medication withdrawal in focal epilepsy. NeuroImage: Clin. 2015;1(8):560–71.
9. Doležalová I, Brázdil M, Hermanová M, Janoušová E, Kuba R. Effect of partial drug withdrawal on the lateralization of interictal epileptiform discharges and its relationship to surgical outcome in patients with hippocampal sclerosis. Epilepsy Res. 2014;108(8):1406–16.
10. Khateb M, Bosak N, Herskovitz M. The effect of anti-seizure medications on propagation of epileptic activity; a review. Front. Neurol. 2021;27(12):674182.