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Case Report

Continuous ictal discharges with high frequency oscillations confined to the non-sclerotic hippocampus in an epileptic patient with radiation-induced cavernoma in the lateral temporal lobe

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ABSTRACT

Intraoperative electrocorticography recording is recommended for treating cavernoma-related epilepsy. However, interictal paroxysmal epileptiform activity is generally able to be recorded, but is not always identical to the epileptogenic zone.

We surgically treated a 15-year-old girl with drug-resistant epilepsy associated with radiation-induced cavernoma in the right lateral temporal lobe. Electrocorticography revealed paroxysmal activities in the cortex around the cavernoma. Additionally, continuous subclinical "ictal" discharges with high-frequency oscillations confined to the histologically non-sclerotic hippocampus were recorded. Following additional hippocampectomy, a good seizure outcome was obtained.

Intraoperative electrocorticography and high-frequency oscillation analysis revealed high epileptogenicity in the non-sclerotic hippocampus of this patient.

1. Introduction

Surgery for an epileptogenic cerebral cavernous malformation (cavernoma) in the temporal lobe, and the necessity of additional hippocampectomy remains in dispute [1]. When the cavernoma directly involves the hippocampus, the decision to undertake medial resection is relatively straightforward [2,3]. However, when medial structures are not involved the potential risks and benefits of medical resection must be considered carefully, on a case-by-case basis [1]. Previous electrophysiological/histopathological assessment in patients with lateral temporal cavernoma suggested a proclivity for the epileptogenic zone to encompass the medial structures, and for hippocampal sclerosis to be present [4]. Even if the extrahippocampal cavernoma is the initial origin of an electroencephalography (EEG) abnormality and/or epilepsy, it is postulated that the hippocampus is more vulnerable to secondary epileptogenesis after repeated EEG abnormality with or without seizures. This theory is referred to as "dual pathology" when coexistence of hippocampal sclerosis with an extrahippocampal cavernoma is present [1,5]. To evaluate these phenomena, guidance using intraoperative electrocorticography (ECoG) recording has been recommended [1,3,6]. Although intraoperative ECoG does not require placement of depth electrodes, it is generally accepted that the area that generates paroxysmal epileptiform activity on ECoG recorded during the operation is not always identical to the epileptogenic zone [7,8]. We surgically treated a patient with drug-resistant focal epilepsy associated with a cavernoma in the lateral temporal lobe, in whom continuous "ictal" discharges with high-frequency oscillation, confined to the ipsilateral non-sclerotic hippocampus, were recorded on the intraoperative ECoG after lateral temporal resection. Good seizure outcome was obtained following additional hippocampectomy. Herein, we discuss the epileptogenic mechanisms of this patient.

2. Case reports

A16-years old left-handed girl underwent radiation therapy and chemotherapy for a rhabdomyosarcoma of the left maxillary sinus with left orbital and temporal invasion at the age of 2 months. Radiation therapy included bilateral irradiation at a dose of 30.6 Gray (Fig. 1a) and right-angled irradiation at 14.4 Gray (Fig. 1b). The calculated irradiation dose to the right lateral temporal lobe was 33 Gray. Her chemotherapy regimen was VAC (vincristine, a ctinomycin and cyclophosphamide) therapy. Although complete tumor remission was obtained, she developed microcephaly, panhypopituitarism, left impaired vision due to

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cataract, left mild facial palsy of the peripheral type, and lack of permanent teeth as sequelae of the treatment. Her school grades were average. When she was 14 years old, she developed focal epilepsy manifest as focal aware sensory seizures, which began with a sick feeling that was often followed by a sense of *déjà vu* and dysesthesia of her left upper extremity. Although she was treated with optimal doses of various anti-seizure drugs including carbamazepine, levetiracetam, lacosamide, topiramate, perampanel and clobazam, she began having episodes one to three times a day.

Presurgical evaluation was performed at 15 years of age. Interictal EEG demonstrated frequent paroxysmal epileptiform activity (Fig. 1a, black arrow) and temporal intermittent rhythmic delta activity (TIRDA) (Fig. 1b, black arrow) over the right temporal region (F8 and T4 on the international 10–20 system of electrode placement). Habitual focal aware seizures, followed by dysesthesia in her left upper limb, were captured over the course of a three-day video-EEG monitoring session. At that time, EEG indicated that ictal discharge began in the right anterior temporal region (Fig. 1c, F8, black arrow). Although she frequently complained of feeling sick, the EEG failed to consistently reveal any abnormalities.

Magnetic resonance imaging (MRI) demonstrated a de novo cavernoma in the right middle temporal gyrus (Fig. 1f-h), while this lesion was not noted at the age of 2 months (Fig. 1i). Neither atrophy nor hyperintensity of the ipsilateral hippocampus was observed (Fig. 1d–f). ^{18}Fluorodeoxyglucose-positron emission tomography (FDG-PET) showed hypometabolism in the right medial temporal region as well as the lateral region (Fig. 1g). The Wada test suggested left hemisphere dominance for language and bilateral memory participation.

Subsequently, she underwent right fronto-temporo-parietal craniotomy (Fig. 2a) under general total intravenous anesthesia using propofol

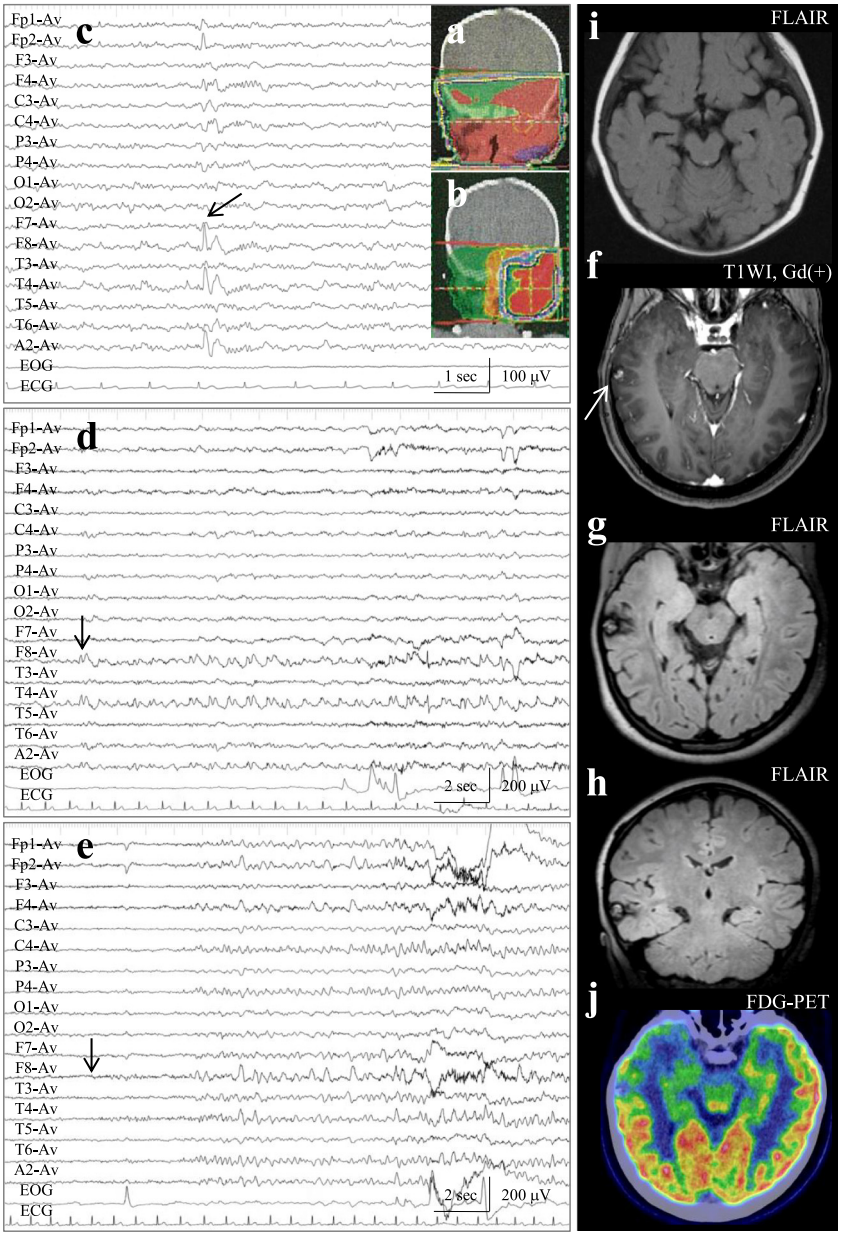

Fig. 1. (a, b) Interictal electroencephalography (EEG) demonstrates paroxysmal activity (a, black arrow) and temporal intermittent rhythmic delta activity (TIRDA) (b, black arrow) over the right temporal region (F8 and T4 on the international 10–20 system of electrode placement). (c) Ictal EEG indicates that ictal discharge began in right anterior temporal region (F8, black arrow). (d) T1-weighted magnetic resonance images (T1WI; tilted axial view oriented along the long axis of the hippocampus) demonstrated an enhancing tumor with gadolinium (Gd) contrast (white arrow). On tilted axial (e) and (f) coronal views of fluid-level attenuated-inversion recovery (FLAIR) images, no atrophy or hyperintensity of the ipsilateral hippocampus was noted. (g) ^{18}Fluorodeoxyglucose-positron emission tomography (FDG-PET) at sections comparable to (d) and (e) shows hypometabolism in the right medial temporal region as well as the lateral region.

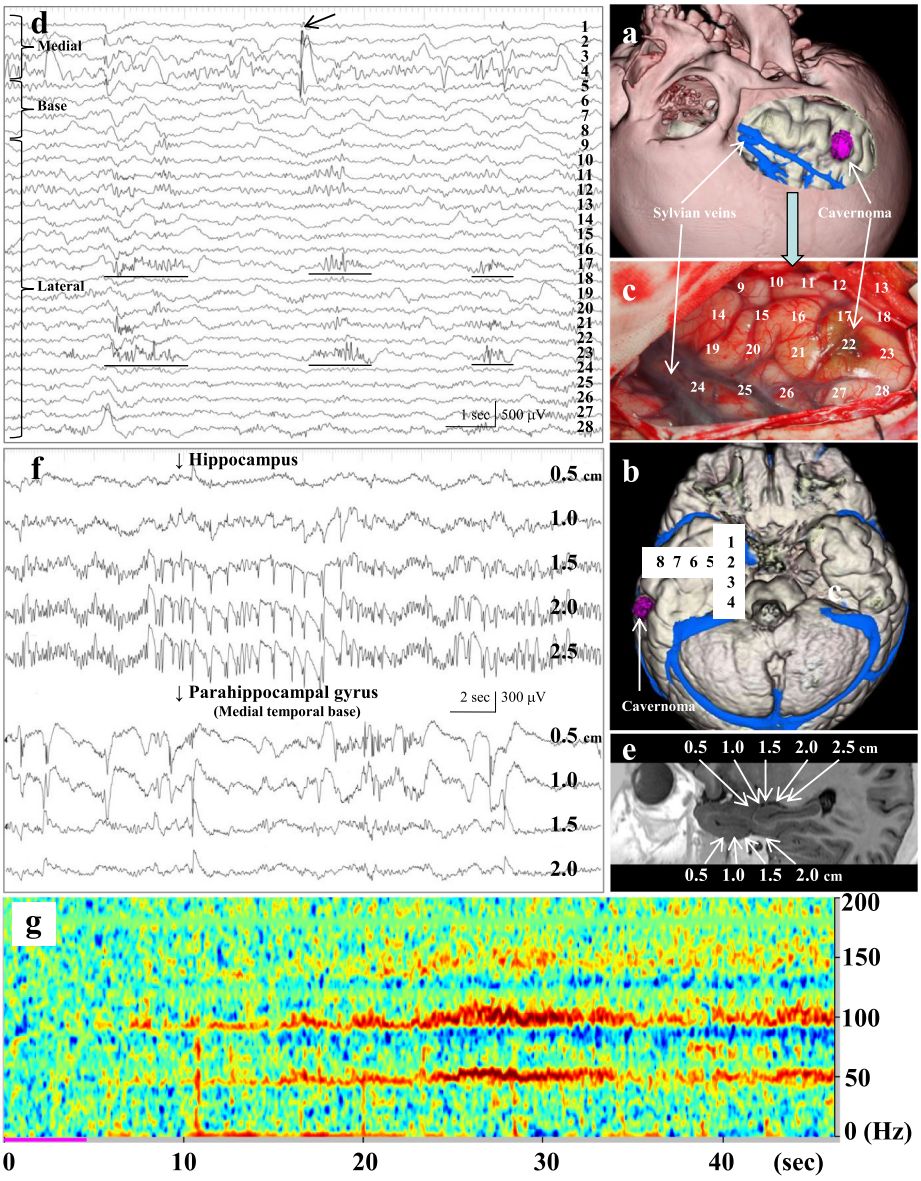

Fig. 2. (a) Three-dimensional reconstruction of the computed tomographic (3D-CT) scan demonstrates the anatomical relationship between the extent of the craniotomy, cavernoma, and Sylvian veins. (b) An intraoperative electrocorticogram (ECoG) (monopolar recordings referred to the nasion), which was recorded from the medial (Electrodes No. 1–4), basal (5–8), and lateral (10–28) surfaces of the right temporal lobe, reveals high frequency paroxysmal discharges on the lateral surface, especially on electrodes No. 17 and 23, where the cortex is brownish because of hemosiderin deposit surrounding the cavernoma (black lines). Independent paroxysmal discharge with a high-amplitude spike and wave complex (black arrow) were also recorded from the medial temporal lobe. (c, d) The position and the number of the subdural electrodes are indicated on the intraoperative photograph and 3-D CT scan. (e) Intraoperative ECoG (monopolar recordings referred to the nasion) recorded from the hippocampus (upper 5 traces) and parahippocampal gyrus (lower four traces). The numbers indicate the distance of the recording electrodes from the hippocampal head and anterior edges of the medial temporal lobe, as is shown on the sagittal view of the 3D short-tau inversion-recovery magnetic resonance imaging. (f) Continuous high-frequency ictal discharges were recorded from the electrodes over the hippocampus, located 1.5–2.5 cm from the hippocampal head. Although frequent paroxysmal discharges were recorded from the parahippocampal gyrus, it was not synchronized with the hippocampal discharge. (g) High frequency oscillations (HFO) activity determined by time-frequency analysis (temporal spectral evolution) of the intraoperative ECoG recording (e), located 0.5 cm from the hippocampal head.

and remifentanil. A trapezoid strip electrode with eight electrodes [10] was placed adjoining the medial and basal aspects of the temporal lobe, so that four electrodes were at the medial aspects of the parahippocampal gyrus in an anteroposterior orientation, and another four were at the basal surface with a mediolateral orientation, as previously described [7,11] (Fig. 2b). A 5 × 4 subdural grid electrode was also placed on the lateral temporal lobe (Fig. 2c). The first intraoperative ECoG, which was recorded from the medial, basal and lateral aspects of the temporal lobe, revealed frequent paroxysmal discharges on the lateral surface (Fig. 2d, black lines) where the cortex surrounding the cavernoma was brownish (Fig. 2c. Independent paroxysmal discharges with high-amplitude spike-and-wave complexes (Fig. 2b) were also recorded from the medial temporal lobe.

After lateral temporal resection including the cavernoma, the inferior horn of the lateral ventricle was exposed. Strip electrodes were placed along the long axis of the hippocampus and parahippocampal gyrus (Fig. 2e), and the second intraoperative ECoG was recorded from these electrodes for 15 minutes. Continuous ictal discharges were recorded from the electrodes on the hippocampus, 1.5-2.5 cm from the hippocampal head (Fig. 2f, upper 5 traces). HFO activities were determined by time-frequency analysis (temporal spectral evolution) of the ECoG activities on the electrode at 0.5 cm from the hippocampal head (Fig. 2g). Although frequent paroxysmal discharges were also recorded from the parahippocampal gyrus, they were not synchronized with the hippocampal discharge (Fig. 2f, lower 4 traces). An additional hippocampectomy was performed.

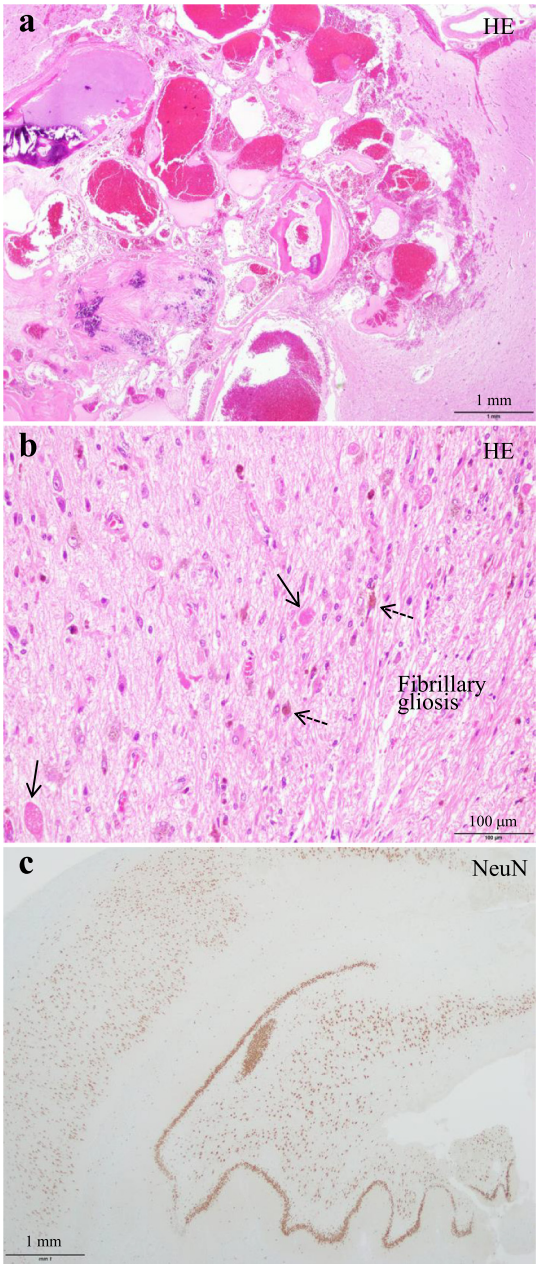

Fig. 3. (a) The histological findings (hematoxylin eosin staining, HE) of the cavernoma show a channel of abnormally dilated vessels of varying sizes and partially hyalinized vessel walls without apparent elastic lamina or smooth muscle layers. Ossification is focally noted in the abnormal vessel walls. (b) The surrounding cerebral tissue shows severe gliosis including fibrillary gliosis and formation of axonal spheroids (black arrows), while hemosiderin depositions (black dotted arrows) were mild. (c) Immunohistochemistry for NeuN in the hippocampus did not show either pyramidal cell loss or granule-cell dispersion.

Her postoperative course was uneventful. A postoperative EEG showed disappearance of the paroxysmal activity in the right temporal region. Even after reduced dosages of anti-seizure drugs, she was seizure-free in the year following the operation. The histological findings of the cavernoma revealed a conglomerate of dilated vessels with fibrocollagenous walls of various thicknesses (Fig. 3a). The surrounding cerebral tissue showed severe fibrillary gliosis, the formation of numerous axonal spheroids (Fig. 3b, black arrows), and mild hemosiderin deposition (Fig. 3b, black dotted arrows). No effect of radiation such as necrosis or hyalinized vessels was seen in the surrounding cerebral tissue, and no hippocampal sclerosis was observed (Fig. 3c).

3. Discussion

In the present case, the cavernoma was located outside the region covered by the previous irradiation. Furthermore, histological examination of the temporal lobe around the cavernoma failed to reveal any damage due to radiation. These findings argue against the idea that the cavernoma was radiation-induced in a strict sense [9].

Intraoperative ECoG findings indicated two independent foci of the paroxysmal activity; the lateral temporal lobe around the cavernoma and the medial temporal lobe. Because the paroxysmal ECoG activity of the lateral temporal lobe had a tight topographical relationship with the cortex around the cavernoma, this area was considered epileptogenic, and the decision was made to resection the lateral temporal lobe that included the cavernoma. Similar to our presurgical EEG observations here, another report [10] has also recently demonstrated that TIRDA could be an EEG marker that is independent of hippocampal activity and represent a temporal neocortical epileptogenic zone.

Among the various types of paroxysmal discharges commonly seen in the medial temporal lobe, in this case, we recorded continuous "ictal" discharges with high frequency oscillations from the hippocampus. We previously reported that during the limited time for recording intraoperative ECoG, ictal discharge or electrical seizure activity could be obtained from highly epileptogenic areas such as the hippocampus in patients with the medial temporal lobe epilepsy [7,11] or the frontal cortex in patients with radiation necrosis-associated frontal lobe epilepsy [12]. These recordings may result in the decision to perform additional resection of the area. High-frequency oscillations with ictal activity on ECoG is now suspected to be a marker of highly epileptogenic areas [13]. Although few previous studies have reported high-frequency oscillations obtained from the hippocampus via intraoperative ECoG, the presence of ictal discharges from the hippocampus in this patient could indicate that high-frequency oscillation within the hippocampus is also a marker of highly epileptogenic areas.

One notable finding in this case is that the epileptiform discharges were strictly confined to the hippocampus and could not be recorded from the parahippocampal gyrus. The most plausible reason for this is related to the structure of the hippocampus itself. Because the parahippocampal gyrus through CA1 to CA4 and the dentate gyrus is shaped like a spiral, the excitatory postsynaptic potentials might cancel each other out, resulting in a closed electrical field [14]. Although subdural recordings from the medial temporal base (parahippocampal gyrus) are generally believed to reflect hippocampal activity [15,16], our findings indicate that paroxysmal discharges on ECoG strictly confined to the hippocampus could be missed if one only looks at these recordings.

Based on simultaneous EEG and ECoG recordings, we previously demonstrated that discharges originating in the medial temporal lobe could not be detected via EEG until the discharge extended to the cortex convexity [17]. Importantly, this hippocampal activity was not detected on preoperative EEG examination and explain why preoperative EEG failed to reveal any abnormalities when the patient complained of her aura of feeling sick.

Another notable finding in the present case is that although intraoperative ECoG recordings pointed out two potential independent generators of epileptogenesis, hippocampal sclerosis—as a second pathology—was not observed either on neuroradiological or histological examinations. The most plausible reason for this is the short preoperative duration of the patient's epilepsy [2]. The patient in the current study underwent surgery about 1.5 years after the onset of her epilepsy. Among the preoperative non-invasive examinations, only FDG-PET showed involvement of the medial temporal lobe. However, this does not directly justify the decision to undertake the additional hippocampectomy because FDG-PET-derived areas of hypometabolism are known to sometimes extend outside the epileptogenic zone [18].

Although the exact epileptogenic relationship between the lateral temporal cavernoma and the non-sclerotic hippocampus could not

be clarified without invasive chronic subdural or depth-electrode recording (which is the gold standard), perioperative multimodal examinations, including intraoperative ECoG, did reveal that the cavernoma was epileptogenic and that the hippocampus was also potentially epileptogenic in this case. Complete freedom from drug-resistsant focal epilepsy was obtained following surgical resection with ECoG guidance.

Disclosure

The authors declare no conflicts of interest associated with this manuscript.

Ethical statement

All procedures performed in this report were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Written informed consent was obtained from the patient and her parents to report in the journals.

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