

Case Report

Anatomo-electro-clinical correlations of hypermotor seizures with amygdala enlargement: Hippocampal seizure origin identified using stereoelectroencephalography

Tomotaka Ishizaki ^{a,*}, Satoshi Maesawa ^{a,b}, Daisuke Nakatsubo ^{a,b}, Hiroyuki Yamamoto ^{b,c}, Masashi Shibata ^a, Sachiko Kato ^a, Mari Yoshida ^d, Jun Natsume ^{b,c}, Minoru Hoshiyama ^b, Toshihiko Wakabayashi ^a

^a Department of Neurosurgery, Nagoya University Graduate School of Medicine, 65 Tsurumai, Showa, Nagoya, Aichi 466-8550, Japan

^b Brain and Mind Research Center, Nagoya University, Nagoya, Aichi, Japan

^c Department of Pediatrics, Nagoya University Graduate School of Medicine, Nagoya, Aichi, Japan

^d Department of Neuropathology, Institute for Medical Science of Aging, Aichi Medical University, Aichi-gun, 1-1 Yazakokarimata, Nagakute, Aichi 480-1195, Japan

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1. Introduction

In epilepsy, an epileptiform discharge originating from the epileptogenic zone spreads temporo-spatially through the neural networks of the brain, and the ictal manifestation changes reflects its electroclinical propagation. The propagation depends on the anatomical and functional connections between each region in the brain and differs according to the type of seizure (i.e., a frontal seizure propagates more rapidly than a temporal seizure) [1]. Therefore, during the preoperative evaluation for epilepsy surgery, it is important to elucidate the temporo-spatial spread, anatomically and electrophysiologically, and to hypothesize the epileptogenic focus and propagation in association with the symptoms. This concept is called the anatomo-electro-clinical correlation (AEC), proposed by Talairach et al. [2], and is crucial for successful epilepsy surgery in order to formulate the hypothesis of the AEC preoperatively using multiple modalities, such as video-electroencephalography (VEEG) monitoring, fludeoxyglucose-positron emission tomography (FDG-PET), and magnetoencephalography (MEG) [3]. Intracranial EEG (iEEG) is a gold standard for this purpose

Abbreviations: EEG, electroencephalography/electroencephalogram; AEC, anatomo-electro-clinical correlation; MEG, magnetoencephalography; iEEG, intracranial EEG; SEEG, stereoelectroencephalography; MTLE, mesial temporal lobe epilepsy; TLE, temporal lobe epilepsy; AE, amygdala enlargement; FLE, frontal lobe epilepsy; SEEG, stereoelectroencephalography; HS, hippocampal sclerosis; sLORETA, standardized low-resolution brain electromagnetic tomography analysis; VEEG, video-EEG; FCD, focal cortical dysplasia.

* Corresponding author.

E-mail address: tomotakaishizaki@gmail.com (T. Ishizaki).

when the non-invasive evaluation is discordant, and currently, the advanced technology of stereoelectroencephalography (SEEG) is especially helpful for interpreting the AEC in complex cases [4].

Mesial temporal lobe epilepsy (MTLE) with amygdala enlargement (AE), an MTLE subtype, is characterized by amygdala-related symptoms such as mood disorders, including anxiety and depression, in addition to typical MTLE symptoms [5]. The semiology of frontal lobe epilepsy (FLE) is different, and is characterized by unilateral clonic seizures, asymmetric tonic seizures with or without awareness loss, and hypermotor seizures.

We report here a rare case of drug-resistant epilepsy with AE, with successful identification using SEEG of the seizure onset zone, which was not in the amygdala but in the hippocampus, and the symptomatic zone in the ipsilateral frontal lobe. This case was considered rare because the manifestations were typical for frontal lobe seizures including hypermotor seizures, but AE was observed in the imaging study. Furthermore, this case is clinically valuable because the AEC in this case was successfully interpreted using SEEG; it originated from the hippocampus and not the enlarged amygdala, and propagated to the frontal lobe. The epileptic discharges probably spread via the uncinate fasciculus to the frontal lobe, and the ictal manifestation including hypermotor seizures developed. We report detailed SEEG results in addition to findings from other evaluations including analysis using advanced MEG.

2. Case report

A 12-year-old, right-handed boy with drug resistant epilepsy and unremarkable medical, developmental, and family history experienced his first seizure at the age of 6 years. The seizures, characterized by sudden immobility, staring, and oral automatism with impaired awareness, had occurred frequently thereafter, and they showed high-amplitude spikes in the left temporal lobe on electroencephalograms (EEGs). A diagnosis of temporal lobe epilepsy (TLE) was made. Seizures were controlled with carbamazepine (0.5 mg/kg/d) for several years. However, seizures recurred at the age of 11 years, although the characteristics were different from those experienced previously, beginning with epigastric discomfort and vomiting, followed by impaired awareness with extending and shaking of the right upper limb, rotation of the body,

and occasionally resulting in a fall. Carbamazepine was increased to 200 mg/d, but was discontinued due to the prevalence of half-pitch lower sound perception. Subsequently, treatment with 100 mg/d of zonisamide was initiated, but was discontinued due to marked appetite loss. Seizures occurred frequently (several times a month) and could not be controlled by specific combinations of anti-seizure drugs (levetiracetam 800 mg/d and clobazam 20 mg/d). Thus, the patient was referred to our department for surgical treatment.

On an initial scalp EEG, negative spikes were sporadically observed at F7 and T3, with positive spikes in the left fronto-parietal areas (Supplementary Fig. 1). Brain magnetic resonance imaging (MRI) revealed AE in the left hemisphere without hippocampal sclerosis (HS) (Fig. 1A). FDG-PET revealed a generally low uptake in the left temporal lobe; however, no uptake was observed on methionine-PET (Fig. 1B, C). The standardized low-resolution brain electromagnetic tomography analysis (sLORETA) of MEG revealed that the current originated from the hippocampus at the interictal spike onset and propagated to the orbitofrontal cortex and the entire frontal lobe (Fig. 1D).

VEEG monitoring with scalp electrodes showed that all captured seizures were similar, initiating with a sudden right upper limb extension (Supplementary Fig. 2A), followed by hypermotor movements causing violent shaking of the right arm (Supplementary Fig. 2B). The seizure

duration was 1 min (Supplementary Fig. 2C). Hypermotor seizures associated with FLE, rather than TLE, was considered as the ictal manifestation, although the seizure onset zone on the scalp EEG was unclear because of motion artifacts.

The second evaluation step involved iEEG monitoring including SEEG, with the insertion of depth electrodes in the hippocampus, amygdala, anterior temporal tip, posterior temporal lobe, orbitofrontal cortex, and anterior cingulate cortex. Three strip electrodes also covered the lateral surface of the temporal and frontal lobes. Video-iEEG monitoring interestingly revealed that the iEEG changes did not originate in the amygdala (Fig. 2-1). The fastest activity was observed in the hippocampal head; this consisted of several large-amplitude spikes followed by low-amplitude fast rhythmic activity (Fig. 2-2). Ictal discharges propagated posteriorly (Fig. 2-3), followed by attenuation (Fig. 2-4). Subsequently, fast rhythmic waves appeared in the subdural electrodes on the external temporal lobe (Fig. 2-5). Finally, the seizure activity propagated to frontal areas, and the patient's usual seizure symptoms were then visible (Fig. 2-6, 7).

These findings identified the anterior hippocampus as the seizure onset zone, with the frontal lobe being the symptomatic zone. We deduced that the epileptogenic zone included both the hippocampus and enlarged amygdala. Selective amygdalohippampectomy was

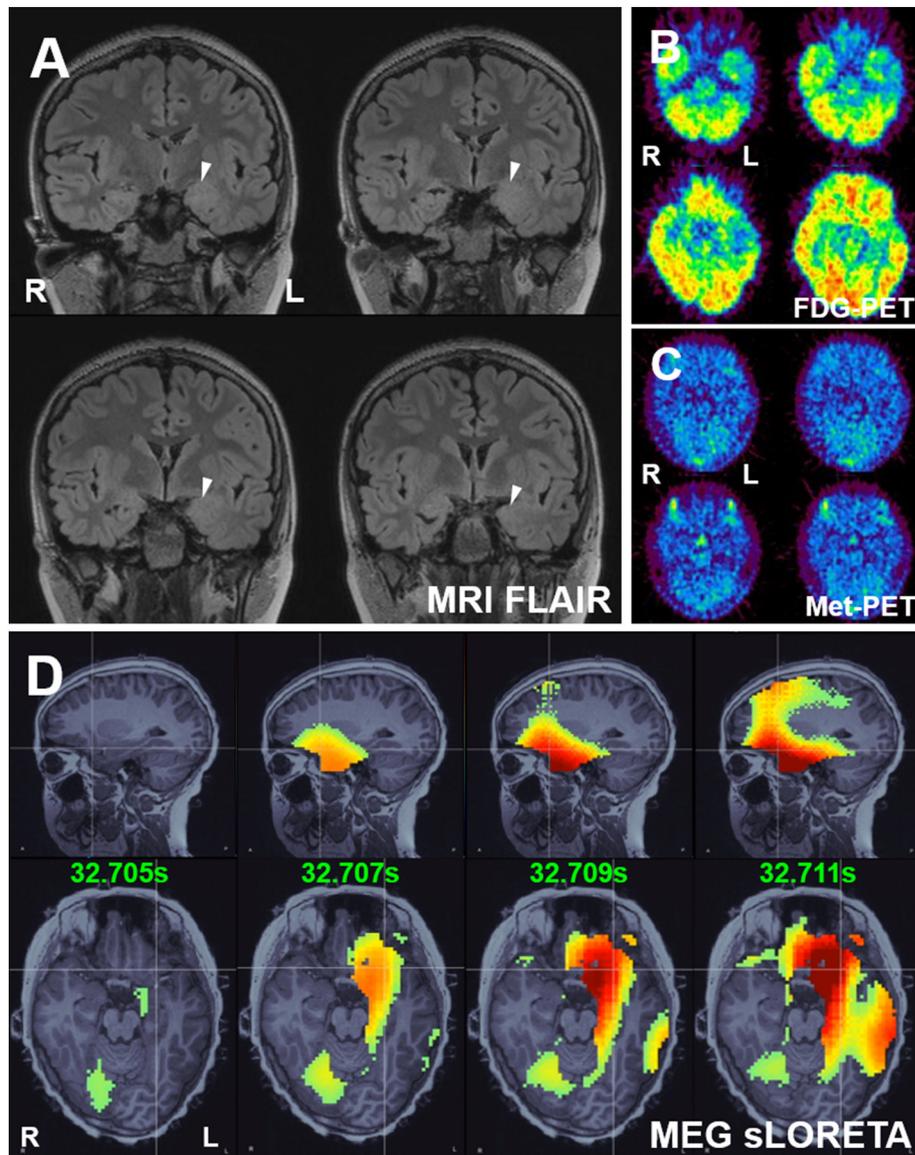


Fig. 1. Results of preoperative images including MRI coronal FLAIR images (A), FDG-PET axial images (B), methionine-PET axial images (C), MEG sLORETA sagittal and axial images (D).

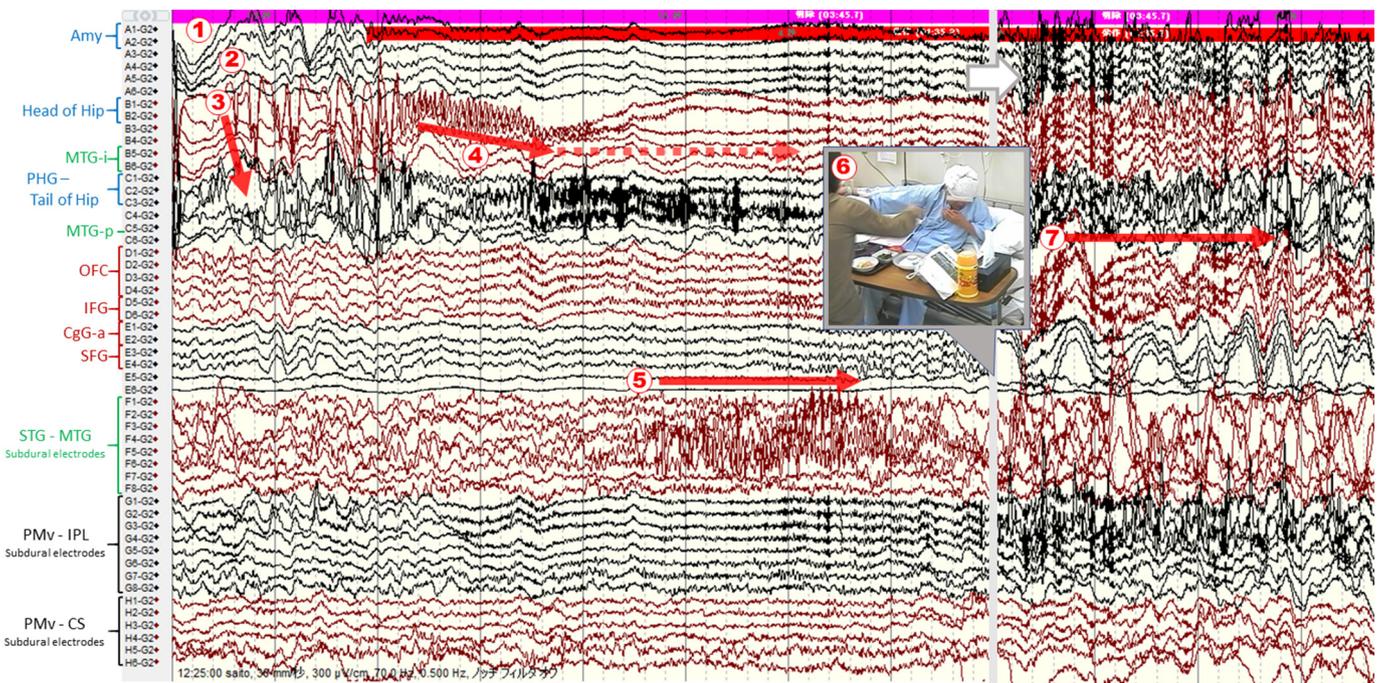


Fig. 2. Ictal EEG during video-iEEG monitoring. Amy: amygdala, Hip: hippocampus, MTG-i: middle temporal gyrus-intermediate, PHG: parahippocampal gyrus, MTG-p: middle temporal gyrus-posterior, OFC: orbitofrontal cortex, IFG: inferior frontal gyrus, CgG-a: anterior cingulate gyrus, SFG: superior frontal gyrus, STG: superior temporal gyrus, MTG: middle temporal gyrus, PMv: ventral premotor cortex, IPL: inferior parietal lobule, CS: central sulcus.

performed. Intraoperatively, frequent spikes were observed in the hippocampus (Supplementary Fig. 3A). Postoperative MRI confirmed that the hippocampus and the amygdala were resected (Supplementary Fig. 3B).

Postoperative pathological findings showed dyslamination in the amygdala. Aggregated small neurons in the surface layer of the cortex and abnormal axons projecting parallel to the cortex were also observed. However, neither dysmorphic neurons nor balloon cells were observed (Supplementary Fig. 4). The enlarged amygdala pathology was classified as focal cortical dysplasia (FCD) type I. Pathological alterations in the hippocampal regions CA1–CA3 could not be determined owing to changes in the surgical procedure. The hippocampal regions of the subiculum, CA4, and dentate gyrus were observable. In a region of the granule cell layer of the dentate gyrus, the cells appeared somewhat larger, and granule cell dispersion was suspected. The subiculum and CA4 showed no neuronal loss, dysmorphia, or pathological gliosis. However, because the hippocampal CA1 could not be examined adequately, the existence of HS was unknown.

The postoperative course was uneventful, and the patient was discharged on postoperative day 12. Currently, at 22 months after surgery the patient is seizure-free, with a seizure outcome of Engel's class IA. No learning disabilities were noted postoperatively (Supplementary Table 1).

3. Discussion

It has been reported that focal seizures with impaired awareness are observed in TLE with AE, with a high probability of 67%–100% [6]. Additionally, emotion disorders such as anxiety or depression have been recognized in 90% of these cases [5], and are considered to be caused by the direct activation of the amygdala [6]. In the case presented herein, focal seizures with impaired awareness and oral automatism were observed in an early stage, which changed to hypermotor seizures in the later stages. Hypermotor seizures arise from the activation of the prefrontal cortex and temporal lobe [7]. Extension of the right upper limb and bilateral asymmetric tonic seizures (similar to a fencing posture) are attributed to excitation

of the mesial frontal lobe. Versive seizures, considered to be the ictal manifestation of the lateral premotor cortex and frontal eye fields, were not observed. Therefore, we speculated that the symptomatic zone may be located in the medial frontal lobe and prefrontal cortex.

The seizures did not originate in the enlarged amygdala, but in the hippocampus, in our case; this observation has been confirmed, using intraoperative EEG, by Minami et al. [8]. The amygdala is connected to the anterior temporal lobe and orbitofrontal cortex via the uncinate fasciculus [9,10]. It has been suggested that an epileptic discharge generated in the temporal lobe rapidly propagates via the uncinate fasciculus to the orbitofrontal cortex [11,12]. Thus, we assumed that the ictal discharge originated in the hippocampus and spread to the limbic system via the enlarged amygdala, causing nausea and vomiting, and propagated through the orbitofrontal cortex to the frontal lobe via the uncinate fasciculus, causing hypermotor seizures. However, as far as we are aware, there is no report that clearly demonstrates such propagation using iEEG. A similar case was reported by Tezer et al. with the ictal manifestation beginning with a hypermotor seizure of FLE to oral and hand automatism of TLE [13]. In this case, it was observed using subdural electrodes that the epileptogenic discharge propagating from the orbitofrontal cortex spread to the temporal lobe. However, this propagation pattern is in contrast to our case presented herein.

In the present case, interictal MEG spikes were analyzed using sLORETA with distributed source analysis. This analysis clearly showed that the ictal discharge originating from the mesial temporal lobe propagated through the uncinate fasciculus to the orbitofrontal cortex, as shown in Fig. 1D. Using this novel MEG method, some studies have emphasized the clinical importance of focus detection in epilepsy patients [14]. The analysis of ictal discharges using MEG is expected to develop with further research.

Reports of surgical and pathological findings of MTL with AE are scarce. This not only is likely because this condition is generally well controlled with anticonvulsants [15], but also could be because ictal manifestation is difficult to differentiate from emotional disorders; therefore, it is not common that these cases reach surgical treatment

[8]. The pathological findings reported are various, and in recent years, the pathological findings of AE have been considered to be heterogeneous [8,16,17]. Minami et al. reported that 10 of 11 surgical specimens of AE had characteristic pathological findings of closely aggregated hypertrophic neurons with vacuolization in the background matrix. Vacuolization due to enlarged dendrites was detected in both an AE group and an HS control group; however, it spread more diffusely in the AE group than in the control group [8]. Kim reported that, as a result of the pathology in MTLE with AE, eight patients had FCD. The pathological degree was mild in all eight patients with FCD, in that seven had FCD 1A and one had minimal malformations of cortical development. Five of eight FCD cases had HS but did not show the radiological findings of HS. Mild neuronal loss and gliosis were observed in the hippocampal CA1 in all 5 cases with HS [16]. On the other hand, no apparent hippocampal abnormalities have been observed in cases of AE [17].

In the present case, dyslamination in the amygdala, aggregated small neurons in the surface layer of the cortex, and abnormal axons projecting parallel to the cortex were observed. However, neither dysmorphic neurons nor balloon cells were observed, and vacuolization was also not clearly evident. As a result, the enlarged amygdala pathology was classified as FCD type I. Because of a technical problem in the pathological analysis of the hippocampus, regions CA1–CA3 could not be observed, leaving only the subiculum, CA4, and dentate gyrus. The granule cell layer of the dentate gyrus showed somewhat enlarged cells, and granule cell dispersion was suspected. The subiculum and CA4 showed no neuronal loss, dysmorphia, or pathological gliosis. Based on previous reports of the pathological findings of AE, it may be that mild neuronal loss and gliosis seen in HS would have been observed in regions CA1 to CA3.

The mechanism of AE is still unclear, and various causes have been indicated [5]. The pathology has been found to contain FCD, long-term epilepsy associated tumors, and the results of neuroinflammatory process [6]. In recent years, involvement of autoimmune-mediated encephalitis has been reported as one of the causes of AE [18], but there is no previous illness suspected in the present case. The pathological findings also could not help determine the cause of AE.

4. Conclusions

We report herein a rare case of epilepsy with AE and FLE symptoms, and hippocampal seizure origin identified using SEEG. The enlarged amygdala pathology was classified as FCD type I. These findings are clinically significant for AEC and pathological considerations of epilepsy with AE.

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ebcr.2018.09.011>.

Conflict of interest and acknowledgments

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Ethical statement

Informed consent was obtained from the patient and parents for the research.

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