



Case Report

Emotional stimuli-provoked seizures potentially misdiagnosed as psychogenic non-epileptic attacks: A case of temporal lobe epilepsy with amygdala enlargement

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ABSTRACT

The association between emotional stimuli and temporal lobe epilepsy (TLE) is largely unknown. Here, we report the case of a depressed, 50-year-old female complaining of episodes of a “spaced out” experience precipitated by emotional stimuli. Psychogenic non-epileptic attacks were suspected. However, video-EEG coupled with emotional stimuli-provoked procedures and MRI findings of amygdala enlargement, led to the diagnosis of left TLE. Accurate diagnosis and explanation improved her subjective depression and seizure frequency. This case demonstrated that emotional stimuli can provoke seizures in TLE and suggested the involvement of the enlarged amygdala and the modulation of emotion-related neural circuits.

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1. Introduction

Psychogenic non-epileptic attacks (PNEA) are paroxysmal behaviors that resemble epileptic seizures [5,21]. In contrast with epileptic seizures, PNEA are not associated with excessive or hypersynchronous electrical discharges in the brain [16]. PNEA constitute one of the most important differential diagnoses of drug-resistant epilepsy because the management of PNEA as epileptic seizures can lead to significant iatrogenic harm [21]. In addition, PNEA pose a substantial burden on patients, their families, and the healthcare system [1]. Video-EEG (VEEG) remains the gold standard diagnostic tool for PNEA and/or epilepsy by allowing clinicians to reach a confident and reliable diagnosis [3,16].

The diagnosis of PNEA is challenging because PNEA and epileptic seizures share many similar features [5]. While PNEA are often triggered by emotional stimuli, recent studies demonstrated that emotional stimuli are also exacerbating factors for patients with drug-resistant epileptic seizures [8,19]. However, the association between emotional stimuli

and temporal lobe epilepsy (TLE) is largely unknown. We present a case of emotional stimuli-provoked seizures in TLE with amygdala enlargement (AE), which can easily be misdiagnosed as PNEA. Further, we discuss the mechanisms associated with emotional stimuli and AE.

2. Case presentation

A depressive, 50-year-old, right-handed housewife, complaining of episodes of a “spaced out” experience precipitated by emotional stimuli, was referred to the epilepsy-monitoring unit of general hospital A for suspected PNEA and/or possible drug-resistant epilepsy. The patient had no past (personal or family) history of epilepsy or febrile convulsion, and did not use alcohol or illegal drugs. Three years prior to admission, she was involved in a traffic accident in which her mother-in-law, a fellow passenger, was severely injured. While the patient did not receive a head trauma, as the driver, she considered herself responsible for the incident. Later, she became depressed and began taking an antidepressant after consultation with her primary care physician. One year later, when the car accident was spoken of in a family conversation, she suddenly became unconscious. One month later, she experienced a similar seizure while being interviewed, at the prosecutor's office, during an investigation into the accident. At this point, sodium valproate (VPA) was prescribed. Since then, whenever the topics of either the traffic

Abbreviations: ECD-SPECT, 99mTc-ethyl cysteinat dimer brain single photon emission computed tomography; EEG, Electroencephalogram; FDG-PET, 18F-fluorodeoxyglucose positron emission tomography; MEG, Magnetoencephalography; MRI, Magnetic resonance imaging.

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accident or her mother-in-law's injury arose, she exhibited a paroxysmal episode manifesting as different forms of confusion such as saying "Umm... Umm... Where are we? What are you doing?," stepping without purpose, or walking around while spilling coffee from the cup in her hand.

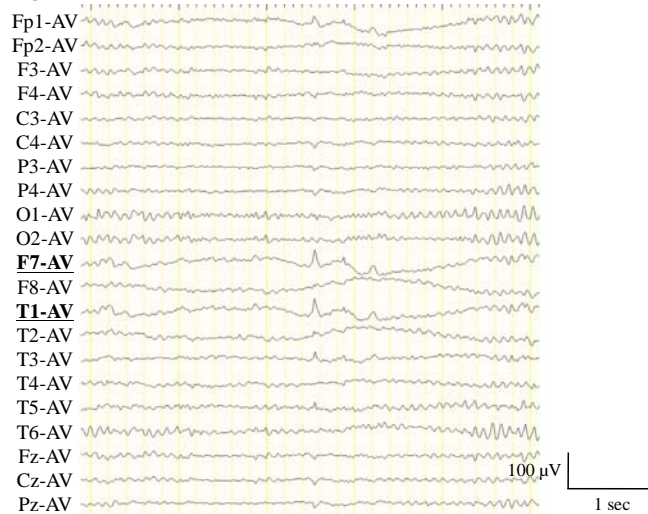
Six months later, the patient started to be prescribed carbamazepine (CBZ), which resulted in fever and epidermal rash, leading to a diagnosis of drug-induced hypersensitivity syndrome (DIHS). She was admitted to the department of dermatology at hospital A; prednisolone was prescribed and CBZ was discontinued. During her one-month hospitalization, the patient did not exhibit any episodes of confusion that had been previously observed. After discharge, these episodes resumed with a frequency of 3–4 times per month, associated with emotional stimuli caused by mentions of the accident or injury; nevertheless, generalized tonic-clonic seizures (GTCS) were absent and repeated EEG recordings did not show any pertinent positive findings. Six months later, the patient was referred to the epilepsy-monitoring unit of hospital A for suspected PNEA and/or epilepsy. Her daily medication on admission was 800 mg VPA, 1000 mg levetiracetam (LEV), and 12.5 mg sertraline. VPA and LEV administration was phased out before VEEG.

During hospitalization, VEEG detected five seizures, two of which were habitual seizures that were provoked by multimodal stimuli. Seizures were triggered by either talking about the emotional distress

experienced due to the traffic accident or reading and writing an emotion-provoking questionnaire (sentence completion test). One spontaneous typical seizure in TLE was documented. Auditory-stimuli (big tones), photo-stimuli, and hyperventilation did not lead to seizures. Interictal EEG showed only low-voltage spikes at F7 and T1, which were not consistently replicated in subsequent recordings (Fig. 1A).

After having explained the importance of recording habitual seizures during the VEEG session, one of the authors (H.T.) intentionally challenged the patient by making emotional stimuli-provoking remarks in order to provoke a habitual seizure, with the informed consent of the patient and her husband. During the "provoking" session (Fig. 1B), the patient heard: "You mean your seizures seem to happen just after you talk about your mother-in-law or think about the car accident, right? That's quite unbelievable." or "If you avoid stressors, your seizures should become manageable." After weakly replying, "Yes, yes..." she exhibited a seizure. Her husband attested it as a habitual seizure, and contrary to our expectations, detailed analysis of the VEEG revealed that jaw-clicking and head-nodding symptoms were associated with approximately 6-Hz bilateral and synchronous discharges, mainly in the left temporal area. The semiology of these seizures was typical of left mesial TLE, including a prodromal aura in the abdomen, automatisms, and dystonic posture of the right upper extremity. A postictal twilight

A) Interictal EEG



B) Ictal EEG

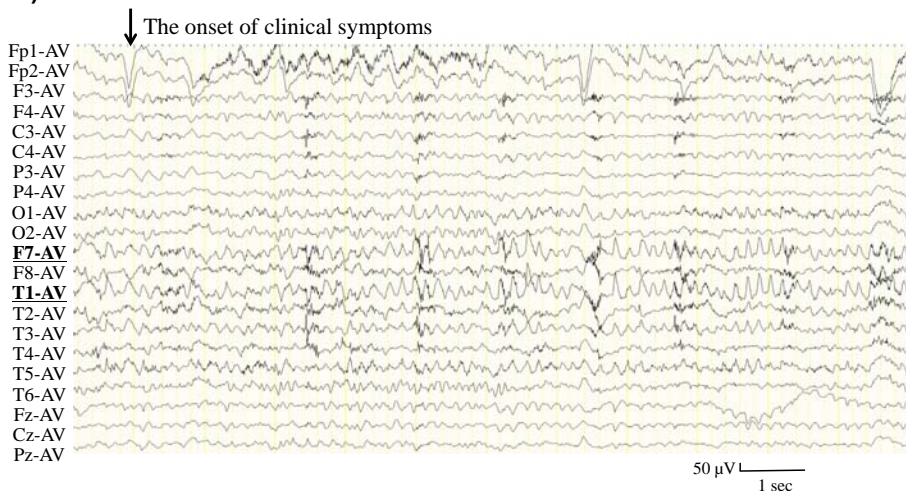


Fig. 1. Interictal EEG (A) and ictal EEG (B) A: Interictal discharge was seen at F7, T1 but could not always be replicated. (Time Constant, 0.3 s; High cut filter, 50 Hz; Average) B: Ictal evolution with maximal voltage at F7, T1. (Time Constant, 0.1 s; High cut filter, 50 Hz; Average).

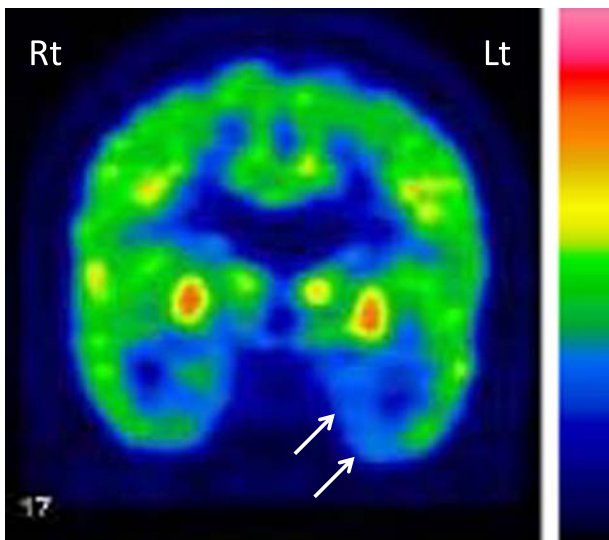


Fig. 2. FDG-PET (coronal section) Decreased glucose metabolism in left mesial temporal lobe including anterior entorhinal cortex (arrows). Rt, right; Lt, left.

state followed the seizure. The FDG-PET (Fig. 2) and ECD-SPECT suggested left mesial TLE. The MRI indicated slight AE and signal elevation (Fig. 3A) with slight changes in the left temporal tip (loss of gray-white matter differentiation, Fig. 3B) and in the left hippocampus (damaged three-layered structure, Fig. 3C). Additionally, the MEG was consistent with the diagnosis.

Lamotrigine (LTG) was then administered, only to be discontinued after the patient developed a slight fever and erythema on the next day. Treatment was readjusted to VPA and LEV. After the patient and her husband were informed about the diagnosis of TLE, based on the VEEG findings, she stopped experiencing habitual seizures during hospitalization. Her depression improved markedly and subjective global assessment of her quality of life, using the Quality of Life in Epilepsy Inventory (QOLIE)-31 [9], improved from 30 (on admission) to 80 (4 months after discharge), despite incomplete remission of the seizures. After the LEV and VPA treatment was discontinued, and for 6 months after discharge, gabapentin (GBP) was administered at

doses of up to 1800 mg/day. This reduced the frequency of seizures to once every 3 months, at 1.5 years after discharge. Epilepsy surgery was recommended to the patient; however, the patient and her husband opted for an alternative treatment by perampanel (PER), a novel and recently approved drug. Treatment with 2 mg/day PER has successfully suppressed seizures without any side effect for over 5 months to the present day, at 2 years after discharge.

3. Discussion

We reported a case of emotional stimuli-provoked seizures in TLE, which can easily be misdiagnosed as PNEA. We initially assessed that the seizures afflicting the patient were PNEA on the basis of ambiguous, repeated interictal EEGs (interpreted to fall within the normal limits), multi-drug resistant seizures [4], a lack of prominent MRI findings such as hippocampal sclerosis, and personal history, which is described as follows: seizures commenced after a “traumatic event” (traffic accident experienced by the patient) and occurred in the presence of family or other witnesses; a seizure-free period was recorded during the one-month hospitalization when the patient was separated from her family; improvement in the patient condition was indicated on avoidance of references to the accident (suspected “gain from illness”). However, a detailed medical investigation using VEEG and other imaging tests led to the final diagnosis of TLE. This case demonstrates the importance of conducting a comprehensive assessment in cases of stimuli-provoked seizures before confirming the diagnosis as PNEA.

In the following text, we discuss three conditions: (1) temporal lobe epilepsy with amygdala enlargement, (2) emotional stimuli-provoked seizures and the involvement of the amygdala, and (3) integration of biological and psychological approaches for treatment.

3.1. Temporal lobe epilepsy with amygdala enlargement (TLE with AE)

Recent studies have shown that patients with late onset TLE without hippocampal sclerosis often have AE [17,18]. A history of emotional disorders such as depression or anxiety, and memory decline, both evident in this case, are common features of TLE with AE. Interictal epileptiform discharge due to TLE with AE is difficult to detect using scalp EEG. Further, the occurrence of seizures during sleep and their semiology are both typical of TLE with AE [17].

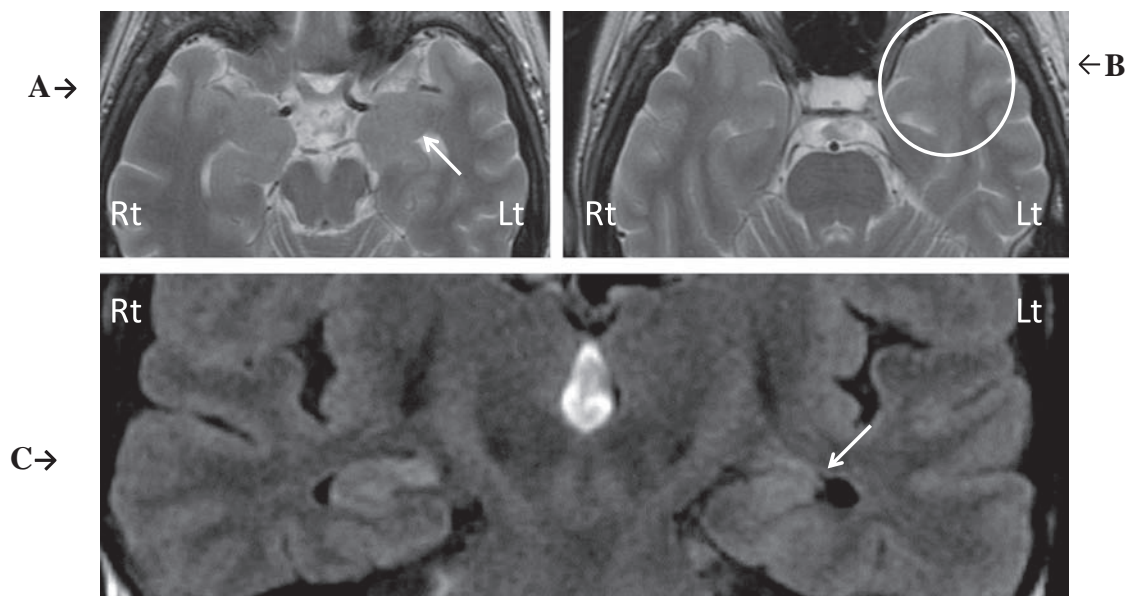


Fig. 3. MRI A: T2 weighted axial section. Slight enlargement and high intensity of the left amygdala (arrow) are detected. Due to a methodological limitation, volumetry is not performed. B: T2 weighted, axial section. Loss of gray-white matter differentiation of the left temporal tip (circle) is detected. C: Fluid-attenuated inversion recovery, coronal section. Three-layered structure is damaged in the left hippocampus (arrow). Neither cortical dysplasia nor tumor is detected. Rt, right; Lt, left.

In the present case, we believed the traffic accident could have resulted from a focal seizure with impairment of consciousness. Based on the observations made during the seizure-provoking sessions, depression appears to have been caused by perceived criticism in the patient when her family members or other individuals mentioned the incident. The case could have been misdiagnosed without the VEEG findings, because the manifestations of AE are often non-specific; additionally, GTCS in TLE with AE are not common, which can potentially hamper the correct diagnosis.

3.2. Emotional stimuli-provoked seizures and the involvement of the amygdala

Emotions can trigger PNEA; however, previous studies reported only a general link between emotional stimuli and epileptic seizure frequency. Exposure to emotional precipitants such as memories of sexual abuse or being in the presence of a certain person can reportedly provoke epileptic seizures. However, only a few reports have demonstrated a direct relationship between epileptic seizures and emotional precipitants [7,23]. Cognition-induced epilepsy is widely used to designate seizures precipitated by specific cognitive tasks such as reading or speaking aloud and is a subtype of “reflex epilepsy” or “reflex seizures” [22,24]. Photosensitive epilepsy and reading epilepsy are the most commonly encountered types of reflex epilepsy. However, recent reports suggest that “higher-order” seizure triggers are more common than previously thought [22]. Thus, the use of the more inclusive terms, “provoked seizure” and “provoked epilepsy” were recommended to indicate the unmistakable interaction between the various general and specific factors [6,11].

Although the pathophysiology of seizures triggered by emotional stimuli is unclear, secretion of multiple hormones, possible neuroanatomic involvement, network hyperexcitability, and an excitation/inhibition balance (E/I balance) of interneurons have been suggested as its possible causes [7,13,14,22,23]. Since the primary amygdala nuclei and basic circuits and functions are conserved across species, the amygdala is believed to be associated with emotional processing [10]. Following significant recent advances in imaging techniques, the bidirectional association of the limbic system, including the amygdala, and focal seizures in TLE have been widely studied [2]. Long-lasting inflammation might be associated with AE. However, the mechanism leading to AE in TLE has not been identified yet [17]. In the present case, a causal association between AE and epileptic seizures was not proven. It is possible that the amygdala of the patient was innately susceptible to AE before the car accident and/or AE could have been enhanced by emotional circuit excitation following the traumatic event.

Nonetheless, this case highlighted the direct association between TLE and emotional stimuli caused by both talking and reading about the traumatic event, as seen during the provoked seizure, suggesting that the amygdala may be associated with emotional stimuli-provoked seizures. We speculate that amygdala excitation and refractory temporal lobe epileptic seizures possibly have an accelerative effect on each other.

3.3. Integrations of biological and psychological approaches for treatment

The combination of anti-seizure drugs and emotional stimuli management resulted in considerable improvement in the present case. Optimizing medication with careful attention to adverse effects is crucial. Previous reports have demonstrated that patients with TLE with AE show dramatic improvement after medical therapy [2,12]. In the present case, CBZ and LTG unfortunately caused adverse dermatological effects. Although VPA and LEV partially alleviated seizure frequency, GBP and PER successfully remitted her seizures after discharge.

Regarding the psychological aspects of the case, informing the patient of the correct diagnosis and explaining the management of provoking factors were deemed important for treatment, in accordance

with the protocol that is recommended for patients with PNEA [15]. During hospitalization, we encouraged the patient not to think about her mother-in-law or the traffic accident, as these thoughts appeared to be conditioned stimuli for her seizures [22]. After the patient understood the diagnosis of TLE and the role of stressors in triggering the condition, she experienced a dramatic decrease in seizure frequency and the subjective global assessment of quality of life recorded by the patient herself showed prominent improvement. Since the biomedical therapy was unchanged during hospitalization, explaining the condition to the patient might have offered certain psychological or cognitive therapeutic benefits.

In the provoking session, we used non-masked (overtly presented) stimuli related to the psychological trauma. However, previous studies have shown that the amygdala also responds to masked stimuli in patients with posttraumatic stress disorder [20]. Thus, we should have used masked stimuli first to ensure a more cautious and ethical clinical practice; nevertheless, recording habitual seizures during VEEG was considered the first priority during hospitalization.

Our results demonstrate that emotional stabilization can be effective in patients with emotional stimuli-provoked seizures, caused by TLE associated with amygdala dysfunction. Intractable seizures can alter cognition; conversely, activating specific cognitive networks can directly lead to seizures and affect their frequency [22]. Accordingly, the patient's emotions triggered the seizures and vice versa in the present case. Further research on cases of emotional stimuli-provoked seizure in TLE may clarify the function of the amygdala circuit, the pathophysiology of provoked seizures, and the management of psychological trauma without amygdala activation.

4. Conclusion

We reported a case of emotional stimuli-provoked seizures in TLE with AE. Certain forms of emotional stimuli can provoke seizures in susceptible individuals with epilepsy. We suspect that modulation of the emotional circuit by the amygdala is associated with this phenomenon.

Accurate diagnosis of PNEA and/or epilepsy is the first essential step in treating patients with refractory seizures. A thorough investigation is needed before the diagnosis of PNEA is confirmed. Our experience further confirms that monitoring epilepsy with VEEG and other imaging tests is important for differentiating refractory epilepsy from PNEA. Correct diagnosis might resolve the distress and seizure frequency of patients with PNEA and/or TLE. Further studies are warranted to clarify the mechanism of emotional stimuli-provoked seizures in TLE with AE and to suitably manage the concurrent psychological trauma.

Disclosures

None of the authors has any conflict of interest to disclose.

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