



## A complex case with generalized epilepsy, probable focal seizures, and functional seizures

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### ABSTRACT

In this patient, now 42 years old, genetic generalized epilepsy (juvenile myoclonic epilepsy) manifested itself at the age of 13. At the age of 39, she experienced a status episode with prolonged ICU treatment. She was left with a left-sided hippocampal sclerosis and probably focal seizures. In addition, since the age of 24, the patient also experiences functional seizures on the background of a borderline personality disorder. While generalized epileptic seizures could be controlled with antiseizure medication (ASM), the patient was multiple times admitted to Emergency Departments for her functional seizures with subsequent intensive care treatments, including intubation. As a complication, the patient developed critical illness polyneuropathy and myopathy, resulting in wheelchair dependence. Additionally, she acquired a complex regional pain syndrome after extravasation of ASM. The report demonstrates the uncommon development of hippocampal sclerosis after a generalized tonic-clonic status epilepticus and the poor treatability of functional seizures as compared to generalized and focal seizures.

### Introduction

Juvenile myoclonic epilepsy (JME) remains the most common form of genetic generalized epilepsy, impacting 5–10 % of individuals with epilepsy, with an occurrence rate of 1–2/1000,000 [1], typically emerging during adolescence. It is characterized by myoclonic seizures, often accompanied by generalized tonic-clonic seizures and absence seizures, as well as electroencephalography patterns showing generalized spike and polyspike waves. Despite appropriate response to antiseizure medication (ASM), approximately 35 % of patients exhibit resistance to treatment [2].

Psychiatric disorders are highly prevalent among individuals with idiopathic generalized epilepsy (IGE), with rates reaching as high as 51 %, with mood/affective disorders affecting up to 40 % of cases, and anxiety disorders impacting up to 30.8 % of cases. In individuals with juvenile myoclonic epilepsy (JME), personality disorders affect up to 11 %, while psychotic disorders are observed in up to 4 % of epilepsy

patients [3].

Functional seizures (FS), also known as dissociative seizures or psychogenic nonepileptic seizures, manifest as paroxysms of impaired awareness and motor control, arising from a complex neuropsychiatric origin. Often mistaken for epileptic seizures due to convulsive movements and reduced responsiveness, this misdiagnosis can lead to ineffective and potentially harmful treatments [4,5].

The estimated annual incidence of functional seizures is 1.4 to 4.9 per 100,000 people, representing over 10 %–27 % of seizure emergencies and approximately 30 % of cases in specialized epilepsy centers [4]. A systematic review revealed that epilepsy occurred in 22 % of FS patients, while FS was present in 12 % of epilepsy patients [6]. Furthermore, depression and anxiety were more prevalent in FS patients compared to those with epilepsy, while stress and suicide risk showed no significant difference between the groups [7].

Epileptologists mainly look after patients with one of these three types of chronic seizure disorders: generalized epilepsy, focal seizures,

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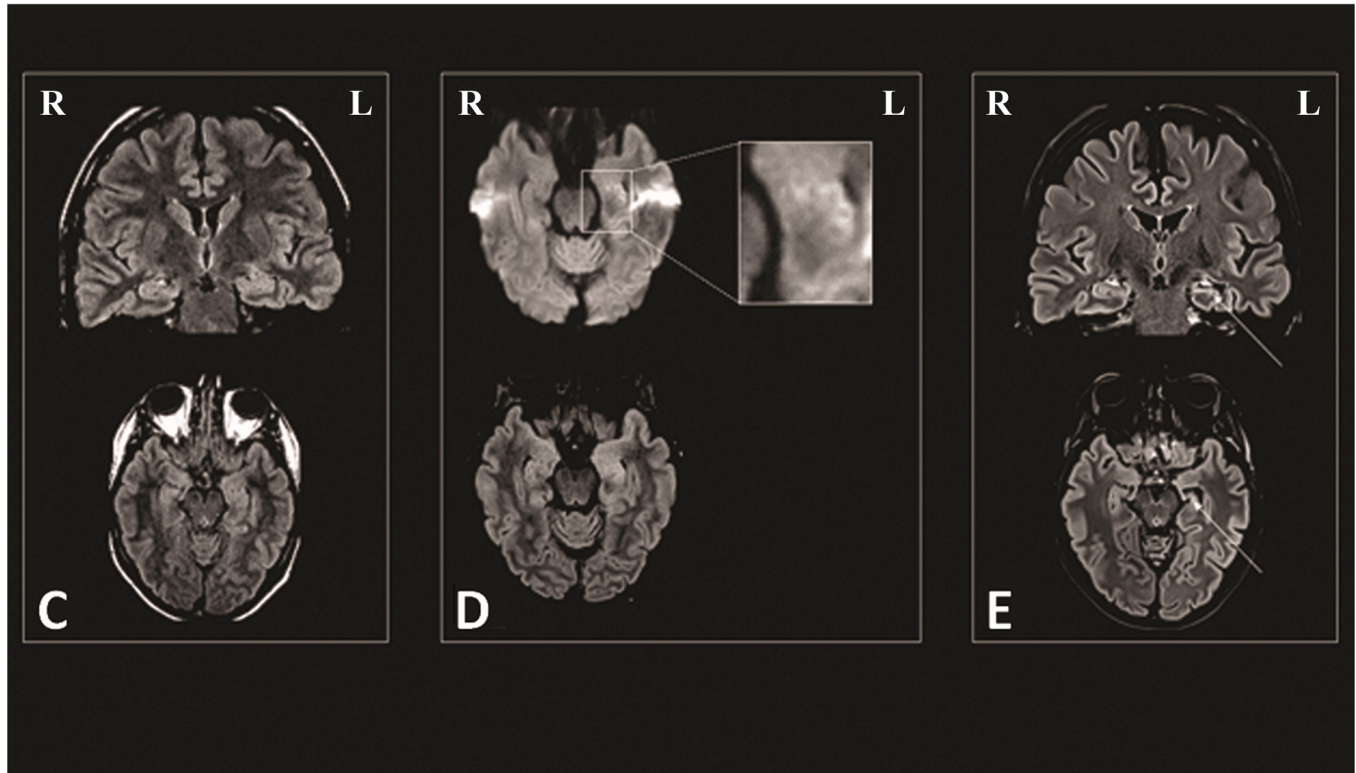
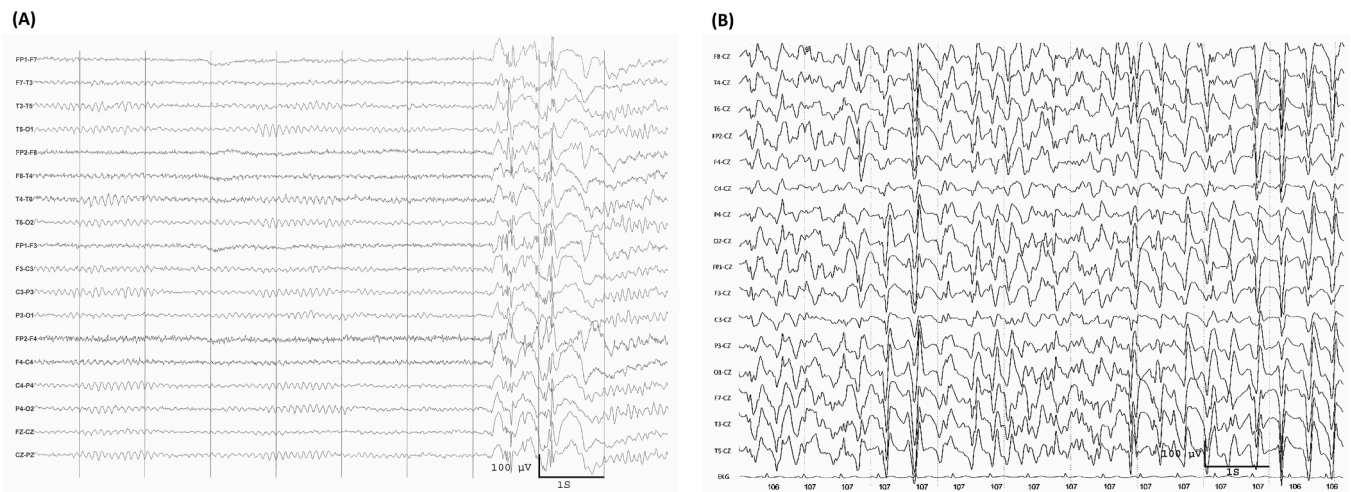
or functional seizures. Some patients may have epilepsy and functional seizures. Here, we present the very rare situation of a patient having all three conditions. The functional seizures presented the most significant challenge in this patient.

**Case report**

*The stage with generalized seizures*

After uneventful pregnancy, birth and early development, at the age of 13, this patient with no family history of epilepsy was diagnosed with

absences. An absence episode lasting 3 s during hyperventilation was documented with generalized 3/s spike-wave activity on the EEG. The patient was started on ethosuximide. One year later, two tonic-clonic seizure occurred, both upon awakening. Valproic acid was added, and the patient became seizure-free, even after discontinuation of ethosuximide. Starting at age 16, VPA was tapered down. After two or three seizure-free years without ASM, absences reoccurred, and VPA was started again resulting in complete or near-complete seizure freedom. She trained as a foreign language secretary and later worked as a secretary or an IT system administrator.



**Fig. 1.** EEG and MRI findings. (A) EEG during hyperventilation at the age of 25. Please note the generalized polyspike-wave complexes (bipolar montage, “double banana”). (B) EEG showed a status epilepticus at the age of 39 years (referential montage, CZ). (C-E) Serial brain magnetic resonance images (MRI). (C): study at age 25, coronal and axial Fluid-attenuated inversion recovery (FLAIR) sections showing normal findings, especially no hippocampal sclerosis. (D) study at age 39 close to the ICU treatment, axial FLAIR (below) showing perifocal edema in the hippocampal head, axial diffusion-weighted imaging (above) showing laminar necrosis (window with enlarged detail); (E) study at age 41, coronal and axial FLAIR sections showing left-sided hippocampal sclerosis (arrows).

### The stage with functional seizures and generalized seizures

At the age of 24, the seizure situation deteriorated, presenting both functional seizures and epileptic seizures. New seizures emerged, distinct from typical epileptic tonic-clonic seizures experienced at the age of 14, which induce confusion and require post-seizure sleep. These new episodes involved closed eyes, irregular arm movements, and arc de cercle, diagnosed as functional seizures. Furthermore, unlike known absence seizures lasting less than 30 s with eyelid and occasional shoulder myoclonia, these new episodes lasted 11 min, characterized by jerking of arms and legs, also assessed as functional. Juvenile myoclonic epilepsy (JME) as well as functional seizures (with a probable diagnosis certainty according to [8]) were diagnosed after several admissions to several hospitals, two of which were major epilepsy centers. Treatment was administered among these different hospitals. Phenobarbitone (100 mg/d, 21 µg/ml) was added to valproate (2000 mg/d, 90 µg/ml). Several brain MRIs gave normal results. An EEG, recorded at the age of 25 at our rehabilitation department, revealed generalized polyspike-wave complexes during hyperventilation (Fig. 1A).

The patient was repeatedly and thoroughly informed about the diagnosis at two epilepsy centers. At this center, this was done in a calm and supportive atmosphere, with the patient alone and together with her husband with information similar to that of the NEST study as a basis [9]. The patient was advised about genuine symptoms, labels of the condition, cause and maintaining factors, treatment, and expectations. The information linked FS primarily to mood, stress and trauma and introduced the concept of dissociation. Despite these careful explanations and after multiple admissions to various neurological departments, the patient did not agree with the proposed diagnosis and concepts and did not accept the recommended psychotherapy. It was reported that there was anxiety and a lack of alignment with the treatment teams. She was diagnosed with borderline personality disorder (BPD), known risk factor for difficulties in conveying the diagnosis of FS [10]. Functional seizures continued. At the age of 26, the patient attempted suicide using her ASM, which included valproate, phenobarbitone, chloral hydrate and clobazam at that time. At the age of 34, as a treatment complication during the management of a status episode (unclear, if epileptic or functional), extravasation of ASM possibly phenytoin, occurred, resulting in a complex regional pain syndrome. Since then, the patient has been receiving opioid therapy to manage this condition. It is unknown to the authors if modern approaches like desensitization were recommended or even tried in this patient. Following the onset of functional seizures, the patient never achieved seizure freedom, leading to continuous admissions to different hospitals and intensive care units. Additionally, admissions were frequently and swiftly interrupted due to her psychiatric comorbidities. Consequently, many available ASMs on the market, including valproate, phenobarbital, topiramate, gabapentin, clobazam, lamotrigine, levetiracetam, brivaracetam, clonazepam, and zonisamide, were attempted in various combinations over the years without achieving seizure control. This included off-label medications for generalized epilepsy, such as gabapentin and phenobarbital. These complications arose during her brief treatment at emergency centers, intensive care units, or general neurological clinics.

She has experienced various forms of functional seizures, lasting up to 90 min at a frequency of up to every 2–3 days. There were even repeated series of functional seizures during one day. Differentiating between epileptic and functional seizures was challenging for emergency doctors, as the functional seizures presented with semiology roughly comparable to generalized tonic-clonic epileptic seizures. This led to intubation and admission to the intensive care unit with a presumptive diagnosis of status epilepticus (SE) more than five times per year, following the failure of emergency benzodiazepine medication.

### ICU treatment for SE, development of hippocampal sclerosis

Over time, the semiology of functional seizures evolved significantly,

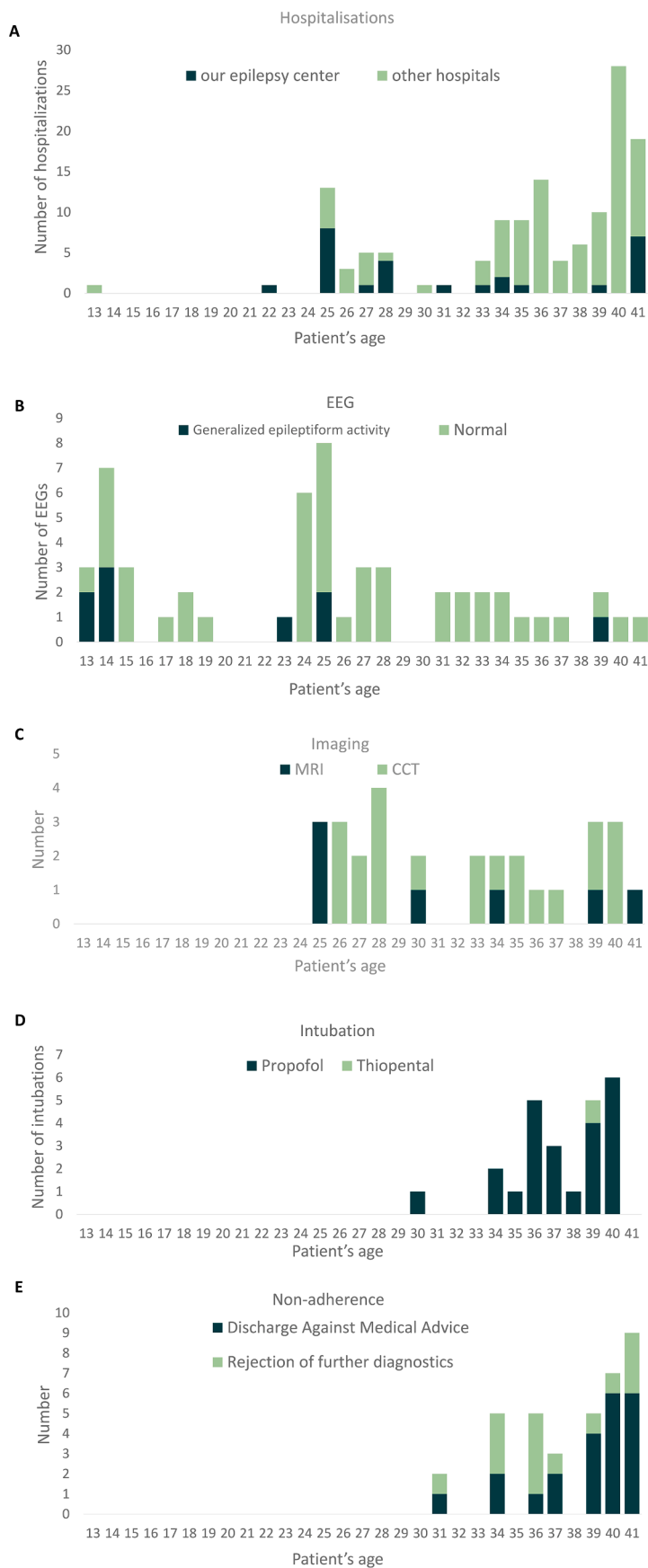
becoming difficult to differentiate from epileptic seizures featuring rhythmic but agonist–antagonist movement of the limbs lasting over 45 min, a congested face without Oxygen saturation drop, oral bleeding through frontal tongue biting, and devoid of postictal symptoms. At the age of 39, the patient was once more admitted to a hospital after “several days with daily generalized seizures” (no more detailed description available). The blood levels of ASM were assessed on the day of admission, revealing phenobarbitone at 36 µg/mL, levetiracetam at 27 µg/mL, gabapentin at 14.2 µg/mL, and lacosamide at 9.1 µg/mL, all within standard “therapeutic ranges”. The first EEG was conducted two days after admission and revealed “generalized spikes and slow waves” according to the report, which did not indicate if this was a continuous or intermittent epileptiform activity. The patient had more seizures that were interpreted as generalized epileptic seizures. Following the administration of thiopental anesthesia, she was switched again to phenobarbitone, lacosamide, clobazam and levetiracetam therapy, but a follow up EEG revealed SE (Fig. 1B), and she was subsequently treated for one month in the intensive care unit for the SE. The patient acquired a pneumonia and an acute pyelonephritis with septic shock. The tentative diagnosis of Addison’s disease (adrenal insufficiency) was made, and the patient was put on hydrocortisone. A post-extubation MRI revealed a left hippocampal FLAIR hyperintensity and a laminar necrosis on the diffusion weighted images (Fig. 1D), which were not present in the patient’s previous MRI performed in 2006 (Fig. 1C). Upon discharge, the patient had significant muscle weakness in all four limbs (tetraparesis) and depended for walking on a wheelchair. This was interpreted as critical illness polyneuropathy and myopathy. The patient refused a neurophysiological investigation to objectify this diagnosis.

### Present situation

From the age of 40, the patient has presented frequently to our department as an emergency due to an increased frequency of seizures. She was electively admitted for a comprehensive assessment at age 42. During the admission conversation, the patient reported experiencing absence seizures and occasional symmetric myoclonic jerks since discharge from the ICU treatment at age 39. She also mentioned experiencing a peculiar sensation in her abdomen and twitching on the right side of her body suggesting probable focal seizures arising from the left hemisphere, potentially including the medial temporal lobe. At that time, the pharmacotherapy included a combination of six antiseizure medications, some of them being licensed for focal seizures: phenobarbitone, clonazepam, levetiracetam, lacosamide, clobazam, and gabapentin. The patient exhibited labile affect and displayed verbal aggression towards the nursing staff. MRI revealed left hippocampal sclerosis, likely a result of a previous episode of SE (Fig. 1E). Neural antibody panel testing in serum was negative. Despite recommendations for continued hospitalization to potentially document seizures by camera surveillance or the inspection by the hospital staff, the patient discharged herself against medical advice after two days. She refused a video-EEG monitoring and psychotherapy.

The patient’s previous hospital admissions were reviewed, and a retrospective analysis was conducted on her medical records. This analysis included EEG reports, the number of intubations, MRI and CCT findings, as well as instances of discharge against medical advice. The results are summarized in Fig. 2.

To reflect on the complex course of the disease, a multi-professional case conference was held (neurology, psychiatry, nursing staff, social service). As a result, these measures were offered: (1) a prolonged long-term video EEG to the patients to clarify the frequency and severity of generalized, focal and functional seizures; (2) outpatient or inpatient psychotherapy; (3) repeated outpatient consultations to build a constant therapeutic relationship including psychotherapeutic elements (treatment contract, accepting-structuring conversation) in The Mara (Dept. of Epileptology); (4) information of the local first aid rescue service to bring the patient always to this department after seizures to avoid



**Fig. 2.** Investigations, intubations, and non-adherence to medical advice from the age of 13 to the age of 41. (A) This graph illustrates the number of hospitalizations. (B) EEG recordings per year with normal and pathological EEGs. (C) MRIs and CCTs per year. (D) Number of intubations per year. (E) Annual frequency of discharge against medical advice and rejection of further diagnostic procedures.



iatrogenic damage caused by overtreatment of functional seizures.

Unfortunately, the patient refused all offers.

## Discussion

This patient had the rare co-occurrence of generalized seizures (onset age 13), FS (onset age 24) and probable focal seizures (onset age 39). A turning point was one ICU treatment epoch at age 39 with evolution of hippocampal sclerosis resulting in probable focal seizures and epilepsy plus peripheral weakness, presumably a critical illness polyneuropathy and myopathy. In the absence of conclusive electrophysiological evidence, the definitive diagnosis of critical illness polyneuropathy and myopathy remains elusive. Therefore, it is essential to consider functional movement disorder as a plausible differential diagnosis. While the patient still reports on generalized and probable focal seizures, these have not led to emergency admissions or treatment interventions. The dominant problem are the FS. In numerous studies, it has been observed that patients diagnosed with FS tend to have a significantly higher rate of seizure-related readmissions or Emergency Department (ED) visits compared to those with epileptic seizures. The majority of these return visits to the hospital occur through the ED. The reasons for readmission in such cases often encompass factors like breakthrough seizures, the recurrence or emergence of new FS episodes, the presence of active psychiatric symptoms, complications related to ASM, and issues arising from the original admission's medication management [4,11,12].

The difficulty arose from the patient's reluctance to undergo further video-EEG clarification, impacting the assessment of the relative contribution of the three seizure forms. There may be a relation between JME and the psychiatric problems in our patient. A systematic review of 13 studies with varying methodologies and reporting found that personality disorders were present in up to 11 % (BPD 6–9 %) of individuals with JME [3,13,14]. BPD has been diagnosed in our patient. Such patients struggle to establish mutually collaborative relationships, which may be linked to their inability to find value in cooperation. This leads to social difficulties and unpredictable behavior, impacting relationships and therapy and exacerbating the management of functional seizures in our case. [13–15]. Risk factors such as pre-existing epileptic seizures, chronic and unpredictable diseases, and negative healthcare interactions may contribute to functional seizures. Stress is closely tied to numerous psychiatric disorders. A meta-analysis shows increased frequencies of childhood and adulthood stressors preceding Functional Neurological Disorder (FND) symptom onset, particularly when compared to healthy controls [16,17]. Additionally, childhood maltreatment is associated with more severe and frequent relapses of bipolar affective disorder, higher rates of psychiatric comorbidity, and increased suicide attempts [18].

Managing a patient with coexisting generalized epilepsy, probably focal seizures, and functional seizures poses significant challenges. The functional seizures have led to exaggerated and partly harmful diagnostic and therapeutic interventions (see Fig. 2) [19]. We are uncertain whether the HS originated from a generalized tonic-clonic SE at the age of 39 since we are unable to determine definitively whether these seizures were epileptic or functional in nature. Alternatively, the hippocampal sclerosis may have resulted from a nonconvulsive SE, as evidenced by its detection on the EEG conducted seven days after admission, which was accessible to us (Fig. 1B). One potential cause of SE in this case could be medication non-adherence and subtherapeutic serum levels of ASM. However, the ASM blood levels on the day of admission laid within the "therapeutic range", making these explanations less likely. Unfortunately, the patient was managed at a different hospital so that we have only limited data on the episode and our understanding of the exact cause is constrained.

Jungilligens et al. investigates the misdiagnosis of prolonged functional seizures as status epilepticus. Among 1210 patients diagnosed and treated as status epilepticus, 8.1 % were eventually diagnosed with functional seizures, with the highest prevalence observed in adolescents

and young adults. The study suggests incorporating specific protocols for identifying functional seizures in emergency response algorithms, including the use of ictal video, EEG, and postictal laboratory markers. ICU admission rates were high, especially in patients treated with benzodiazepines before reaching the hospital. ICU treatment poses significant distress and risks, including ICU-related post-traumatic stress disorder [20].

A retrospective study on 203 emergency presentations diagnosed with dissociative seizures revealed that emergency physicians correctly diagnosed dissociative seizures in only 12 % of cases, with improvement to 52 % or 62 % after neurology-led workup. Expert assessment based on distinct semiology without ictal EEG showed emergency physicians recognized dissociative seizures in only a quarter of cases. Educational efforts significantly improved diagnostic accuracy among emergency physicians. Benzodiazepines were frequently administered, with a median cumulative dose exceeding recommended limits. While benzodiazepines sometimes halted observable seizure phenomena, their efficacy remains uncertain, and their high doses pose risks of critical sedation and ICU-related complications [21].

In a retrospective study of 69 patients with JME, three women experienced typical absence status and one (1.4 %) had myoclonic status [22]. In another retrospective JME study, 5/133 patients (3.8 %) were diagnosed with SE. Most common was myoclonic SE in four patients (3.0 %), followed by generalized clonic-tonic-clonic SE in one patient, and nonconvulsive SE in another patient (one patient experienced both, myoclonic SE and generalized clonic-tonic-clonic SE). Ictal EEG recordings during SE were available for three patients and showed continuous generalized spike-wave and polyspike and wave discharges with various morphologies. In one patient, the EEG revealed generalized paroxysmal fast activity during the MSE episode [23].

A systematic review of 35 studies on SE explored seizure-induced reversible MRI abnormalities (SRMA) in patients with pre-existing focal and generalized epilepsy, as well as those with their first unprovoked seizure. Five stereotypical SRMA patterns were identified, involving the cortex, subcortical region, hippocampus, claustrum, and splenium. Cortical abnormalities were most common, followed by hippocampal and bilateral claustrum involvement. Additionally, cortical atrophy was identified as a long-term consequence. Hippocampal involvement emerged as the most frequent pattern in refractory SE. The study analyzed clinical and EEG characteristics of SRMA in different SE subtypes, noting unilateral or bilateral SRMA in focal SE and limited data on laterality in generalized SE. Focal seizure patients typically exhibited unilateral SRMA, while generalized seizure patients were more likely to show bilateral signal changes [24]. In view of these studies, it is not unlikely that indeed a generalized SE occurred in our patient. Hippocampal sclerosis may be either a sequelae of SE [25] or a result of the complex ICU treatment [26].

This case highlights the complexities of managing patients with FS and comorbid epileptic and psychiatric conditions, emphasizing the need for a comprehensive and multidisciplinary approach in their care.

In conclusion, this complex case involves generalized and probable focal epilepsy as well as FS. While the epileptic seizures probably could be controlled to a useful degree, the FS proved severe and challenging to manage due to the lack of adherence to treatment recommendations. They occur against the background of an emotionally unstable personality disorder. Psychotherapeutic elements (case conference, treatment contract, conversation) could have been helpful if they had been accepted and implemented by the patient.

## Ethical statement

The Ethics Committee of the University of Münster approved the study protocol (no. 2023-611-f-S) and granted a waiver for patient consent in accordance with the North Rhine-Westphalian law on health data protection (Gesundheitsdatenschutzgesetz NRW).

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None.

## CRedit authorship contribution statement

**Ahmed Elshetihy:** Writing – original draft, Visualization, Investigation, Formal analysis, Data curation, Conceptualization. **Lema Nergiz:** Writing – review & editing. **Thomas Cloppenburg:** Writing – review & editing. **Friedrich G. Woermann:** Writing – review & editing. **Birgitt Müffelmann:** Writing – review & editing. **Christian G. Bien:** Writing – review & editing, Supervision, Resources, Conceptualization.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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