BJPsych Open (2025)
11, e213, 1–5. doi: 10.1192/bjo.2025.10836

Persistent psychiatric symptoms in apparently well-controlled epilepsy: case report

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Background

Epilepsy is frequently accompanied by psychiatric symptoms, including mood disturbances such as depression, irritability and euphoria. Interictal dysphoric disorder (IDD), characterised by depressive and affective symptoms, is typically managed with psychiatric treatment. However, persistent symptoms, despite adequate psychiatric intervention, may indicate an underlying epileptogenic mechanism.

Aims

To highlight the importance of recognising epileptogenic contributions to persistent psychiatric symptoms, even in patients with apparently well-controlled epilepsy.

Method

We present a case report of a Japanese woman in her 40s with well-controlled epilepsy; however, she developed enduring psychiatric symptoms. Clinical features, psychiatric treatments, neurological evaluation and therapeutic outcomes are described.

Results

The patient experienced anxiety, depression, irritability and fear, leading to an initial diagnosis of IDD. Treatment with escitalopram and olanzapine achieved only partial symptom relief. Residual symptoms prompted further investigation, which revealed symptoms suggestive of temporal lobe epilepsy auras. Adjustment of anti-seizure therapy with lacosamide resulted in complete resolution of psychiatric symptoms, marked functional recovery and a reduction in her Hamilton Depression Rating Scale (HAMD-17) score improved from 23 to 6.

Conclusions

This case highlights that even in apparently well-controlled epilepsy persistent psychiatric symptoms may indicate an underlying epileptogenic mechanism rather than a primary psychiatric disorder. Careful evaluation and appropriate optimisation of anti-seizure medication can yield substantial psychiatric and functional improvements, underscoring the importance of multidisciplinary assessment in such presentations.

Keywords

Electroencephalography (EEG); epilepsy; temporal lobe epilepsy; psychiatric symptoms; anti-seizure medication.

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Epilepsy is a neurological disorder that often involves psychiatric symptoms,[1,2] either in association with seizures[3] or independently.[4] In the psychiatric context, Kraepelin and Bleuler rigorously documented affective symptoms in patients with epilepsy, including low mood, irritability and euphoria.[5–7] Building on this understanding, Blumer et al[8] introduced the concept of interictal dysphoric disorder (IDD), which encompasses eight distinct symptoms categorised into three groups: labile depressive mood (anergia, depressed mood, insomnia and pain), labile affective symptoms (anxiety and fear) and specific symptoms (euphoric moods and paroxysmal irritability). The prevalence of IDD has been reported in limited studies, with rates of 19% among outpatients[7] and as high as 57% among in-patients.[9] These findings highlight the clinical significance of recognising IDD in epilepsy care, although its diagnostic boundaries remain debated because of overlaps with mood disorders, anxiety disorders and somatoform disorders under DSM criteria.[10]

In the presented case, the patient's seizures appeared well controlled, and neither the referring physicians nor our initial assessments considered an epileptic mechanism as the primary driver of her psychiatric symptoms. Initial treatment strategies were implemented based on the presumptive diagnosis of IDD, focusing on symptomatic management. However, further investigation suggested that her condition might be predominantly influenced by an epileptogenic mechanism. This realisation prompted a shift in the therapeutic approach, resulting in significant improvement in her psychiatric symptoms. This case report aims to raise awareness among psychiatrists about the potential for epileptic mechanisms to underlie persistent psychiatric symptoms, emphasising the clinical importance of this consideration in practice.

Epilepsy is frequently accompanied by neuropsychiatric comorbidities such as depression, anxiety, irritability and cognitive dysfunction, which significantly affect patients' daily functioning. These symptoms may arise from shared neurobiological mechanisms. As noted by Tolchin et al,[11] understanding these comorbidities is crucial for appropriate diagnosis and care in epilepsy.

Case presentation

A Japanese woman in her 40s, the eldest of two siblings, with no family history of psychiatric disorders, was referred to our department with persistent anxiety and depressive symptoms.

Her perinatal and developmental history were unremarkable, and she had no history of febrile seizures. She had a stable upbringing and completed high school before working as a retail salesperson for over a decade without significant issues. She later became a homemaker after marriage. At the time of admission to our psychiatric ward at Osaka University Hospital, she was living with her husband, but had temporarily returned to her parents' home because of exacerbation of psychiatric symptoms.

https://doi.org/10.1192/bjo.2025.10836 Published online by Cambridge University Press

Her epilepsy was first diagnosed around 20 years ago, after experiencing generalised tonic-clonic seizures. She was initially treated with zonisamide (maximum dose: 200 mg/day), and levetiracetam (maximum dose: 1000 mg/day) was introduced later during the course of her treatment at the neurology department of a local hospital. Following her initial diagnosis of epilepsy in her 20s, the patient had long periods of stable seizure control without any apparent psychiatric symptoms.

Approximately 5 years before admission to our university hospital's psychiatric ward, she began experiencing focal seizures with impaired awareness, characterised by a rising epigastric sensation and paroxysmal fear, without convulsions. During the same period, she developed psychiatric symptoms, including depressive mood and anxiety, which were treated with escitalopram and olanzapine. Despite intermittent symptom relief, she experienced frequent episodes of loss of consciousness, prompting further evaluation at the neurosurgery department of another university hospital with expertise in epilepsy treatment 4 years before admission to our psychiatric ward. Brain magnetic resonance imaging (MRI) revealed enlargement of the left amygdala and hippocampus without progression over subsequent imaging studies, suggesting a non-neoplastic lesion. The patient was subsequently admitted to the same hospital and underwent prolonged video electroencephalography (EEG) monitoring for 5 days. During the admission, she experienced two episodes of seizures characterised by a rising epigastric sensation; however, both episodes occurred when she was in the restroom and the EEG electrodes had been temporarily removed, resulting in the inability to record these events. Additionally, she reported experiencing paroxysmal fear during her hospital stay, but no corresponding EEG changes were observed. After being diagnosed with temporal lobe epilepsy, she resumed anti-seizure medication therapy at the neurology department of a local hospital, where lacosamide (LCM) was introduced as a replacement for the previous regimen of zonisamide and levetiracetam, successfully reducing her focal impaired awareness seizure frequency to a point where seizures had nearly ceased.

One year before admission to our psychiatric ward, she developed persistent, unexplained anxiety lasting most of the day, along with episodes of extreme irritability and fear, and somatic symptoms such as chest discomfort. At that time, both escitalopram and olanzapine had been discontinued, as her psychiatric symptoms had remained well controlled up to that point. These symptoms progressively intensified, leading to a depressive episode with suicidal ideation, which she expressed to her family. She was urgently admitted to a psychiatric hospital and diagnosed with major depressive disorder. During her admission, she experienced anxiety that persisted for most of the day and episodes of intense irritability and fear. During her treatment with sertraline as the primary agent, her symptoms only partially improved. After approximately 2 months in hospital, she was discharged home. However, residual anxiety and low motivation persisted, prompting her family, after researching treatment options online, to request electroconvulsive therapy (ECT). This led to her referral to our Department of Psychiatry at Osaka University Hospital, which is equipped with facilities for ECT, for further evaluation.

Hospital course

In this case, ECT was not immediately conducted. Instead, thorough evaluation and adjustments to pharmacological treatment were agreed upon as the initial approach, after discussions with the patient and her family. At the time of admission, the patient was on lacosamide 100 mg daily and had experienced no generalised tonic-clonic or impaired-awareness seizures for at least 2 years. The patient was considered highly adherent to her medication regimen, and no significant side-effects were observed throughout her clinical course. In addition, she had no notable medical comorbidities and was not taking any medications other than anti-seizure and psychotropic drugs.

EEG revealed small-amplitude, sharp-wave-like activity in the bilateral temporal regions, but these findings were not definitive for epileptiform discharges (Fig. 1). In the current admission, video-EEG was not repeated. At the time of admission, the clinical focus was on psychiatric symptoms, and an epileptogenic mechanism was not initially suspected. Furthermore, the patient had remained clinically stable without seizures for over 2 years, and a 5-day video-EEG evaluation had already been conducted during a previous admission. In light of these factors, repeated EEG testing – including extended or video-EEG – was not pursued, and routine EEG was deemed sufficient for the current assessment. Laboratory tests, including thyroid function, showed no abnormalities. Cerebrospinal fluid analysis, including testing for anti-N-methyl-D-aspartate receptor antibodies, showed no abnormalities, ruling out autoimmune encephalitis. Additionally, chest and abdominal computed tomography scans to investigate potential paraneoplastic syndromes revealed no significant findings. Brain MRI demonstrated left amygdala enlargement (Fig. 2a and b), consistent with findings from imaging conducted 2 years prior at another institution, with no significant changes over time. Consultation with neurosurgery concluded that surgical intervention was not indicated, as her seizures were well controlled. This consultation was prompted by the MRI findings of amygdala and hippocampal enlargement, and aimed to assess whether surgical treatment might be indicated in light of a possible underlying structural lesion, thereby helping to exclude a structural aetiology requiring neurosurgical intervention before initiating psychiatric treatment, which focuses on functional abnormalities.

On admission, her Hamilton Depression Rating Scale (HAMD-17) score was 23, indicating prominent depressive mood, anxiety and psychomotor retardation. Notably, no obvious psychosocial stressors – such as substance use, marital or financial difficulties, or epilepsy-related psychosocial burden – were identified during clinical interviews. Based on her presenting symptoms, including depressed mood, insomnia, anxiety, fear and paroxysmal irritability, the treatment approach was initially guided by the assumption of IDD. Sertraline, which had previously been ineffective, was replaced with escitalopram, a medication that had previously been effective in managing her psychiatric symptoms without causing adverse effects, and olanzapine, which had also been well tolerated in the past, was added to address anxiety and improve sleep. Early morning awakening improved, but anxiety symptoms slightly alleviated and remained residual.

Further inquiry revealed episodes occurring two to three times daily, characterised by a rising epigastric sensation and paroxysmal irritability and fear, accompanied by palpitations and sweating. These symptoms were consistent with temporal lobe epilepsy auras. However, these episodes did not occur during the routine EEG session performed during admission, and thus no corresponding EEG changes were recorded.

Lacosamide was initially titrated to 200 mg daily, which reduced the frequency of these episodes by more than half, and led to a mild improvement in persistent anxiety and depressive mood. Increasing the dose to 300 mg further decreased the frequency of these episodes, accompanied by noticeable improvement in psychiatric symptoms, including occasional smiles and greater responsiveness with improved psychomotor activity. Finally, at 400 mg daily, the paroxysmal episodes resolved completely, and the patient's psychiatric symptoms improved to a level allowing

https://doi.org/10.1192/bjo.2025.10836 Published online by Cambridge University Press

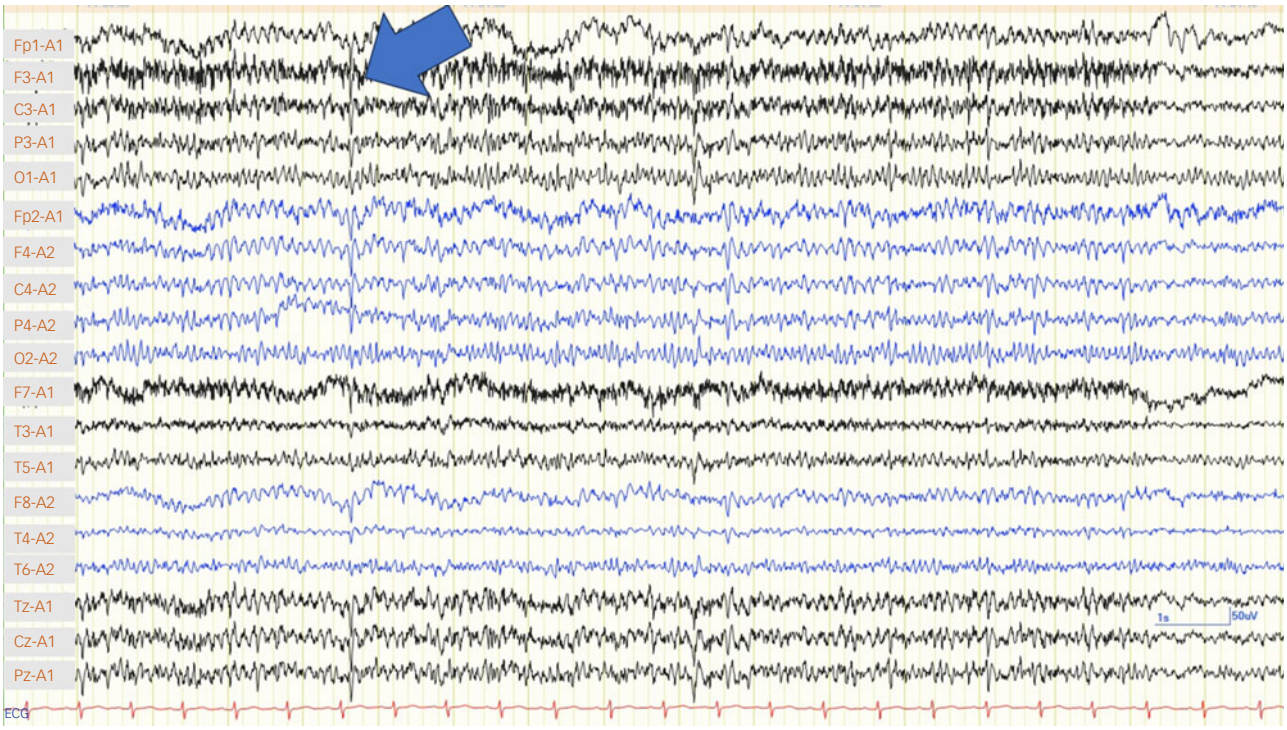


Fig. 1 Clinical electroencephalography (EEG) with 19 channels of bilateral ears' reference. The figure illustrates EEG activity during resting-state with eyes closed. Although the amplitude is small and the possibility of artifacts cannot be excluded, the downward-pointed activity indicated by the arrow marks a time point at which potential activation in the auricular region could be observed across multiple channels. This can occasionally be observed as interictal activity in temporal lobe epilepsy. Aside from this, no clear epileptogenic activity was observed, and the overall EEG findings were interpreted as normal.

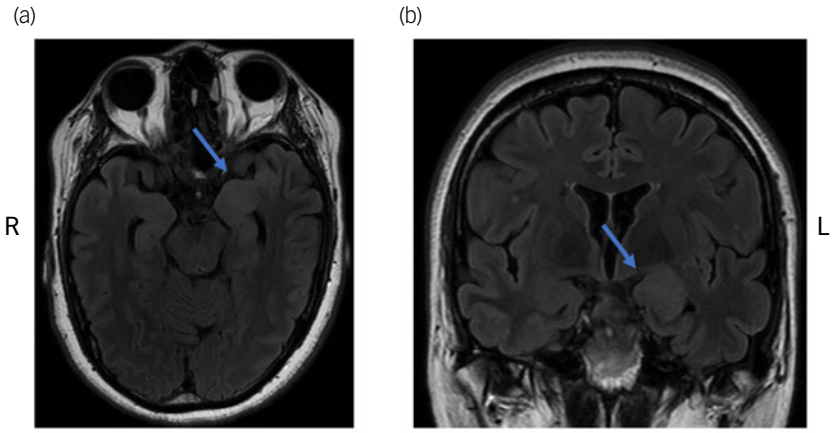


Fig. 2 Brain magnetic resonance image. (a) An axial fluid-attenuated inversion recovery (FLAIR) image, demonstrating mild hyperintensity and enlargement of the left amygdala (arrow). (b) A coronal FLAIR image, similarly showing enlargement of the left amygdala (arrow).

discharge. Concurrently, her motivation improved significantly, and she actively participated in occupational therapy. Her HAMD-17 score decreased to 6 at discharge. The patient had not received psychological therapy before admission to our department. During her hospital stay, psychological intervention was considered; however, her condition was not suitable for such therapy at the time, and her symptoms improved promptly following anti-seizure medication adjustment. After approximately 2.5 months of hospital stay, including successful trial home visits, the patient was discharged home. At discharge, the patient was prescribed lacosamide 400 mg/day, escitalopram 20 mg/day and olanzapine 10 mg/day. During out-patient follow-up, both escitalopram and olanzapine were gradually tapered and discontinued without recurrence of psychiatric symptoms. The clinical course is summarised in a timeline (Table 1), illustrating the onset and progression of seizures and psychiatric symptoms, as well as treatment changes and response during hospital stay.

Discussion

This case highlights the complex interplay between epilepsy and psychiatric symptoms. The patient was considered to have well-controlled epilepsy and the predominant symptoms were

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Table 1 Timeline diagram of the clinical course: summary of seizure and psychiatric symptom progression, major diagnostic findings, treatment changes and outcomes over time

20 years ago (approximately)	• First generalised tonic-clonic seizure • Diagnosis of epilepsy, zonisamide initiated, later replaced by levetiracetam
5 years ago (approximately)	• Onset of focal seizures with epigastric aura and fear • Emergence of psychiatric symptoms improved with escitalopram and olanzapine (later discontinued)
4 years ago (approximately)	• Interictal discharges (EEG), amygdala enlargement (MRI) • Diagnosis of temporal lobe epilepsy • Lacosamide started, replacing levetiracetam
1-year period before admission	• Persistent psychiatric symptoms • Suicidal ideation, psychiatric admission (another hospital) • Sertraline initiated after period without psychotropics
Referral to, and admission at, our hospital	• Referred for ECT evaluation • Admitted to our department • No seizures for over 2 years
Week 1–5 during hospital stay	• HAMD score of 23, sertraline replaced with escitalopram, olanzapine added • Lacosamide 100 mg/day
Week 6 during hospital stay	• Lacosamide increased to 200 mg/day • Fewer anxiety/fear episodes
Week 7 during hospital stay	• Lacosamide increased to 300 mg/day • Increased social interaction
Week 8–9 during hospital stay	• Lacosamide increased to 400 mg/day, HAMD score of 6 • No anxiety/fear episodes
Week 10 during hospital stay	• Discharged
After discharge	• Olanzapine and escitalopram were tapered, then stopped • Remained symptom free after discontinuation

EEG, electroencephalography; MRI, magnetic resonance imaging; ECT, electroconvulsive therapy; HAMD, Hamilton Depression Rating Scale.

psychiatric, leading to initial diagnostic uncertainty and suboptimal treatment. The improvement in psychiatric symptoms following anti-seizure medication optimisation emphasises the importance of recognising epilepsy's psychiatric manifestations.

Notably, the patient had experienced no generalised tonic-clonic or impaired-awareness seizures for 2 years, demonstrated no overt seizure activity during her hospital stay and showed no evident epileptogenic activity on EEG. Consequently, the initial treatment approach focused solely on addressing her psychiatric symptoms, which proved ineffective. This case underscores the critical need to consider an epileptic mechanism's potential influence on psychiatric symptoms, even in the absence of overt seizure episodes. Timely recognition and treatment of such mechanisms can significantly enhance patient outcomes.

According to previous research,[7] the diagnosis of IDD can be made when at least three of the eight symptoms proposed by Blumer et al[8] are present. Although a standardised assessment inventory for IDD was not employed, the diagnosis in this case was based on careful clinical judgement. The patient presented with depressed mood, insomnia, anxiety, fear and paroxysmal irritability, fulfilling the threshold and supporting the diagnosis. Additionally, selective serotonin reuptake inhibitor therapy and augmentation with olanzapine, as described in prior reports on the treatment of IDD,[12] were considered appropriate approaches. Although its classification remains debated,[13] it can offer a useful framework in some cases. In the present case, although we considered this perspective, treatment based on it was insufficient, suggesting the need for alternative approaches. During out-patient follow-up, both escitalopram and olanzapine were successfully tapered off without any recurrence of psychiatric symptoms. The absence of symptom relapse after discontinuation of psychotropic medications supports the interpretation that her psychiatric symptoms were secondary to an epileptogenic process rather than a primary mood or anxiety disorder.

The patient also reported pervasive anxiety lasting most of the day. Although there was no direct evidence linking this to seizure activity, it is plausible that this anxiety was related to anticipatory fear of seizures.[14] Supporting this, once the paroxysmal episodes of irritability and fear were resolved with increased lacosamide, her pervasive anxiety also subsided. This observation highlights the potential connection between anticipatory anxiety and seizure-related mechanisms, underscoring the need to address underlying epileptic processes to alleviate persistent psychiatric symptoms.

From another perspective, the presence of amygdala enlargement in this patient adds further complexity. The amygdala plays a central role in the pathophysiology of temporal lobe epilepsy[15] and is intricately linked to emotional processing, particularly fear, and is known to have strong anatomical and functional connections with the prefrontal cortex, playing a critical role in the regulation of emotions.[16] Structural abnormalities in this region may contribute to both ictal and interictal psychiatric manifestations. In this case, the resolution of her psychiatric symptoms following effective epilepsy control underscores the significance of addressing the epileptogenic focus in managing comorbid psychiatric conditions.

In addition, previous research has suggested that lacosamide may exert direct psychotropic effects. For example, a study by Cuomo et al reported its effectiveness in improving mood symptoms and functioning in patients with bipolar disorder without epilepsy.[17] Although the diagnostic context differs from our case, these findings suggest that lacosamide may exert mood-stabilising effects in patients with bipolar disorder. However, in our case, no history of manic episodes was identified, and the clinical picture was not consistent with bipolar disorder. Thus, the improvement is more likely attributable to the effective control of an underlying epileptogenic mechanism.

One limitation of this case is that serum lacosamide levels were not measured. Therefore, we cannot confirm a direct pharmacokinetic relationship between blood concentration and the observed therapeutic effects.

As part of the safety evaluation during her hospital stay, a routine ECG was performed at admission, which showed no abnormalities, including atrial fibrillation. Although episodes of paroxysmal irritability and fear were occasionally accompanied by palpitations, no other symptoms suggestive of cardiac involvement were observed. During lacosamide titration, the patient remained clinically stable, and no new cardiac signs emerged. Therefore, additional ECG monitoring was not conducted during the in-patient stay. The patient remains under out-patient follow-up without cardiovascular symptoms to date.

To conclude, this case highlights the challenge of distinguishing psychiatric symptoms of epilepsy from primary psychiatric disorders. Despite well-controlled seizures and no overt epileptogenic findings on EEG, the patient exhibited persistent psychiatric symptoms, and the possibility of an underlying epileptogenic mechanism was initially overlooked in favour of an IDD diagnosis. Although selective serotonin reuptake inhibitors and olanzapine were appropriate for IDD, these treatments failed to address the underlying epileptogenic mechanism. The resolution of symptoms following anti-seizure medication optimisation emphasises the

https://doi.org/10.1192/bjo.2025.10836 Published online by Cambridge University Press

importance of considering epilepsy in psychiatric presentations, even without overt seizures.

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First received 10 Feb 2025, final revision 10 Jul 2025, accepted 31 Jul 2025

Data availability

All data generated or analysed in this study are available from the corresponding author upon reasonable request, and after additional ethical approval regarding data provision to individual institutions.

Acknowledgements

We would like to express our sincere gratitude to all the staff involved in the treatment and care of this patient, for their dedication and support.

Author contributions

M.H. was responsible for study conceptualisation and design, and drafting of the manuscript. R.S., S.T. and M.I. were responsible for data collection and contributed to data interpretation. All authors provided critical feedback on the analysis and manuscript. All authors have read and approved the final version of the manuscript.

Funding

This case report received no specific grant from any funding agency, commercial or not-for-profit sectors.

Declaration of interest

None.

Ethical standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2013. All procedures involving human patients were approved by the ethics committee of Osaka University Hospital (approval number: 18470). Written informed consent for publication was obtained from the patient before the preparation of this report.

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