■ Clinical commentary

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Epileptic Disorders

De novo psychosis after left temporal lobectomy: a case of forced normalization?

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ABSTRACT

Forced normalization is a clinical entity defined by the appearance of psychiatric disturbance following control of epileptic seizures that were previously uncontrolled. It was first described by Landolt in 1953. The first cases described were mostly psychosis, however, subsequent work suggested that any behavioural disturbance of acute/or subacute onset concomitant with seizure control could be considered as forced normalization. We report the case of a 65-year-old, right-handed Caucasian patient who was followed in the Epilepsy Centre of Marseille, for left temporal drug-resistant epilepsy. The frequency of seizures was one seizure per month at the time before surgery. Left anterior temporal lobectomy was proposed based on presurgical evaluation. The patient remained seizure-free after surgery, but he presented with an episode of acute psychosis three months after. At this point, EEG was performed, showing rare left temporal epileptiform activity mainly provoked by hyperventilation, with breach rhythm over the left temporal surgical. The appearance of acute psychosis after cessation of epileptic seizures and reduced epileptiform activity on the EEG led us to question the forced normalization process in this case. Another hypothesis would be the effect of surgery itself, since there is an increased risk of any psychiatric disturbance unrelated to seizure cessation during the postoperative period. In conclusion, psychosis in this case could have resulted from the combination of several factors, including the effect of surgery itself and seizure cessation. This case illustrates the need for specific psychiatric care in the perioperative period in patients with epilepsy.

Key words: forced normalization, epilepsy surgery, psychosis, temporal lobe seizure, partial epilepsy, drug-resistant epilepsy

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Forced normalization (FN) is a clinical entity defined by the appearance of psychiatric disturbance following control of epileptic seizures that were previously uncontrolled. It was first described by Landolt [1]. The first cases described were mostly psychosis, however, subsequent studies have suggested that any behavioural disturbance of acute/or subacute onset concomitant with seizure control could be considered as FN [2]. Nevertheless, in a recent systematic review, psychosis was reported to be the most frequent expression of FN, representing up to 86.4% of cases [3]. Most cases arose following antiepileptic medication modification (48.5%), but FN was subsequent to surgery in 30% of cases [3]. The mechanism of FN remains poorly understood, but highlights a possible antagonistic relationship between epilepsy and psychosis. In the case of FN after surgery, the appearance of psychosis also raises the alternative hypothesis of psychosis as a complication of surgery. Indeed, some

authors found that about a quarter of patients present with psychiatric disturbance and/or clear exacerbation of pre-existing symptoms in the weeks following surgery [4]. Here, we report a case of acute psychosis appearing after left temporal lobectomy in a 65-year-old man with no psychiatric past history. We discuss the different factors that could have led to the appearance of *de novo* psychosis in this case, with peculiar attention to the FN hypothesis.

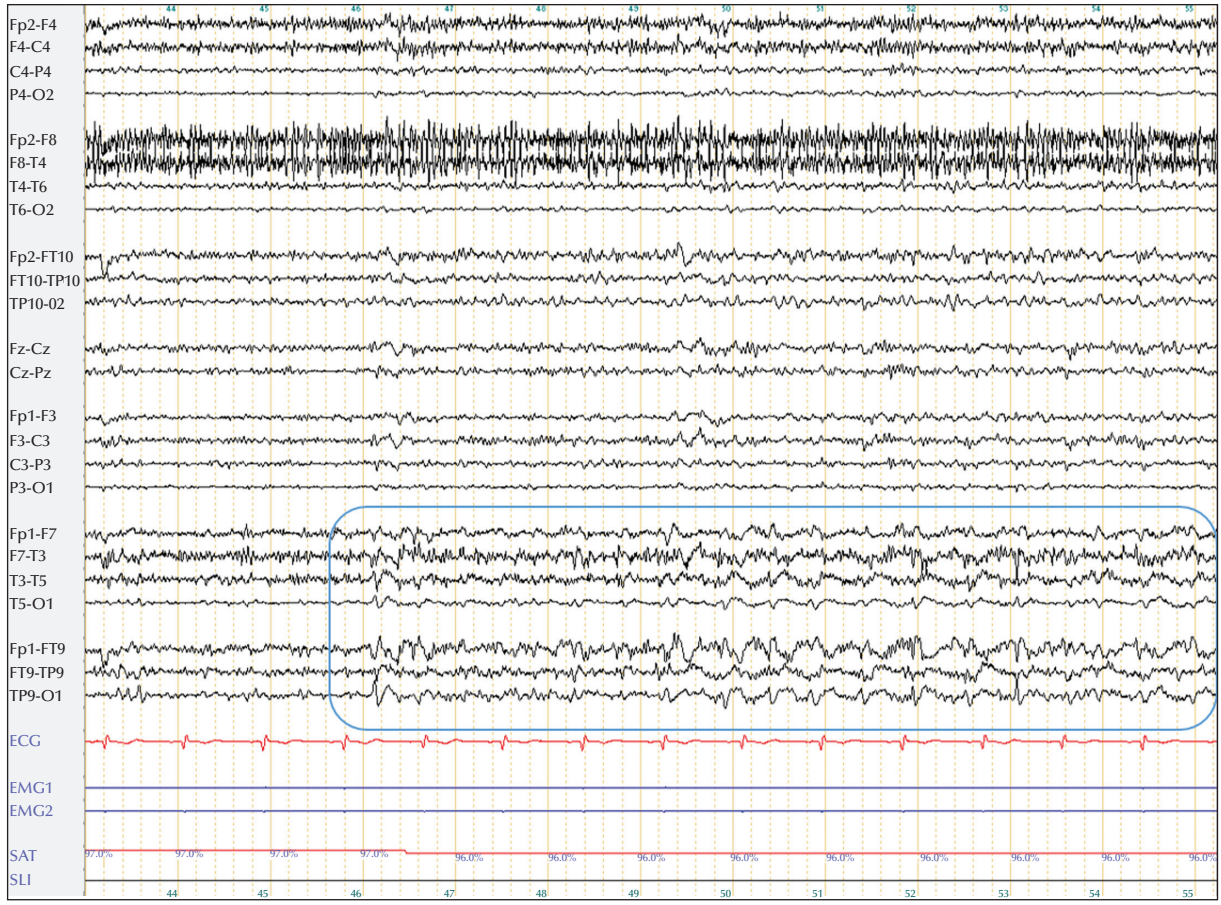
Case study

We report the case of a 65-year-old, right-handed male Caucasian patient, whose clinical care was managed in the Epilepsy Centre at Marseille. Past medical history revealed a previous history of febrile convulsions at the age of 18 months. He then developed his first focal seizures with impaired awareness at the age of nine years, which continued despite antiepileptic drug (AED) treatment until the age of 23 years. Seizure semiology was characterized by altered contact, delusional symptoms and subsequent amnesia of the seizure. At the age of 45 years, he then developed symptoms of epilepsy again, presenting with focal seizures with impaired awareness, characterized by a strange feeling in his head, loss of contact and aphasia lasting for two minutes. At this stage, seizures remained frequent despite trials of various antiepileptic medications including phenytoin, then levetiracetam at therapeutic doses. He was on carbamazepine at 800 mg and levetiracetam at 2,500 mg daily when he was referred to our epilepsy centre for a one-week video-electroencephalography (EEG) recording. At this time, he was having about one seizure per month. A short psychiatric examination revealed a non-elevated score on the Generalized Anxiety Disorder screening scale (GAD-7) of 4/21 (cut-off=7 based on the validated French version) as well as a normal score of 8/24 on the Neurological Disorders Depression Inventory (Epilepsy) (NDDI-E) screening scale (cut-off=15 based on the validated French version). Magnetic resonance imaging (MRI) showed left hippocampal atrophy confirming the aetiology of hippocampal sclerosis. Fluorodeoxyglucose positron emission tomography (FDG-PET) revealed left anterior temporal hypometabolism, predominating in the medial temporal region. Neuropsychological examination (WAIS-III) revealed a normal intellectual level without visuo-verbal dissociation. Surface video-EEG revealed interictal paroxysmal activities over left temporal and fronto-temporal electrodes (*figure 1*). Seizures were characterized by a rhythmic ictal discharge over left temporal and left fronto-temporal electrodes. The symptomatology of the seizures was characterized by a prodromal feeling of uneasiness, change in gaze more or less associated with aphasia, with no loss of awareness, no automatisms, and no secondary generalization, with seizure duration of less than one minute. The pre-surgical evaluation concluded a diagnosis of left mesio-temporal epilepsy due to hippocampal sclerosis. Therefore, left anterior temporal lobectomy was proposed and carried out, with no peri-operative or immediate post-operative complications. The patient became seizure-free immediately following surgery, but post-surgical examination at two months showed systematized delusional paranoid thought. His paranoid ideation was centred on his neighbours; he thought that his neighbours considered him to be a "voyeur" since they saw him looking out of the window. This delusional thinking slowly increased, as he began to report that maybe his doctors were also a part of this conspiracy. His thought processes otherwise appeared normal. First-line antipsychotic treatment with risperidone was started at an initial dose of 2 mg, then progressively increased up to 8 mg. It is noteworthy that his daily dose of levetiracetam (2,500 mg daily) had not been changed in the post-surgical period, making this unlikely to be the cause of the appearance of psychotic symptoms.

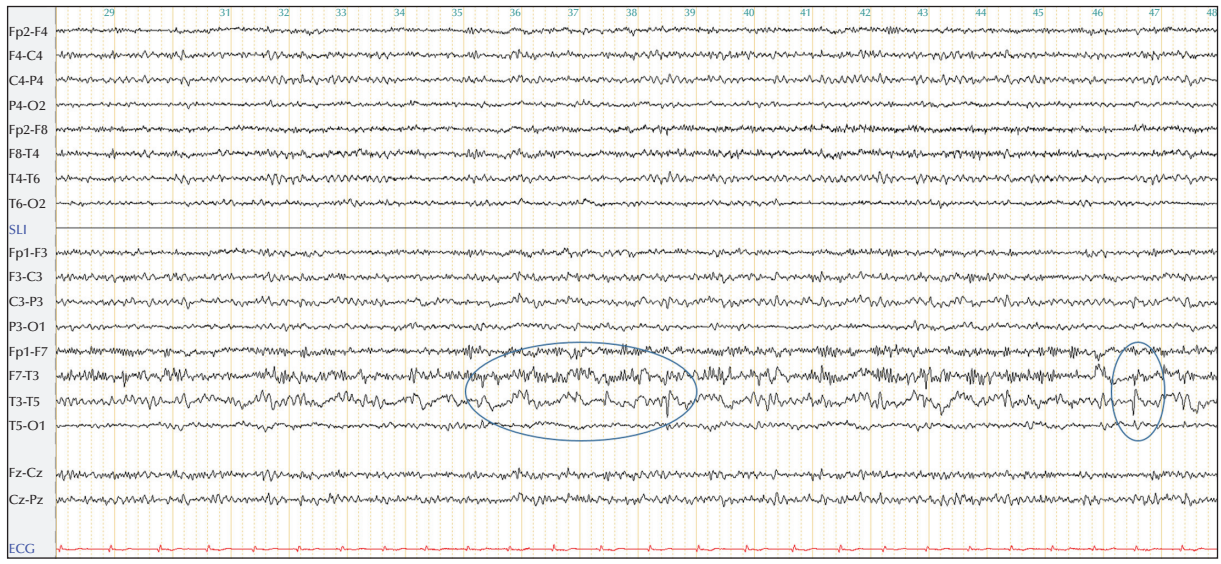
During a short hospital stay in the epilepsy centre, haloperidol was introduced with the aim of replacing risperidone. At this point, which was three months after surgery, EEG was performed, showing rare left temporal epileptiform activity mainly provoked by hyperventilation, with breach rhythm over the left temporal surgical resection zone (*figure 2*). Since his delusional symptoms were somewhat resistant, he was then transferred to a psychiatric clinic and treatment modification continued during a short stay of one month and a half. Haloperidol was increased up to a dose of 7 mg per day and risperidone was stopped. There was no change in antiepileptic drugs. As his symptoms progressively improved, he was able to return home. Two months later, psychiatric evaluation revealed almost complete cessation of psychotic symptoms. Four months later, it was noted that he began to acknowledge and question his symptoms, even linking the paranoid symptom to a tendency that he had developed during childhood when he was ashamed of his seizures, at that time being very worried and suspicious about what others might think of him. He currently remains seizure-free.

Discussion

This case highlights a relatively rare complication of epilepsy surgery, i.e. *de novo* psychosis. In this case, psychotic symptoms appeared during a period of seizure cessation, raising the hypothesis of the FN process. However, in the literature, *de novo* psychosis



■ **Figure 1.** Before surgery, the EEG showed left temporal spikes during hyperventilation that could spread to the right side. The patient did not experience any psychotic symptoms at this time.



■ **Figure 2.** Three months after surgery, the patient experienced acute psychosis and the EEG showed rare left temporal spikes, mostly during hyperventilation (reduced in comparison with *figure 1*).

does not always appear in the absence of seizures after surgery. This raises the question of the effect of surgery itself on psychiatric complications and on psychosis in particular. We discuss below the effect of surgery itself on the appearance of postsurgical psychosis as well as the putative link to seizure cessation.

Epilepsy surgery constitutes huge psychological and physical stress for the patient. Epilepsy surgery, especially temporal lobectomy, has long been proven to be associated with psychiatric complications [5]. In most cases, it is related to psychiatric comorbidity before surgery but *de novo* psychiatric conditions may also appear after temporal lobectomy. The only identified risk factor for developing *de novo* psychosis after surgery is the presence of presurgical interictal acute psychotic disorder [6]. The reported incidence of *de novo* psychosis after epilepsy surgery varies depending on the studies. In one study of a cohort of 106 patients who underwent resective surgery for intractable epilepsy [7], 88% of patients suffered from temporal lobe seizures. The authors reported a rate of 6% of *de novo* psychosis after epilepsy surgery, and identified that psychiatric complications occurred more frequently in multilobar epileptic foci and in patients undergoing deep brain stimulation of the anterior nuclei of the thalamus. These authors did not specify whether *de novo* psychosis was related to seizure cessation or not. Another prospective study [8] concerned 50 patients mainly with temporal epilepsy (44 temporal and four frontal), of which 14% were reported with *de novo* psychosis (six cases). In this study, psychosis occurred in the temporal lobectomy group. Two of these six cases appeared in relation to seizure cessation, raising the question of the FN process. In the other four patients, psychosis appeared without seizure cessation, suggesting that several different mechanisms might be implied in *de novo* post-surgical psychosis.

In one series, 2.6% of cases developed psychosis after surgery with a small subgroup of 1.6% showing no previous history of psychosis [9]. In this series, however, the cases were *de novo* interictal psychosis in patients with persistent seizures after surgery. This study also suggests that surgery *per se* could have an effect itself on psychiatric complications, independent of seizure cessation. In another series of 298 patients who had temporal lobectomy for intractable epilepsy, four developed post-ictal psychosis for the first time after surgery and continued to have seizures after surgery [10].

Apart from epilepsy surgery, few studies have addressed the effect of neurosurgery itself on psychiatric disturbance. One review [11] targeted neuropsychiatric complications associated with brain tumour resection, outside of epilepsy. The authors mostly focused on depression and anxiety, which were mostly related to tumour prognosis. There are very few data on psychosis after surgery, suggesting that this remains very rare. One case report [12] described a patient who underwent total resection of a malignant astrocytoma in the temporal lobe and developed transient psychosis, unrelated to epilepsy, suggesting an effect of surgery itself on psychosis.

From another perspective, psychiatric complications after epilepsy surgery could also result from seizure cessation and the difficulties some patients experience in handling a seizure-free lifestyle [13, 14]. In our case, although the patient no longer had seizures, he still had difficulty in coping with relationships, without any formal reason that may account for this difficulty. Other authors have emphasized that psychosis mainly occurs with a premorbid personality trait of the schizophrenic spectrum (Cluster A) [4]. In the present case, despite no psychiatric history, the patient showed evidence of leading a relatively lonely life, raising the possibility of a premorbid personality disorder. He relates his relationship issues to his epilepsy, reporting that people laughed at him when he was a child, and that he then became suspicious of others later during his life. Indeed, he was able to relate his symptoms to his premorbid personality trait after his psychotic symptoms improved.

A last hypothesis is that of a psychotic episode linked to seizure cessation, involving the FN process. FN was defined by Krinshnamoorthy [2] as the association between the presence of acute behavioural disturbance and concomitant reduction of epileptic activity on EEG and/or seizure cessation for at least one week in a patient with epilepsy. The present case fulfils these diagnostic criteria since the patient has been seizure-free for two months after surgery when psychotic symptoms developed. Moreover, during the period in which he presented with psychotic symptoms, the EEG showed less epileptic activity than while the patient experienced no psychotic symptoms (*figure 2*). In another case report of a 14-year-old woman with Dravet syndrome [15], psychosis with catatonia was related to seizure cessation. Interestingly, when her AED treatment (phenobarbital) was reduced, her psychosis with catatonia improved, together with a resurgence of myoclonic seizures and worsening of EEG showing epileptiform activity. These observations clearly suggest an antagonism between epilepsy, epileptic activity and psychosis.

The mechanism for such antagonism remains poorly understood. As psychosis is more frequent in temporal lobe epilepsy, dysregulation in the limbic areas provoked by temporal lobe epilepsy could predispose to development of psychosis [16].

Conclusion

Based on the literature, the psychotic episode could relate to the combination of several factors, including the effect of surgery itself and seizure cessation. Seizure cessation could enhance the risk of psychosis via a neurophysiological mechanism that acts antagonistically between psychosis and epilepsy, *i.e.*, the FN process. An additional factor could be the paradoxical psychological stress related to seizure cessation, which varies between patients.
This case illustrates the need for specific psychiatric care in the perioperative period for patients with epilepsy, since this is a period with particular risk for patients, despite all the expectations that patients and doctors have about the perspective of seizure cessation that surgery offers in most cases. ■

Supplementary material.
Summary slides accompanying the manuscript are available at www.epilepticdisorders.com.

Disclosures.
The authors have no conflicts of interest to disclose.

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TEST YOURSELF

(1) Forced normalization concerns patients developing psychosis after epilepsy surgery. True or false?

(2) Epilepsy surgery may sometimes lead to psychiatric decompensation despite successful seizure cessation. True or false?

(3) Psychosis is the most frequent psychiatric disturbance encountered in forced normalization. True or false?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com.