

# Does antiepileptic drug withdrawal predispose patients undergoing temporal lobe epilepsy surgery to late onset of psychiatric morbidity? A report of three cases

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## Abstract

Surgery is an established and increasingly utilized treatment option in medically refractory temporal lobe epilepsy. Many psychiatric problems are known to complicate in the postoperative period. Most studies have a follow-up period of less than 24 months. We report the cases of three patients who developed severe psychiatric problems in the late postoperative period after successful temporal lobectomy for refractory epilepsy — Psychosis, major depression with psychosis, and severe anxiety disorder, respectively. None of the patients had past or family history of psychiatric disease. All three patients had undergone anterior temporal lobectomy on the right side for intractable epilepsy. They remained absolutely seizure-free after surgery. We conclude that psychiatric morbidity may arise *de novo* long after temporal lobectomy. This association between temporal lobectomy for epilepsy and late onset psychiatric morbidity should be carefully studied. Mechanisms underlying this late complication require deeper understanding of the effects of epilepsy surgery.

## Key Words

Anxiety, antiepileptic drug (AED) withdrawal, depression, psychiatric, temporal lobe epilepsy surgery

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## Introduction

Epilepsy is closely interlinked with much psychiatric comorbidity. The most common psychiatric problems in patients with epilepsy include depression, anxiety, and schizophrenia such as psychosis and alcohol and drug dependence.<sup>[1]</sup> Psychosis in epilepsy patients has been known since a long time and is quite common but not exclusively associated with temporal lobe epilepsy. It can be classified as ictal, postictal, and interictal psychosis; forced normalization associated with reduction of seizures; and *de novo* psychosis after epilepsy surgery.<sup>[2]</sup> Antiepileptic drugs (AEDs), especially levetiracetam and topiramate, have also been reported to cause many psychiatric side effects.<sup>[3]</sup> In recent years, surgery has become an established

and increasingly utilized treatment option for patients with intractable epilepsy, especially those with temporal lobe epilepsy. Many psychiatric problems are known to arise after temporal lobectomy. However, the follow-up period was limited to 6-12 months in most studies. Only a few studies had a follow-up period of 24 months.<sup>[4]</sup> There is sparse mention in the literature about the *de novo* appearance of psychiatric symptoms occurring late or greater than 2 years postoperative period following a successful epilepsy surgery.

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We report three cases in which the patients developed a serious psychiatric condition, as late as 5 years after the surgery.

## Case Reports

On long-term follow-up of the patients who underwent epilepsy surgery at our center, those who were asymptomatic for at least 2 years following the surgery and presented with a serious psychiatric condition after that were identified. Three such patients, all of whom had previously suffered from temporal lobe epilepsy and were refractory to medical treatment fulfilled our inclusion criteria. They underwent anterior temporal lobectomies on the right side and were followed up by a team of neurologists, neurosurgeons, and psychiatrists. These patients had no previous history of psychiatric diseases. They remained absolutely seizure-free postoperatively and were doing well socially and educationally prior to the onset of psychiatric symptoms.

### Case 1

A 15-year-old boy with normal birth and developmental history and no history of febrile seizures or encephalitis-like illness had a history of seizure onset at the age of 2.5 years. The seizures were automotor in type with ictal speech and were, therefore, localized at the nondominant temporal lobe. Video-electroencephalography (VEEG) was suggestive of ictal onset from the right anterior temporal region. It was concordant with the finding of right mesial temporal lobe sclerosis on magnetic resonance imaging (MRI). Ictal single-photon emission computed tomography (SPECT) revealed hypoperfusion in the right mesial temporal lobe. There was no history of any psychiatric comorbidity. The seizures remained refractory to the medical treatment; therefore, the patient underwent a right selective amygdalohippocampectomy. He remained seizure-free following the surgery. There were no symptoms of anxiety, depression, or psychosis during the first 2 years after the surgery but the patient had two episodes of nonepileptic events after 2 years. The patient developed feelings of constant sadness and worthlessness, along with feelings of guilt and suicidal ideations 2 years after the surgery. He also started excessive alcohol consumption. At that time, he was on valproate, oxcarbazepine, and clobazam as a part of his antiepileptic treatment. He was diagnosed with major depression as per the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM IV) criteria, and was started on oral escitalopram at a dose of 10 mg/day, to which he responded adequately within 2 months, and the medication had to be continued for the next 1 year. He developed features of mania with inflated ideas 5 years after the surgery. The development of mania coincided with tapering and then withdrawal of sodium valproate, which had been part of his AED treatment, which we had decided to taper very slowly. He was restarted on sodium valproate and initiated on antipsychotic treatment with risperidone. He gradually improved and is presently doing fine.

### Case 2

Our second patient was a 14-year-old boy with no antecedents who had seizure onset at the age of 4 months and the seizures were those of an initial epigastric rising sensation as aura, along with orofacial automatisms and ictal verbalization. The VEEG report was suggestive of right anterior temporal

localization, MRI showed right mesial temporal sclerosis, and ictal SPECT showed right mesial temporal focus. He underwent a right temporal lobectomy. The patient developed pyogenic meningitis in the immediate postoperative period, which was managed with antibiotics. He remained seizure-free and started attending school. He was good in studies and remained so for the next 6 years. After 6 years of surgery, he developed severe anxiety symptoms that coincided with the withdrawal of sodium valproate. At that time, he was also on clobazam, which was continued but since he was started on oral sertraline and clonazepam and had about 60% relief in his anxiety symptoms, clobazam was also gradually tapered off.

### Case 3

Our third patient was a 10-year-old girl who had a normal birth and developmental history. There was no history of febrile seizures or encephalitis or head injury. She had seizure onset at the age of 6 years. The seizures were left head versive with oral and hand automatisms. Her MRI was suggestive of right temporal lobe atrophy, VEEG showed a right anterior temporal region focus, and SPECT revealed right mesial temporal hypoperfusion. The seizures were pharmacoresistant and she underwent a right temporal lobectomy for the same. Postoperatively she did not have any recurrence of seizures but had depression in the early postoperative period for about 1 month. The patient overcame it without medication, and did extremely well at school and socially. Postoperatively, 6 years later, she developed abnormal behavior with hallucinations and delusions of prosecution. This was the time during which her last AED carbamazepine was being tapered off. She was diagnosed with psychosis and was started on antipsychotic treatment with risperidone. She responded well and became asymptomatic within about 20 days but the medication was continued for nearly 6 months after which it was tapered off. Carbamazepine was not reintroduced.

## Discussion

Patients with medically intractable epilepsy are known to have a higher incidence of psychiatric disorders.<sup>[5]</sup> Epilepsy surgery has been associated with an improvement in psychosocial adjustment.<sup>[6]</sup> However, some psychiatric complications may occur after the surgery as well.<sup>[6]</sup> It has been seen that the prevalence of depression and anxiety is higher in temporal lobe resections as compared to extratemporal resections though seizure freedom was more with temporal lobe surgery.<sup>[7]</sup> Psychiatric diagnosis being more common in patients with right compared to left temporal lobe seizure focus, both before and after surgery, has been reported.<sup>[8]</sup> However, no such association was observed in a few recent studies.<sup>[4]</sup> Filho *et al.* conducted a study that aimed at verifying the presurgical predictors for psychiatric disorders following epilepsy surgery in a group of 115 temporal lobe epilepsy patients. The prevalence of psychiatric disorders presurgically was 40.8%. Remission of psychiatric problems was seen in 54% of the patients. *De novo* appearance of psychiatric complaints was seen in 9.6% of the patients. Preoperative depression, interictal psychosis, and contralateral epileptiform discharges were identified as the risk factors associated with postsurgical psychiatric comorbidities.<sup>[9]</sup>

Multiple nonsystematic reviews have been conducted in the past regarding psychiatric outcomes of epilepsy surgery. A review by Foong *et al.* suggests that affective disorders, namely, depression, anxiety, and psychosis are the most frequently reported postsurgical psychiatric disturbances.<sup>[10]</sup> Obsessive compulsive disorder has also been reported to either recur postoperatively or appear *de novo* after the epilepsy surgery.<sup>[11]</sup> Somatoform disorders other than conversion disorders have been reported after temporal lobectomy.<sup>[12]</sup>

Macrodimitris *et al.* conducted a systematic review of the existing literature on psychiatric outcomes associated with respective epilepsy surgery.<sup>[4]</sup> The aim of this meta-analysis was to determine the prevalence and severity of the psychiatric problems before and after surgery and to determine the incidence of *de novo* psychiatric problems after surgery. Inclusion criteria for the search were patients with partial epilepsy undergoing lesionectomy, lobectomy, corticectomy, and selective amygdalohippocampotomy. Their initial search identified 68 articles on the psychiatric comorbidities as an outcome of epilepsy surgery. However, 13 studies met all the inclusion and exclusion criteria and were, therefore, included for the systematic review. Depression, anxiety, and overall psychological adjustment were the most common outcomes explored. The results concluded in various spheres of psychiatric outcomes are as follows.

### Depression

The majority of studies comparing depression demonstrated improvements in depression postsurgery. On the other hand, three studies by Altshuler *et al.*, Mattson *et al.* and Mc Lellan *et al.* reported no change for depressive symptoms either before or after surgery. These studies, however, suggested that the improvement in depression was negated by the appearance of *de novo* depression postsurgically in some patients. The prevalence of *de novo* depression ranged 18.2-4%. The risk factors for this *de novo* complaint were continued seizures after surgery and a past history of depression.

### Anxiety

Most studies demonstrated a decreased prevalence of anxiety after surgery. Three studies demonstrated no change in anxiety levels while three studies reported a prevalence of *de novo* anxiety ranging from 6.9% to 13%. The predictors for these *de novo* anxiety symptoms were continued seizures after surgery and a past history of anxiety.

General psychiatric outcomes after epilepsy surgery — Six studies explored the other general psychiatric outcomes after surgery. Four of these studies reported improvements and out of the remaining two, one study showed no change while another one demonstrated improvement coinciding with seizure freedom.

### Anger and psychosis

The only article studying anger was that by Meldolesi that reported improvement in the anger symptoms. The study conducted by Deinsky *et al.* was the only one on psychosis. This study demonstrated a 1.1% prevalence of *de novo* psychosis in patients undergoing temporal and frontal resections. Another study by Blumer *et al.* reported a

prevalence of 14% for *de novo* psychosis in patients undergoing mainly temporal lobectomies.

Two studies explored psychiatric disorders in a subset of pediatric cases. Mclellan *et al.* studied the psychiatric issues in children and adolescents. The rate of “one or more psychiatric diagnosis” in the sample remained at 72% after surgery, with 16% of patients improving, but 12% developing a *de novo* complaint. The second study by Smith *et al.* suggested that there were few changes after surgery, and the prevalence of behavioral and psychosocial issues remained high during the pre- and postsurgery periods.

It was concluded that the majority of psychiatric complaints occur after surgery within the first year. It was generally seen that continued seizures were associated with a higher incidence of psychiatric complaints. Also, a prior history of psychiatric disease predisposes the patients to develop these postoperatively. However, *de novo* appearance of these psychiatric complaints is also known. Other predictors, such as laterality, age at onset, and gender, probably did not have much predictive value in psychiatric outcomes after epilepsy surgery. Some factors, such as family history, level of social support, and life stress, were not considered in the studies.

Majority of the studies included in this large systematic review had a follow-up of 6-12 months. In the current report, we have detailed a much later *de novo* appearance of severe psychiatric problems in the three patients who underwent anterior temporal lobectomy.

In a prospective study on detailed evaluation of psychiatric morbidity, prior to and following the epilepsy surgery, we had observed and reported that 20% patients undergoing temporal lobe surgery for refractory epilepsy developed a *de novo* psychiatric disorder after the surgery, for which no predictive factor could be identified.<sup>[13]</sup> This study was aimed at evaluating the appearance of psychiatric problems during the very early postoperative period. The severe psychiatric problems in patients reported in the current paper had emerged without any past or family history of psychiatric complaints, in the absence of any neurosurgical complication and in a state of absolute seizure freedom. Their emergence interestingly coincided with the withdrawal of either valproate or carbamazepine while the patients had undergone withdrawal of other AEDs earlier postoperatively without any problems. We usually begin tapering AEDs in most of our seizure-free patients undergoing temporal lobectomy after 1-2 years of surgery. A customized approach is adopted, and depending on previous seizure frequency, age and occupation of the patient, social issues, histopathology, and other factors, AED tapering is often achieved over 2-5 years in patients who have an event-free course. Most adults are, however, continued on one AED during their productive years. The same approach had been adopted in the patients reported here.

Valproate and carbamazepine have a mood stabilizing effect and are prescribed in bipolar disorders. This raises the possibility of an association explaining the late emergence of psychiatric symptoms in our patients. However, no withdrawal syndrome presenting with psychiatric complaints has previously been

described for valproate or carbamazepine.<sup>[14]</sup> Stephens *et al.* have mentioned the development of a chronic psychosis in psychiatrically healthy individuals after many months of surgery even when the patients were seizure-free.<sup>[15]</sup> They have suggested that anomalous synaptic regeneration following surgery may be the cause of the development of this late onset *de novo* psychiatric illness. In another study, one patient of the 49 patients undergoing temporal lobectomy had new onset development of depression 3 years in the postoperative period following temporal lobectomy.<sup>[16]</sup>

## Conclusions

To conclude, we report three patients with very late appearance of severe psychiatric morbidity following successful anterior temporal lobe surgery for refractory mesial temporal lobe epilepsy. A possible hypothesis associating mood stabilizing AED withdrawal with this condition has been discussed.

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## Conflicts of interest

There are no conflicts of interest.

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