

Post-traumatic Epilepsies: Prophylactic Antiseizure Medications Are Futile

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Abstract

Objective: Post-traumatic epilepsy (PTE) is a significant sequela of traumatic brain injury (TBI), with a high incidence of drug-resistant epilepsy. The role of prophylactic antiseizure medications (ASM) remains controversial. This study investigates the demographic, clinical, radiological, and electrophysiological characteristics of PTE and evaluates the impact of ASM use.

Methods: We retrospectively analyzed patients diagnosed with PTE at Istanbul University, Istanbul Faculty of Medicine Hospital (1994-2024). Clinical characteristics, imaging findings, electroencephalography results, and ASM use were assessed. Statistical analyses were conducted to explore correlations between trauma severity, epilepsy latency, and ASM efficacy.

Results: There were 67 patients diagnosed with PTE, 73% of whom were male. Severe TBI (bone fracture, hemorrhage, or loss of consciousness >24 hours) was observed in 60% of patients. Bilateral magnetic resonance imaging (MRI) lesions were significantly associated with shorter epilepsy latency ($p<0.01$). Drug-resistant epilepsy was more common in severe TBI cases ($p<0.03$) and patients with longer periods of unconsciousness. ASM use did not influence epilepsy latency or seizure frequency. Three patients exhibited psychogenic non-epileptic seizures.

Conclusion: ASM fails to prevent epileptogenesis and should not be routinely prescribed for seizure prophylaxis in patients with TBI. Trauma severity is a critical predictor of epilepsy onset and drug resistance. The presence of bilateral MRI lesions warrants closer monitoring. Given the complex consequences of TBI, these patients should be closely monitored by multidisciplinary teams.

Keywords: Trauma, antiseizure medications, psychogenic non-epileptic seizures, lesional epilepsy, drug-resistant epilepsy

INTRODUCTION

Traumatic brain injury (TBI) is one of the most common causes of epilepsy, documented as early as the 1700 BC Babylonian papyri.¹ The TBI group accounts for 20% of the cases of symptomatic epilepsy patients referred to a specialist epilepsy center, whereas 5 to 6% of the whole epilepsy cases are expected to arise due to trauma.^{2,3} Post-traumatic seizures are strongly associated with poor functional outcomes and increased mortality.⁴

Seizures encountered following trauma are roughly divided into two groups: early seizures, which occur within the first 14 days post-trauma, and late seizures, which are more significant for the development of epilepsy and occur well after the first 14 days, either following TBI itself or during hospitalization. Up to 80% of the seizures arise within the first year. The pathophysiological basis of the seizures is believed to be associated with blood-brain barrier disruption and brain injury in the early period, while in the late period, excitotoxicity due to the accumulation of free radicals and glutamate plays a role.^{5,6}

Trauma severity, which is an important determinant, is classified as mild (loss of consciousness for less than 30 minutes without skull fracture), moderate (loss of consciousness lasting no more than 24 hours regardless of the presence of a skull fracture), and severe (loss of consciousness exceeding 24 hours accompanied by skull fracture, contusion, or hematoma).³ The predisposition to develop epilepsy after severe trauma, i.e., post-traumatic epilepsy (PTE), has been reported to be as high as 40-50%.

PTE is defined by a tendency to experience recurrent and unprovoked seizures in the long term due to the effects of trauma. Male gender, advanced age (over the age of 65), prior alcohol abuse, history of post-traumatic amnesia, focal neurological signs, presence and duration of loss of consciousness at the initial trauma, and possibly early seizures are associated with a greater risk for developing PTE.^{7,8} Imaging

may be another important guide, as findings such as skull fracture, especially a depressed one, penetrating trauma, midline shift, brain contusion and hemorrhage are associated with an increased risk.^{7,9}

The benefit of using antiseizure medications (ASM) in a prophylactic manner cannot be demonstrated in the long-term prognosis. Although some studies suggest a possible prophylactic effect of ASM such as levetiracetam and phenytoin in early seizures, further research is necessary to confirm their efficacy.¹⁰ Another study shows levetiracetam may be a better alternative for mechanically ventilated pediatric patients.¹¹ However, a great number of studies, in addition to a recent guideline by the Neurocritical Care Society, have demonstrated important points. First, there was no significant reduction in the number of early seizures with ASM use versus no ASM or placebo, challenging the tendency to prescribe ASMs for early seizure prophylaxis.^{12,13} Secondly, there was no significant effect of ASM for preventing late seizures, hence dashing the hopes on a true anti “epileptic” effect of ASM in such cases. Thirdly, patients receiving ASM had experienced side effects due to the therapy. Eventually, the final outcome was not improved by the ASM, with randomized trials, showing neutral effects on mortality and possibly worse overall epileptogenic effects, neurologic and cognitive outcomes, though the latter may be reversible upon drug discontinuation.^{14,15} This has led to the recommendation of “either prophylactic ASM (initiated during index hospitalization) or no ASM could be used in patients hospitalized with moderate-severe TBI” and if it is initiated, it should be used for a short duration, i.e. ≤ 7 days in this guideline.¹⁶

Although the current literature suggests otherwise, a tendency to prescribe ASM to trauma patients persists and even creeps into some local guidelines, leading to unnecessary use of ASM, resulting in futile side effects and increasing economic costs.^{17,18} The lack of consensus on the duration of such treatment strategies further deepens this dilemma.

This study aims to define the demographic, clinical, radiological, and electrophysiological characteristics of PTE patients followed up in our tertiary center, as well as to reveal the course and prognosis of the disease with specific attention to the use of ASM.

METHODS

Patients diagnosed with PTE at the İstanbul University, İstanbul Faculty of Medicine Epilepsy Unit between 1994 and 2024 were included in the study. Patients were excluded if they had a history of epilepsy or other factors that may explain their epilepsy etiology. Clinical characteristics, imaging, electroencephalography (EEG)

findings, antiseizure drug use, and clinical progression were retrospectively analyzed.

The severity of head trauma was classified as mild (loss of consciousness less than 30 minutes without skull fracture), moderate (loss of consciousness less than 24 hours regardless of skull fracture), or severe (presence of skull fracture, cerebral contusion, or hematoma with loss of consciousness more than 24 hours).³ Patients whose seizures persisted despite the use of at least two appropriately chosen, and adequately dosed ASM were defined as having drug-resistant epilepsy.

This study was approved by the İstanbul University Clinical Research Ethics Committee (approval no: 2025/214, date: 28.04.2025).

Statistical Analysis

Statistical analyses were performed using SPSS version 25.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics used to summarize the data included frequencies and percentages for categorical variables, and median and interquartile ranges (IQR) for non-normally distributed continuous variables. The chi-square test was used to compare categorical values, and the Mann-Whitney U and Kruskal-Wallis tests were utilized since the data distribution was not normal within categories, according to the Shapiro-Wilk test. Following significant chi-square test results, Cramér’s V was employed to determine the effect size and strength of association between the nominal variables.

RESULTS

There were 67 patients fulfilling the diagnosis of PTE with their data available. The demographic findings and data are summed up in Table 1. Among the included patients, 73% (n=49) were male, and 27% (n=18) were female. The median patient age was 54.50 (IQR: 40.75-62.50). Severe trauma (bone fracture, hemorrhage, or loss of consciousness for more than one day) was observed in 60% of patients. The median latency for epilepsy onset post-TBI was 24 months (IQR, 6-96 months). The median age at trauma occurrence was 18 years (IQR, 8-31 years). The trauma was encountered during childhood in 28 patients (44%). Acute symptomatic seizures were present in only three of the patients.

Unconsciousness after trauma was reported in 25.4% of the patients (n=17). The presence of unconsciousness was associated with neither age at trauma nor the epilepsy latency. Refractoriness of epilepsy was not associated with the presence of unconsciousness either. The duration of the unconsciousness showed a significant correlation with the refractoriness ($p<0.029$, $\phi_c=0.718$).

A family history of epilepsy was present in seven patients (11%). Focal seizures with impaired awareness were observed in 61% of the patients, while 60% experienced focal-onset seizures evolving into bilateral tonic-clonic seizures. Regarding seizure frequency, 45% of the patients had monthly seizures, 23% had yearly seizures, 22% had weekly seizures, 5% experienced daily seizures, and only 5% of the patients were seizure-free. Psychogenic non-epileptic seizures coexisted in three patients. Status epilepticus history was noted in eight patients (12%). None of these patients experienced status epilepticus at the time of trauma. One patient experienced his first seizure manifested as status epilepticus.

MAIN POINTS

- Trauma is one of the leading causes of epilepsy.
- Prophylactic antiseizure medications use does not significantly reduce epilepsy latency, severity, or seizure frequency.
- Coexistence of psychogenic seizures highlights the need to address psychological trauma alongside physical injury.
- Bilateral magnetic resonance imaging lesions are associated with shorter latency to epilepsy onset and are often seen in severe traumatic brain injuries.
- Epilepsy surgery is a viable option and should be considered in drug-resistant patients.

Brain magnetic resonance imaging (MRI) findings showed trauma-related sequelae, most commonly multifocal (48%), followed by frontal (34%), temporal (9%), and parietal (7%) lobes. There were no cases with isolated occipital involvement, and isolated infratentorial involvement was observed in only 1 patient. Lesion lateralization was most commonly observed on the left side (42%), followed by right-sided lesions (36%) and bilateral lesions (22%). MRI findings were normal in seven patients (11%).

Table 1. Demographic and clinical details of the patients

	% (n)
Gender	
Female	27% (18)
Male	73% (49)
Age (median, IQR)	54 (40-62)
Trauma severity	
Mild	15% (10)
Moderate	25% (16)
Severe	60% (39)
Unconsciousness period	
Unknown	66% (44)
None	2% (1)
Minutes	3% (2)
Days	10% (7)
Weeks	10% (7)
Months	9% (6)
Family history of epilepsy	11% (7)
Trauma recurrence	17% (11)
Epilepsy latency (month, median, IQR)	24 (6-96)
Antiseizure medication	
Carbamazepine	46% (29)
Levetiracetam	30% (19)
Phenytoin	22% (14)
Prophylactic antiseizure medication	16% (9)
Seizure types	
Focal motor, aware	8% (5)
Focal motor with impaired awareness	61% (41)
Focal to bilateral tonic-clonic seizure	60% (39)
Seizure frequency	
Daily	5% (3)
Weekly	22% (13)
Monthly	45% (27)
Yearly	23% (14)
Seizure-free	5% (3)
Neurological examination	
Motor findings	25% (15)
Speech abnormalities	16% (10)
Cognitive problems	28% (17)

IQR: Interquartile range

EEG findings are summed up in Table 2. EEG showed background slowing in 72.1% of cases and approximately one third of these patients had moderate to severe slowing (21.3%). Focal epileptiform activity was observed in 57% of the patients, most commonly in the frontal and temporal regions. EEG was normal in eleven patients (18%). Non-convulsive status epilepticus was detected in two patients. Cramér's V test revealed a significant medium-sized correlation between the lateralization of EEG and MRI findings as expected ($p < 0.001$, $\phi_c = 0.405$).

As for the epilepsy treatment, the most commonly preferred ASMs were carbamazepine and levetiracetam, with carbamazepine prescribed for 46% of patients and levetiracetam for 30%. Drugresistance was observed in 37% of patients.

Table 2. Radiological and electrophysiological characteristics of the patients

	% (n)
MRI localizations	
Frontal	34% (19)
Temporal	9% (5)
Parietal	7% (4)
Occipital	-
Infratentorial	2% (1)
Multifocal	48% (27)
MRI lateralizations	
Left	42% (23)
Right	36% (20)
Bilateral	22% (12)
EEG background activity	
Normal	28% (17)
Slow-mild	54% (33)
Slow-moderate/severe	21% (13)
EEG lateralization	
None-normal	18% (11)
Left	33% (20)
Right	23% (14)
Bilateral	20% (12)
EEG focal findings-slowing	57% (35)
Frontal	48% (29)
Temporal	42% (28)
Central	12% (8)
Parietal	12% (8)
Occipital	0% (0)
EEG focal findings-epileptiform	57% (35)
Frontal	36% (22)
Temporal	31% (19)
Central	10% (6)
Parietal	8% (5)
Occipital	0% (0)

MRI: Magnetic resonance imaging, EEG: Electroencephalography

Prophylactic ASM was initiated in 16% (n=9) of the patients. All of these patients had a history of moderate or severe trauma. Seven underwent surgical interventions, and ASMs were initiated during post-operative intensive care follow-up in the absence of seizures. Among patients who received prophylactic ASM, the median epilepsy latency was 12 months (IQR: 4-90 months). The most commonly prescribed ASMs were levetiracetam, carbamazepine, and phenytoin. None of the patients remained seizure-free. Four patients met the criteria for drug-resistant epilepsy despite the use of two appropriately selected and adequately dosed ASMs. No significant differences were found between those who used prophylactic ASM and those who did not in terms of epilepsy latency, seizure frequency, or drug resistance ($p>0.58$).

Latency, seizure frequency, and drug-resistant epilepsy rates were similar between those with childhood trauma and those with adulthood trauma ($p>0.17$). Drug-resistant epilepsy was significantly more common in patients with severe TBI ($p<0.03$). Patients with bilateral MRI lesions had a shorter epilepsy latency ($p<0.01$). MRI lateralization showed a consistent correlation with trauma severity: bilateral lesions were expected in more severe cases, while milder TBIs were more likely to have normal MRIs ($p<0.001$, $\phi_c=0.458$).

DISCUSSION

This study further emphasized that the prophylactic use of ASM does not contribute to the latency or severity of developing epilepsy. Bilateral traumatic involvement causes hastier epileptogenesis and earlier seizures. The severity of the trauma and longer periods of unconsciousness are risk factors for drug-resistant epilepsy. Coexistence of psychogenic seizures reminds the clinician that trauma is a multifaceted event exceeding mere physical damage. Therefore, a multidisciplinary approach may be required in such cases.

The risk factors described in the literature for PTE include male sex, existence of focal neurological signs, duration of unconsciousness, and fixed imaging findings, all of which were found to be more common in our PTE cohort, consistent with the literature.⁷⁻⁹ It is also well known that the risk of seizures and epilepsy increases in proportion to the severity of TBI.¹⁹ Our study shows that drug-resistant epilepsy is more common in patients with a history of severe trauma in a cohort of PTE patients, highlighting that trauma severity is associated not only with the development of epilepsy but also with the development of drug resistance.

EEG findings were consistent with the imaging as expected. No correlation was found between lesion localization on brain MRI and seizure occurrences. However, the presence of bilateral MRI lesions is significant, as it warrants a shorter latency to epilepsy onset. This is believed to be due to the severity of the TBI because more severe TBIs are more likely to cause bilateral, multifocal involvement in the brain parenchyma, leading to prominent neuroinflammation and remodeling.²⁰ This is an important, albeit overlooked aspect of the PTEs. In the current era, bits and pieces of the underlying neuroinflammatory process are addressed, but we

are far from grasping the totality of cellular and neuroinflammatory interactions that ultimately give way to epileptogenesis following TBIs.²¹ The lack of biomarkers capable of foreseeing which patient is undergoing the epileptogenesis process after such insult is another important limitation for such studies, resulting in either studies conducted retrospectively or the recruitment of every patient with TBI, leading to unjustifiably high budgets and a waste of resources.

Our study showed that prophylactic use of ASM does not contribute to the latency of the developing epilepsy or severity of the seizures. This is well in line with the previous literature, suggesting that avoiding the prescription of ASM to TBI patients without seizures could be more beneficial, as they do not provide anti-epileptic effects do not stop the epileptogenesis process.^{12,13,16,22,23} Although there have been some positive effects of pharmacological and cellular interventions on animal models, sadly, the attempt to translate these findings into clinical implications has failed.²⁴ Giving TBI patients ASM can lead to unwanted side effects, worsen cognitive outcomes, and cause unnecessary economic burden. Even if prophylactic treatment is initiated, early discontinuation should be planned promptly.¹⁶

Another overlooked aspect is the complex nature of trauma itself, transcending the physical harm aspect. The coexistence of psychogenic seizures in this cohort suggests that psychological trauma may also be a contributing factor. As these patients are mostly followed up by a team of doctors and physiotherapists due to their complex injuries and their aftermath, psychiatric aspects should not be overlooked, and psychiatric evaluation should be considered an essential part of the evaluation and follow-up plan for these patients.²⁵

Study Limitations

The main limitation of this study is the number of patients included; however, since this cohort is diagnosed, treated, and followed up comprehensively from a single center, the insights gained are still quite valuable due to the rather standardized management and approach in addition to the chance to capture nuances. As traumatic encephalomalacia is not a typical lesion considered resectable, our detailed examination allows us to identify cases that could significantly benefit from epilepsy surgery. Summary of a case from this cohort that has undergone resection is presented in Figure 1.

CONCLUSION

In conclusion, this study contributes valuable insights into the clinical, radiological, and electrophysiological features of PTE. It reinforces that ASM are not beneficial as prophylactic agents. TBI severity not only influences epilepsy development, but also it affects the likelihood of drug resistance, and the psychiatric aspect of the trauma should not be overlooked. Given the limitations of current treatment strategies, a shift towards individualized, biomarker-driven approaches and a broader neuropsychiatric perspective in patient management is warranted.

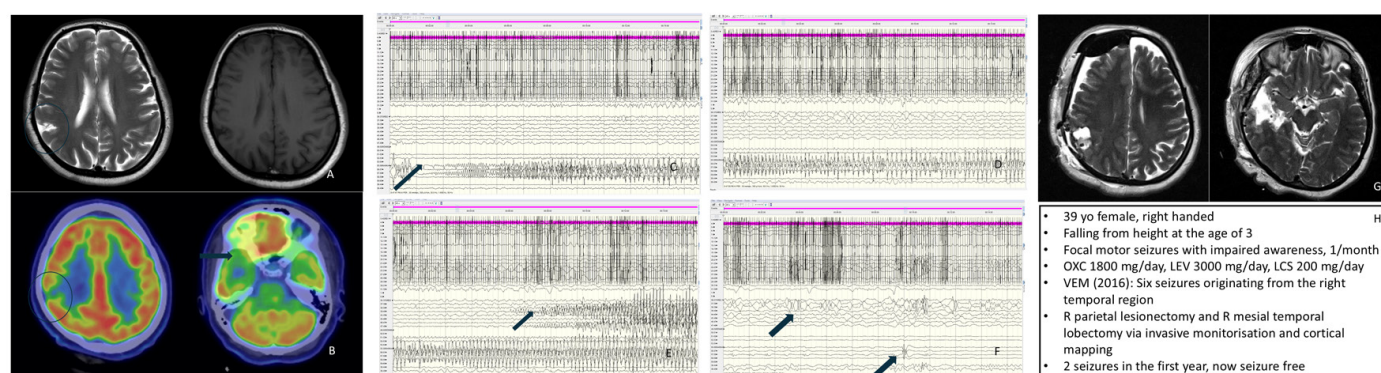


Figure 1. A short case snippet. A) Pre-operative brain MRI showing a T2 hyperintense and T1 hypointense lesion in the right parietal region. B) Brain PET imaging revealing hypometabolism in the right parietal region and pronounced bilateral mesial temporal hypometabolism, more prominent on the right. C,D,E) A seizure originating from the right temporal region electrodes, spreading to the grid electrodes, and becoming generalized during invasive monitoring. F) Invasive EEG monitoring during the interictal period showing independent sharp wave discharges in the right temporal electrodes and the grid electrodes over the parietal lesion. G) Post-operative brain MRI showing encephalomalacic areas consistent with right parietal lesionectomy and right temporal lobectomy. H) short case summary MRI: Magnetic resonance imaging, EEG: Electroencephalography, PET: Positron emission tomography, yo: Years old, OXC: Oxcarbazepine, LEV: Levetiracetam, LCS: Lacosamide, VEM: Video EEG monitoring, R: Right

Ethics

Ethics Committee Approval: This study was approved by the İstanbul University Clinical Research Ethics Committee (approval no: 2025/214, date: 28.04.2025).

Informed Consent: Retrospective study.

Footnotes

Author Contributions

Surgical and Medical Practices: Ö.K., A.D.E., O.A., F.U., N.B., Concept: O.A., N.B., Design: O.A., N.B., Data Collection or Processing: Ö.K., O.A., F.U., N.B., Analysis or Interpretation: Ö.K., A.D.E., F.U., N.B., Literature Search: Ö.K., A.D.E., Writing: Ö.K., A.D.E., F.U., N.B.

Conflict of Interest: No conflict of interest was declared by the authors.

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