

Seizure Control in Patients with Dual Pathologies

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Abstract

Objective: Temporal lobe epilepsy (TLE) is the most common focal epilepsy syndrome and remains medically refractory in a substantial proportion of patients. Dual pathology, defined as the coexistence of hippocampal sclerosis with an additional neocortical lesion, is an important cause of surgical failure when not adequately recognized. This study aimed to evaluate the clinical characteristics and postoperative seizure outcomes of patients with dual pathology compared with those with isolated mesial temporal sclerosis.

Methods: We retrospectively reviewed 125 patients who underwent surgery for TLE between January 2005 and February 2023. Thirty-one patients with dual pathology, defined as hippocampal sclerosis accompanied by a neocortical tumor, were included. A control group consisted of 34 age-matched patients with isolated mesial temporal sclerosis. Clinical features, seizure characteristics, surgical procedures, postoperative outcomes assessed using the Engel classification, and complications were analyzed.

Results: The mean age was similar between the dual pathology and control groups. However, the age at seizure onset was significantly later in patients with dual pathology (26.5 ± 15.9 years vs. 9.2 ± 7.8 years; $p < 0.001$). Generalized tonic-clonic seizures were more frequent in the dual-pathology group, whereas focal seizures with impaired awareness predominated in patients with isolated mesial temporal sclerosis. Engel class I seizure freedom was achieved in 61.3% of patients with dual pathology and in 67.6% of controls, with no significant difference between groups. Postoperative complication rates were comparable.

Conclusion: Despite differences in seizure characteristics and age at seizure onset, postoperative seizure outcomes in patients with dual pathology were comparable to those in patients with isolated mesial temporal sclerosis when both the mesial temporal structures and the associated neocortical lesion were adequately resected. Dual pathology should be considered in patients with TLE who present with mesial temporal sclerosis accompanied by a neocortical tumor, particularly in those with a relatively late age at seizure onset.

Keywords: Dual pathology, epilepsy, resective surgery

INTRODUCTION

Epilepsy is one of the most prevalent neurological disorders globally, affecting approximately 65 million people.¹ Despite advancements in pharmacological treatments, nearly one-third of patients continue to experience medically refractory seizures. Among these individuals, mesial temporal lobe epilepsy (TLE) stands out as a frequent and particularly intractable form, with hippocampal sclerosis (HS) being its most commonly identified pathological correlate. Histopathologically defined by selective neuronal loss and gliosis in the hippocampus, HS is well recognized as a key epileptogenic substrate and a frequent target of resective epilepsy surgery.²

However, in a notable proportion of patients—estimated at 5-20%—HS is not the sole pathological finding.^{3,4} Instead, it coexists with other distinct structural abnormalities, most commonly focal cortical dysplasia, low-grade tumors, or vascular malformations.^{2,5} This phenomenon, termed dual pathology (DP), refers to the coexistence of HS with an extrahippocampal lesion, either visible through neuroimaging or revealed via histopathological evaluation.⁶ While the relationship between these lesions remains unclear—whether one initiates or exacerbates the other, or both arise from shared developmental or acquired processes—their co-existence complicates the localization of the epileptogenic zone and the planning of surgical intervention.⁷

The recognition and proper management of DP are critical for optimizing surgical outcomes. In many cases, seizure freedom is only achieved when both the sclerotic hippocampus and the associated lesion are resected. Conversely, failure to detect a secondary lesion, particularly if occult on imaging, may result in incomplete surgery and persistent postoperative seizures. Moreover, the presence of DP has been associated with a greater seizure burden and more complex neurocognitive profiles.

Despite its clinical importance, DP remains underrecognized and understudied. The variability in presentation, the potential subtlety of extrahippocampal lesions, and the limitations of routine imaging all contribute to diagnostic and therapeutic challenges.

In this context, the present study aims to investigate the prevalence, characteristics, and clinical implications of DP in patients undergoing surgery for drug-resistant TLE, with particular attention to histopathological findings and postoperative outcomes.

METHODS

We conducted a retrospective study of 125 patients who underwent surgery for TLE at the Department of Neurosurgery, Bursa Uludağ University, between January 2005 and February 2023. Among these, 31 patients had DP (HS accompanied by neocortical tumors), and 34 age-matched control patients had mesial temporal sclerosis (MTS) and underwent amygdalohippocampectomy.

All patients underwent a standardized preoperative evaluation that included detailed assessment of seizure semiology, prolonged scalp video-electroencephalography (video-EEG) monitoring, and magnetic resonance imaging (MRI). MRI examinations were performed using an epilepsy-dedicated protocol on a 1.5-Tesla system (Siemens Magnetom Aera). The imaging protocol included thin-slice three-dimensional T1-weighted sequences to evaluate cortical thickness and gray-white matter junction abnormalities, as well as high-resolution axial and coronal T2-weighted and FLAIR sequences aligned with the hippocampal axis.^{8,9} In patients with DP, early postoperative contrast-enhanced MRI (24-48 hours postoperatively) was obtained to assess the extent of resection.

Invasive monitoring techniques, such as stereoelectroencephalography or subdural electrode placement, were not required across the cohort. Video-EEG monitoring and continuous video recordings were obtained using scalp electrodes placed in accordance with the International 10-20 electrode mounting system; 16-32-channel reference, longitudinal, and transverse bipolar montages were used. Spikes, sharp waves, spike-and-wave complexes, temporal intermittent rhythmic delta activity, and continuous focal slow-wave activity (theta or delta) were identified. Electrodes with rhythmic theta or delta waves, spike waves, or sharp waves before ictal activity were considered to indicate the localization of the initial ictal activity. Surgical targets

were determined based on concordance among seizure semiology, scalp EEG findings, neuroimaging results, and discussions of the multidisciplinary epilepsy surgery board.

Comprehensive data collection included demographic characteristics, preoperative seizure features, surgical procedures performed, postoperative seizure outcomes, assessed using the Engel classification system, and documented complications. Seizure types were classified according to the International League Against Epilepsy (ILAE) classification.¹⁰ Surgical outcomes were categorized as Engel class I (seizure free or auras only), class ii (rare seizures), class iii ($\geq 75\%$ seizure reduction), or class IV ($< 75\%$ seizure reduction).¹¹

Surgical Technique

Standard surgical treatment for TLE consists of an anterior temporal lobectomy combined with amygdalo-hippocampectomy. This procedure involves resection of variable portions of the anterior and lateral temporal neocortex, followed by intraventricular subpial microsurgical removal of the mesial temporal structures, including the hippocampus and amygdala. The extent of neocortical and mesial resection was determined based on hemispheric dominance, seizure semiology, and anatomical considerations.

In patients with DP, surgical treatment generally consisted of resection of both the mesial temporal structures, as described above, and of the associated neocortical lesion. Depending on tumor location and anatomical constraints, this was achieved by anterior temporal lobectomy combined with lesionectomy or by tailored resections aimed at the complete removal of all radiologically and histopathologically identified epileptogenic substrates. Resection was defined as gross total when no residual tumor was identified intraoperatively or on postoperative MRI, and as subtotal when the residual tumor volume exceeded 5%.¹²

All surgical decisions were made following evaluation by a multidisciplinary epilepsy surgery board, which convenes monthly and comprises neurosurgeons, neurologists specializing in epilepsy, and neuroradiologists. Surgical candidacy was determined based on concordance among seizure semiology, video-EEG findings, neuroimaging results, and clinical characteristics.

Written informed consent for surgical treatment and use of clinical data for research purposes was obtained from all patients prior to surgery. In patients with DP, additional written informed consent was obtained for surgical intervention encompassing both tumor resection and temporal lobectomy. The study was approved by the Medicana Bursa Hospital Clinical Research Ethics Committee (decision no: 2025/08-2, date: 07.10.2025).

Statistical Analysis

We used IBM SPSS 22 for statistical analysis. Continuous variables were expressed as mean \pm standard deviation and analyzed using Student's t-test, while categorical variables were examined using chi-square tests. A p-value < 0.05 was considered statistically significant throughout our analyses.

MAIN POINTS

- Dual pathology (DP) refers to the coexistence of hippocampal sclerosis (HS) with a neocortical tumor or other structural lesion, which complicates epileptogenic zone localization and surgical planning.
- Among 125 patients with temporal lobe epilepsy, 31 had DP (HS+neocortical tumor) and 34 had isolated mesial temporal sclerosis (MTS).
- Seizure onset occurred earlier in MTS patients, while DP patients had later onset and more frequent generalized tonic-clonic seizures.
- Postoperative seizure control rates were comparable (Engel class I: 61.3% in DP vs. 67.6% in MTS), but tumor recurrence occurred in 32.2% of DP patients.
- Resection of both lesions is essential in DP to achieve optimal seizure control with low complication rates.

RESULTS

Demographic and Clinical Characteristics

The study groups showed comparable age distributions (DP: 29.3±14.8 years; MTS: 30±11.2 years, p>0.05). However, gender distribution differed significantly between groups, with a male predominance in the MTS group (70.5%; n=24) compared to the DP group (45.1%; n=14, p=0.047), which was considered in the interpretation of the results.

Age at seizure onset differed significantly: patients with MTS experienced earlier seizure onset (9.2±7.8 years) compared with DP patients (26.5±15.9 years, p<0.001). Seizure semiology also varied substantially between groups. According to the ILAE classification, generalized tonic-clonic seizures predominated in DP cases (54.8%), whereas focal impaired awareness seizures were more characteristic of the MTS group (52.9%). Other seizure types (tonic-clonic, absence, myoclonic) occurred infrequently in both populations (Table 1).

Pathological Findings

Both groups showed a right-sided predominance of lesions [DP: 61.2% (n=19); MTS: 58.8% (n=20)], though this lateralization difference did not reach statistical significance (p>0.05).

In the DP cohort, oligodendroglioma was the most common coexisting pathology in patients with MTS (48.4%, n=15). Among these, 12 cases were classified as World Health Organization (WHO) grade II, while 3 were identified as WHO grade III (anaplastic) (Table 2). Other notable findings included dysembryoplastic neuroepithelial tumors (DNET) (25.8%, n=8), malignant glial tumors (WHO grade III-IV) (12.9%, n=4), and rare tumor types (collectively 12.9%), each represented by a single case: craniopharyngioma, astroblastoma, mixed oligoastrocytoma, and pleomorphic xanthoastrocytoma.

Total resection was achieved in 77.4% of DP cases versus 100% of MTS cases. Follow-up duration averaged 74±35 months for DP patients and 127±28 months for MTS controls.

Postoperative Outcomes

The seizure control outcomes, assessed using the Engel classification system, demonstrated comparable results between the two study groups. In the DP group, 61.3% (n=19) of patients

achieved Engel class I (seizure-free) status, while 67.6% (n=23) of MTS patients achieved the same outcome. The percentages of patients experiencing rare seizures (Engel class II) were similar in both groups: 6.4% (n=2) in DP vs. 5.8% (n=2) in MTS. Notably, 16% (n=5) of DP patients showed no significant improvement (Engel class IV), compared with 11% (n=4) of MTS patients. The mean follow-up duration was significantly longer in the MTS group than in the DP group (127±28 months vs. 74±35 months; Table 3, Figure 1).

Complications

The postoperative complication profiles differed between the two patient groups. In the DP cohort, 6.5% (n=2) of patients required emergency reoperation for intracerebral hematoma, while 9.7% (n=3) developed surgical site infections requiring treatment. The MTS group showed a different complication pattern, with 2.9% (n=1) of patients developing postoperative hydrocephalus. Statistical analysis revealed no significant difference in overall complication rates between the groups (p=0.095) (Table 4).

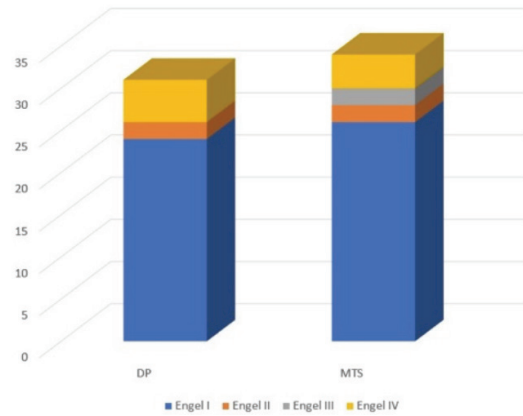


Figure 1. Postoperative outcomes (Engel classification) MTS: Mesial temporal sclerosis; DP: Dual pathology

Table 2. Pathological spectrum in DP

Pathology	n (%)
Oligodendroglioma (WHO grade II-III)	15 (48.4)
DNET	8 (25.8)
Malignant glial tumors (WHO grade III-IV)	4 (12.9)
Craniopharyngioma	1 (3.2)
Astroblastoma	1 (3.2)
Mixed oligoastrocytoma	1 (3.2)
Pleomorphic xanthoastrocytoma	1 (3.2)

DP: Dual pathology, DNET: Dysembryoplastic neuroepithelial tumors, WHO: World Health Organization

Table 3. Postoperative outcomes (Engel classification)

Outcome	DP (%)	MTS (%)	p-value
Class I	61.3	67.6	0.6143
Class II	6.4	5.8	
Class III	0	2.9	
Class IV	16	11	

DP: Dual pathology, MTS: Mesial temporal sclerosis

Table 1. Demographic and clinical characteristics

Variable	DP (n=31)	MTS (n=34)	p-value
Age (years)	29.3±14.8	30±11.2	>0.05
Gender (%)	14 (45.1)	24 (70.5)	0.047*
Seizure onset age (years)	26.5±15.9	9.2±7.8	<0.001*
Seizure types			
- GTC (%)	17 (54.8)	12 (35.2)	
- FIAS (%)	11 (35.4)	18 (52.9)	0.012
- Others (%)	4 (12.9)	4 (11.7)	
Lesion laterality			
- Right	19 (61.2)	20 (58.8)	>0.05
- Left	12 (38.7)	14 (41.1)	

DP: Dual pathology, MTS: Mesial temporal sclerosis, FIAS: Focal impaired awareness seizures, GTC: Generalized tonic-clonic, *: Statistically significant

Table 4. Complication rates

Complication	DP (%)	MTS (%)
Intracerebral hematoma	6.5	0
Surgical site infection	9.7	0
Hydrocephalus	0	2.9

DP: Dual pathology, MTS: Mesial temporal sclerosis

Recurrence

During a mean oncological follow-up of 44.8±35.1 months, tumor recurrence occurred in 32.2% (10 cases) of DP patients. Recurrent cases included 4 oligodendrogliomas (3 WHO grade II and 1 WHO grade III), 2 DNETs, 2 malignant glial tumors (1 WHO grade III and 1 WHO grade IV), and 2 cases of other rare tumor types. The mean time to recurrence was not specifically reported in the study data.

DISCUSSION

Our study demonstrates that, although seizure control rates were slightly lower in the DP group compared with the MTS group, the overall postoperative outcomes were comparable between the groups, and the groups differed in their seizure characteristics.

Most epidemiological features of DP remain controversial due to variations in its definition.¹³ Variations in the definition of DP, low diagnostic sensitivity of MRI, and differences in study populations and methodologies may account for the discrepancies in the reported prevalence of DP and the frequency of associated secondary pathologies.^{14,15} In our study population, 24.2% of patients with drug-resistant epilepsy and HS had DP.

Previous studies have reported a prevalence of DP among patients with TLE that ranges widely, generally from 5% to 20%, depending on diagnostic criteria, imaging sensitivity, and histopathological confirmation.^{3,4,13-15} The relatively higher prevalence observed in our cohort may be partly explained by the inclusion of histopathologically confirmed neocortical tumors and by the long study period, during which improvements in imaging interpretation and surgical pathology likely enhanced recognition of coexisting lesions. Earlier studies have consistently shown that HS is associated with childhood-onset epilepsy, often in the context of febrile seizures, whereas epilepsy related to extrahippocampal structural lesions may present later in life.^{16,17} Consistent with these observations, patients with DP in our series exhibited a significantly later age at seizure onset than those with isolated MTS, suggesting distinct epileptogenic mechanisms and disease trajectories. In instances of DP, excision of both the primary lesion and the HS is essential for improved seizure control.⁴ Occult DP has been reported as one of the causes of failure to achieve seizure control after selective amygdalohippocampectomy in patients with TLE.¹⁸ Occult DP may explain why postoperative seizure outcomes after standard anterior temporal resection for TLE are better than after selective amygdalohippocampectomy, because a more extensive resection increases the likelihood that a neocortical lesion is present in the resected tissue.⁷ Occult DP should always be considered in patients who fail to achieve postoperative seizure control.

Focal cortical dysplasia represents the most common co-occurring pathology in patients with HS.² Our findings revealed a relatively

low prevalence of cortical dysplasia among DP cases. This may be explained by the well-known limitations of MRI in detecting subtle cortical abnormalities. Specifically, cortical dysplasia often remains undetectable on conventional imaging or may resemble gliosis, particularly when accompanied by neuronal and glial proliferation.^{19,20} Consequently, patients with cortical dysplasia in our cohort may have been underdiagnosed, misdiagnosed, or not diagnosed at all. This diagnostic limitation could have led to an underestimation of the true prevalence of DP in our study population.

One significant finding in our cohort was that seizures began much earlier in patients with MTS than in patients with DP. This result is in line with earlier findings that MTS usually manifests early in life, frequently in conjunction with febrile seizures.^{16,17} DP, on the other hand, is more frequently associated with later-onset epilepsy. Since adult-onset seizures are more likely to result in neuroimaging that reveals underlying structural abnormalities, the DP group's older age at seizure onset may affect both diagnostic and treatment timelines.

Furthermore, the observed variations in seizure semiology among the groups could be attributable to differences in epileptogenic networks. Focal impaired awareness seizures were more prevalent in patients with MTS, whereas generalized tonic-clonic seizures were more common in the DP group. This pattern implies that, while MTS usually involves limbic structures and results in more stereotyped seizure manifestations, neocortical lesions in DP cases may promote more rapid seizure generalization or disrupt broader cortical-subcortical circuits.

Although the two groups differed in both underlying pathology and clinical presentation, postoperative seizure freedom rates were comparable, with Engel class I outcomes observed in 61.3% of patients with DP and 67.6% of those with isolated MTS. These results support the effectiveness of surgical intervention in appropriately selected cases. However, a greater proportion of patients in the DP group were classified as Engel class IV (16% vs. 11%), which may reflect the inherent complexity of these cases particularly in achieving complete resection when high-grade or infiltrative tumors are involved, or when the epileptogenic zone is more diffuse. Furthermore, the higher rate observed in the MTS group may be attributable to overlooked focal cortical dysplasia or other occult pathologies.²¹ It is possible that the difference would have been even greater had these pathologies not been missed in the MTS group.

Notably, complete tumor resection was not achieved in approximately 23% of the DP group, which may have further contributed to the group's slightly lower seizure-control rates and the relatively high tumor-recurrence rate of 32.2% observed during follow-up. This is consistent with previous studies reporting a strong association between incomplete resection—especially in low-grade gliomas—and both tumor progression and persistent seizures.²¹ Furthermore, the shorter follow-up period in the DP group (74 months compared to 127 months in the MTS group) may have led to an underestimation of long-term seizure outcomes and recurrence rates.

The DP group demonstrated a heterogeneous histopathological profile, with oligodendroglioma emerging as the most prevalent tumor type, followed by DNET and malignant glial neoplasms. This distribution aligns with previous studies reporting a higher

incidence of certain tumor types—particularly DNET and low-grade gliomas²¹—among patients with pharmacoresistant epilepsy, in whom these lesions frequently coexist with HS in chronic cases. The simultaneous presence of both lesions raises an important and ongoing debate in epilepsy surgery: whether each lesion contributes independently to epileptogenesis or whether one represents the primary epileptogenic focus. In such complex cases—especially when lesions are subtle, multifocal, or radiographically ambiguous—the importance of detailed preoperative planning becomes paramount. High-resolution MRI and complementary imaging modalities, alongside intraoperative tools such as electrocorticography or stereoelectroencephalography, when available, play a crucial role in identifying and guiding the resection of all potentially epileptogenic areas, thereby optimizing surgical outcomes.

Although the overall complication rates were not significantly different between the two groups, the types of complications varied meaningfully. In the DP cohort, a higher incidence of intracerebral hematomas and postoperative infections may be attributed to longer operative durations, more extensive resections, or the technical challenges of removing tumors located near eloquent cortical areas. These differences highlight the importance of tailoring perioperative management strategies according to the specific pathological and anatomical features of each patient.

Study Limitations

Several limitations of this study should be acknowledged. First, the retrospective design and unequal follow-up durations between study groups constitute significant methodological limitations, because the shorter follow-up in the DP group may have led to underestimation of long-term seizure outcomes and tumor recurrence rates. In addition, although age matching was performed, gender matching was not feasible because of the retrospective design and the limited number of patients with DP, resulting in an imbalance in the gender distribution that may be a confounding factor when interpreting the results. Furthermore, the absence of volumetric analysis of tumor burden and the lack of detailed localization of the seizure onset zone using advanced electrophysiological techniques, such as stereoelectroencephalography, limit the precise assessment of the relative epileptogenic contributions of the tumor and the hippocampus in DP cases. Future studies with larger cohorts, a prospective design, and comprehensive electrophysiological mapping are warranted to refine surgical strategies and improve prognostication in this challenging patient population. In addition, multivariate analysis was not performed in this study. Although several factors such as gender, tumor histology, extent of resection, and the presence of infiltrative tumors may influence postoperative seizure outcomes, the relatively small sample size—particularly within the DP subgroup—and the heterogeneity of tumor types limited the ability to construct a reliable multivariate model. Performing such an analysis under these conditions would carry a substantial risk of overfitting and of producing statistically unstable results. Therefore, the findings of this study should be interpreted as exploratory rather than predictive.

CONCLUSION

DP represents an important and potentially underrecognized entity in patients with TLE. Our findings demonstrate that, despite differences in seizure characteristics and age at seizure onset, postoperative seizure control rates in patients with DP are

comparable to those observed in patients with isolated MTS when both the mesial temporal structures and the associated neocortical lesion are adequately resected.

Notably, although age at surgery was similar between the two groups, patients with DP had a significantly later age at seizure onset than those with isolated MTS, who more commonly presented with childhood-onset epilepsy. These findings underscore the importance of considering DP in patients with TLE presenting with MTS accompanied by an additional neocortical lesion and support comprehensive surgical strategies aimed at the resection of all epileptogenic substrates.

Ethics

Ethics Committee Approval: The study was approved by the Medicana Bursa Hospital Clinical Research Ethics Committee (decision no: 2025/08-2, date: 07.10.2025).

Informed Consent: Written informed consent for surgical treatment and use of clinical data for research purposes was obtained from all patients prior to surgery.

Footnotes

Author Contributions: Surgical and Medical Practices: Y.T., P.E., A.B., Concept: P.E., Design: P.E., Data Collection or Processing: Y.T., N.B., Analysis or Interpretation: A.B.D., I.B., A.B., Literature Search: Y.T., P.E., A.B.D., Writing: Y.T., P.E., E.D.

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