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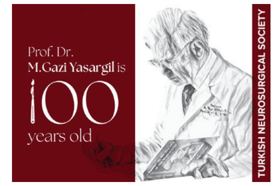

Original Investigation

Stereotactic and Functional

Not to Wait Too Long After Failed Surgery for Intractable Mesial Temporal Lobe Epilepsy: Results of Reoperation at a Tertiary Hospital

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ABSTRACT

AIM: To evaluate the causes and risk factors of seizure recurrence, as well as the outcomes of reoperation in patients who did not achieve sufficient seizure control following surgery for mesial temporal lobe epilepsy (MTLE).

MATERIAL and METHODS: We retrospectively reviewed the hospital charts of patients with medically refractory MTLE who were operated between 1990 and 2021.

RESULTS: A total of 240 patients (127 females and 113 males) with medically refractory mesial temporal lobe epilepsy underwent resective epilepsy surgery. Of these, 12 (5%) required reoperation due to seizure recurrence after the initial surgery. Six out of the 12 patients with available seizure outcome data were included in the study. The cause of seizure recurrence in all patients was remnant tissue. The age at reoperation ranged from 17 to 59 years, and the time between the initial and final surgery ranged from 2 to 20 years. The seizure outcome was Engel Class I in all patients, with follow-up periods ranging from 4 to 21 years.

CONCLUSION: Surgical failure is still prevalent in patients with MTLE, with inadequate resection frequently serving as the primary cause. Reoperation can considerably improve the seizure outcome. Delaying the opportunity for a second surgical intervention should be avoided.

KEYWORDS: Epilepsy, Intractable epilepsy, Reoperation, Surgery, Surgery failure, Temporal lobe epilepsy

ABBREVIATIONS: TLE: Temporal lobe epilepsy, **MTLE:** Mesial temporal lobe epilepsy, **FIASs:** Focal impaired awareness seizures, **FBTCSs:** Focal to bilateral tonic-clonic seizures, **EEG:** Electroencephalography, **MRI:** Magnetic resonance imaging, **ASDs:** Antiseizure drugs, **ATL:** Anterior temporal lobectomy, **DNET:** Dysembryoplastic neuroepithelial tumor

INTRODUCTION

The majority of surgically treated patients diagnosed with medically intractable seizures have temporal lobe epilepsy (TLE). The seizure-free rates following resective surgery range from 60% to 80% in temporal lobe epilepsy (4,5,19,21). However, up to 30% of patients may not benefit from surgical treatment and may continue to experience seizures following surgery (18). The results of studies investigating the outcomes of reoperation in patients with failed epilepsy surgery are encouraging, prompting epileptologists to re-evaluate these patients (2,9,13,14,17,20).

Several studies have reported the outcomes of reoperation for recurring TLE (1,5,10,12). These studies found that more

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complete resection of the mesiobasal structures can prevent seizure recurrence and need for reoperation (7). However, in the case of resective surgeries which provide the best results in terms of seizure-free rate and neuropsychological outcome, the approach and size of the resection remain debatable (18).

The primary aim of this study is to investigate the surgical outcomes in patients with mesial TLE (MTLE) who were re-operated due to seizure recurrence. Additionally, we examine the causes of seizure recurrence after the initial surgery and discuss the surgical tips related to seizure recurrence.

MATERIAL and METHODS

This study is a retrospective consecutive case series from a single center. The study protocol was reviewed and approved by the local ethics committee. The ethical approval was obtained from the Ankara University School of Medicine, Human Research Ethics Committee (Decision No: I2-121-20).

We retrospectively reviewed the hospital charts of patients with medically refractory MTLE who were operated on at the Department of Neurosurgery between 1990 and 2021. Patients who underwent reoperation owing to seizure recurrence after their initial surgical treatment, as well as those patients with postoperative follow-ups and available seizure outcomes, were included in the study. Before the second surgery, all patients had been thoroughly evaluated by an experienced epilepsy center. These evaluations included video-electroencephalography (EEG) monitoring with seizure recording, 1.5 or 3T epilepsy protocol magnetic resonance imaging (MRI), detailed neuropsychological assessment and, when necessary, positron emission tomography (PET) or functional MRI.

We collected data on the demographic features, risk factors for epilepsy, age at seizure onset, seizure types, brain MRI findings before and after the initial surgery, any changes in the frequency and type of seizures post-surgery, pathological findings, time to seizure recurrence after the initial surgery, and seizure outcomes after both the initial and second surgeries. The primary outcome was seizure status following surgery. Seizure outcome was evaluated according to the Engel classification (3).

RESULTS

Between the years 1990 and 2021, 240 patients (127 female and 113 male) with medically refractory MTLE underwent resective epilepsy surgery at our institution. All patients underwent anterior temporal lobectomy (ATL). Of the 240 patients, 12 (5%) underwent reoperation owing to seizure recurrence after the initial surgical treatment. Six of the 12 patients were excluded from the study due to the absence of documented seizure outcomes. We present the data of six patients with MTLE who underwent reoperation owing to seizure recurrence after the initial surgical treatment. The demographic and clinical data of these patients are summarized in Table I. There was no reduction or discontinuation of drug therapy in any of the patients for at least 24 months after the initial surgery.

Recurrent seizures occurred in the first 6 months after the initial surgery in five of the six patients. Patient #6 (see below) had a single seizure at the 6^{th} month, however, recurrent seizures occurred at the 30^{th} month of the initial surgery. Patients #1 and #2 experienced frequent seizures in the early period, shortly after the first surgery (<1 month). The histopathological findings indicated focal cortical dysplasia and DNET in these patients, respectively.

The recurrent seizures were semiologically identical to the preoperative seizures in all patients. Exceptionally, patient #3 had frequent focal seizures and rare, focal to bilateral tonic clonic seizures (FBTCS) before the initial surgery; however, all seizures after the initial surgery were FBTCSs. In all patients, based on video-EEG monitoring, brain imaging results, and evaluations made during patient management conferences, it was concluded that the cause of seizure recurrence after the initial surgery was the residual tissue observed on the brain MRI, specifically in the mesial temporal region. All patients underwent reoperation to complete anterior temporal lobectomy with resection of residual tissues. The patient's age at reoperation ranged from 17 to 59 years. The time from the initial to the last surgery, in terms of reoperation, ranged from 2 to 20 years (Table I).

The follow-up duration after the repeat surgery ranged from 4 to 21 years. The median follow-up time was 15 years. The seizure outcome at last follow-up was Engel Class I (Ia and Ib) with no disabling seizures since surgery.

The histopathological findings showed neoplasms in three patients (patients #2, 3, and 5) and nonneoplastic conditions in the others (patients #1, 4, and 6). In three patients, the diagnosis changed after the second surgery (patient #2: from gliosis to dysembryoplastic neuroepithelial tumor, patient #3: from astrocytoma to grade 1 ganglioglioma; and patient #5: from nonspecific changes to glioneuronal tumor), all of whom were diagnosed with a neoplastic pathology. After the repeat surgery, there were no serious complications. Preoperative and postoperative neuropsychological test results were only available for patient #6, while the results for the other patients could not be retrieved. However, during outpatient evaluations and follow-up phone calls (carried out in previous and recent follow-ups), neither the patients nor their relatives reported any complaints regarding the new onset of memory or language deficits following the most recent surgery.

Detailed examination of each patient is presented below:

Patient #1

The patient was a 41-year-old female with a 17-year history of focal impaired awareness seizures (FIAS) and focal to bilateral tonic-clonic seizures (FBTCS). Regarding her medical history, she had febrile convulsions at the age of 6 months. Brain MRI showed increased hyperintensity in the left mesial temporal lobe structures. She underwent left amygdalohippocampectomy for mesial temporal lobe epilepsy at another hospital at the age of 30 years. In the postoperative follow-up, the frequency of seizures increased by more than 50% in the first month after surgery. Eleven years after the first surgery, the patient was re-evaluated. Interictal electroencephalography revealed epileptiform discharges in the left temporal region. Focal onset seizures with impaired awareness, which were

Table I: The Demographic and Clinical Features of MTLE Patients Re-Operated Due to Failure From Initial Surgical Intervention

	Patient #1	Patient #2	Patient #3	Patient #4	Patient #5	Patient #6
Gender	F	M	F	M	F	M
Risk factors for epilepsy	FS	TBI	Negative	FS	Negative	FS
Age at seizure onset (years)	24	11	5	10	27	13
Type of seizures before 1st operation	Aura>> FIA>> FBTCS	FIA>> FBTCS	Aura>> FIA>> FBTCS	Aura>> FIA	FIA	Aura>> FIA>> FBTCS
MRI findings before 1st operation	Increased hyperintensity in the left mesial temporal lobe structures	Mass lesion in the right temporal region	Mass lesion in the left temporal region	Atrophy and increased hyperintensity in the right mesial temporal lobe structures	Mass lesion in the right temporal region	Atrophy and increased hyperintensity in the left mesial temporal lobe structures
Age at 1st operation (years)	30	16	12	1st: 18 2nd:23	33	39
Side of operation	Left	Right	Left	Right	Right	Left
Type of 1st operation	sAH	GTR+sAH	GTR+sAH	ATL	STR	ATL
Pathology after 1st operation	Cortical dysplasia type 1	Gliosis	Astrocytoma (Grade 1)	HA/S	Non-specific	Glial tissue showing degenerative changes
Outcome after 1st operation. (l-year follow up)	Engel 5	Engel 5	Engel 4	Engel 5	Engel 5	Engel 1
Time of Seizure Recurrence After 1st operation (months)	<1	<1	<2	<6	<6	First seizure: 6th month Recurrent seizures: 30th month
Any change in frequency and type of seizures after 1st operation	No change	No change	No change except all seizures were focal to bilateral tonic clonic seizures	No change	No change	No change
MRI findings before 2nd operation	Remnant tissue on left mesial temporal region	Remnant tissues and encephalomalastic changes in right temporal region	Remnant tissues in left temporal region	Residual tissues in the right mesial temporal region	Residual tissues in the right mesial temporal region	Remnant tissue on left anteromesial temporal region
Concordance of semiology, EEG and MRI before 2nd operation	All	All	All	All	All	All
Age at 2nd operation (years)	41	18	19	30	49	59

Table I: Cont.

	Patient #1	Patient #2	Patient #3	Patient #4	Patient #5	Patient #6
Time to 2nd operation (years)	11	2	7	12	16	20
Type of 2nd operation	ATL	ATL	ATL	ATL	ATL	Resection of remnant tissues seen on MRI
Pathology after 2nd operation	Cortical dysplasia type 1	DNET (grade 1)	Ganglioglioma (grade 2)	HA/S	Mixed glioneuronal tumor	Non-specific gliosis
FU period after 2nd operation (years)	17	17	18	21	10	4
Outcome after 2nd operation (at last FU)	Engel I	Engel I	Engel I	Engel I	Engel I	Engel 1

***F:** Female; **M:** Male; **FS:** Febrile seizure; **TBI:** Traumatic brain injury; **FIA:** Focal impaired awareness; **FBTCS:** Focal to bilateral tonic clonic seizure; **sAH:** Selective amygdalo-hippocampectomy; **GTR:** Gross tumor resection; **STR:** Subtotal tumor resection; **ATL:** Anterior temporal lobectomy; **HA/S:** Hippocampal atrophy/sclerosis; **m:** months; **y:** years.*

semiologically identical to the preoperative seizures arising from the left hemisphere, were recorded during long-term video-EEG monitoring. Remnant tissue in the left mesial temporal region detected on brain MRI (Figure 1A, B) was thought to be responsible for seizure recurrence after the previous surgery. Anterior temporal lobectomy was performed, and the residual tissue in the mesial temporal region was resected at the age of 41 years. The histopathological findings were compatible with cortical dysplasia type 1. After the second surgery, the patient remained seizure-free for 2 years, at which point antiseizure drugs (ASDs) were gradually discontinued during follow-up. The patient has now been seizure-free for 17 years.

Patient #2

This is an 18-year-old male who had FIASs characterized by unresponsiveness, oral automatisms and FBTCS for 6 years. He had intractable seizures despite using multiple anti-seizure drugs. Brain MRI showed a mass lesion in the right temporal region involving the mesial structures. Consequently, the patient underwent right temporal mass resection via stereotactic surgery at the age of 16 years at another hospital. The histopathological findings of the surgical specimen indicated gliosis. After the initial surgery, the seizures continued and the seizure frequency increased by > 100%. Thus, the patient was re-evaluated. In long-term video EEG monitoring, interictal EEG showed focal epileptiform discharges at the right temporal region, and generalized spike-waves. Additionally, three seizures (two FIASs and one FBTCS) with right hemisphere ictal onset were recorded. Remnant tissues and encephalomalacia were detected in the mesial temporal region on brain MRI (Figure 2A). In the second surgery performed two years after the first operation, ATL was combined with gross total tumor resection. (Figure 2B). The specimen was histopathologically identified as a dysembryoplastic neuroepithelial tumor (DNET). In the postoperative follow-up, the patient has remained seizure-free for 17 years.

Patient #3

The third case is that of a 19-year-old female who had been followed with a diagnosis of focal epilepsy for 13 years. She was diagnosed with intractable left MTLE based on the results of presurgical evaluation, so the patient underwent left-sided amygdalohippocampectomy at the age of 12 years at another hospital. After the surgery, the surgical specimen was histopathologically identified as an astrocytoma (grade I). Two months after the initial surgery, she began to experience seizures. Preoperatively, she had FIASs that rarely progressed to bilateral tonic-clonic seizures. However, postoperatively, all seizures evolved into bilateral tonic-clonic seizures. The patient was monitored in the video EEG monitoring unit, where two FBTCSs with left temporal region onset were recorded. Remnant tissue was detected in the mesial temporal region on MRI (Figure 3A). Gross total tumor resection, along with ATL, was performed at our institution (Figure 3B). The histopathological findings were consistent with a grade 2 ganglioglioma. In the postoperative follow-up, the patient has remained seizure-free for 18 years.

Patient #4

The fourth case, which was previously reported, is that of a 30-year-old male with a >10-year history of focal seizures (6). He was diagnosed with HS-related mesial temporal lobe epilepsy based on the video-EEG and brain MRI results. His seizures were resistant to medical treatment; therefore, he underwent surgery first at the age of 18 and second at the age of 23 years for right temporal lobe epilepsy at two different centers. After both surgeries, the patient began experiencing seizures approximately 6 months later. The semiology of the seizures remained unchanged. The patient was re-evaluated for possible surgical treatment. Long-term scalp video-EEG monitoring was not informative regarding the lateralization of the seizures, so invasive monitoring with subdural strip electrodes was performed. During invasive video EEG monitoring,

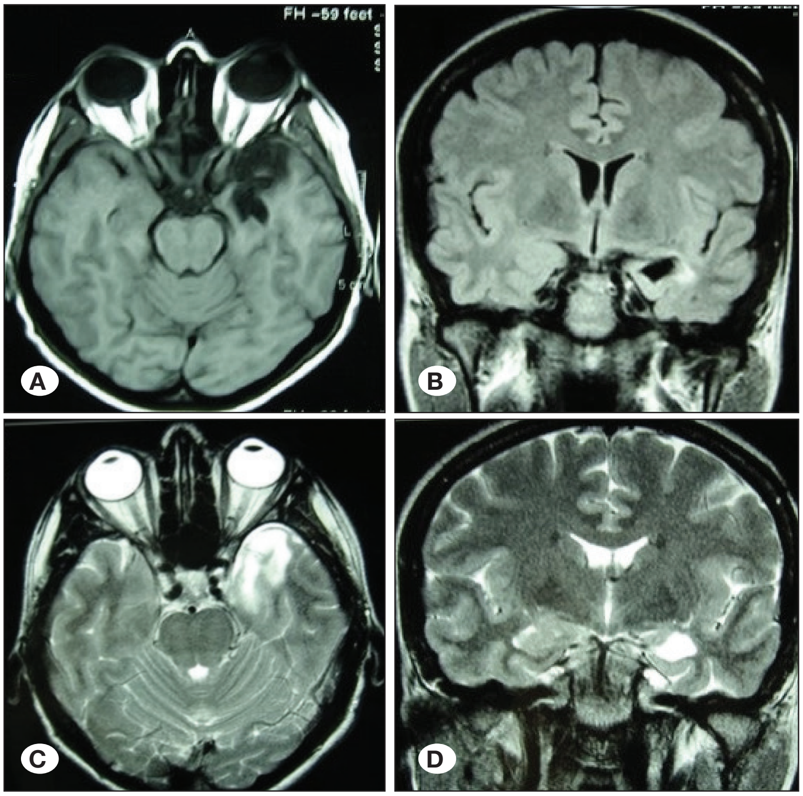

Figure 1: T1 (**A:** axial, **B:** coronal) and T2 (**C:** axial, **D:** coronal)-weighted brain magnetic resonance imagings of patient #1 show remnant tissues in the anteromesial regions of the left temporal lobe after the first surgery.

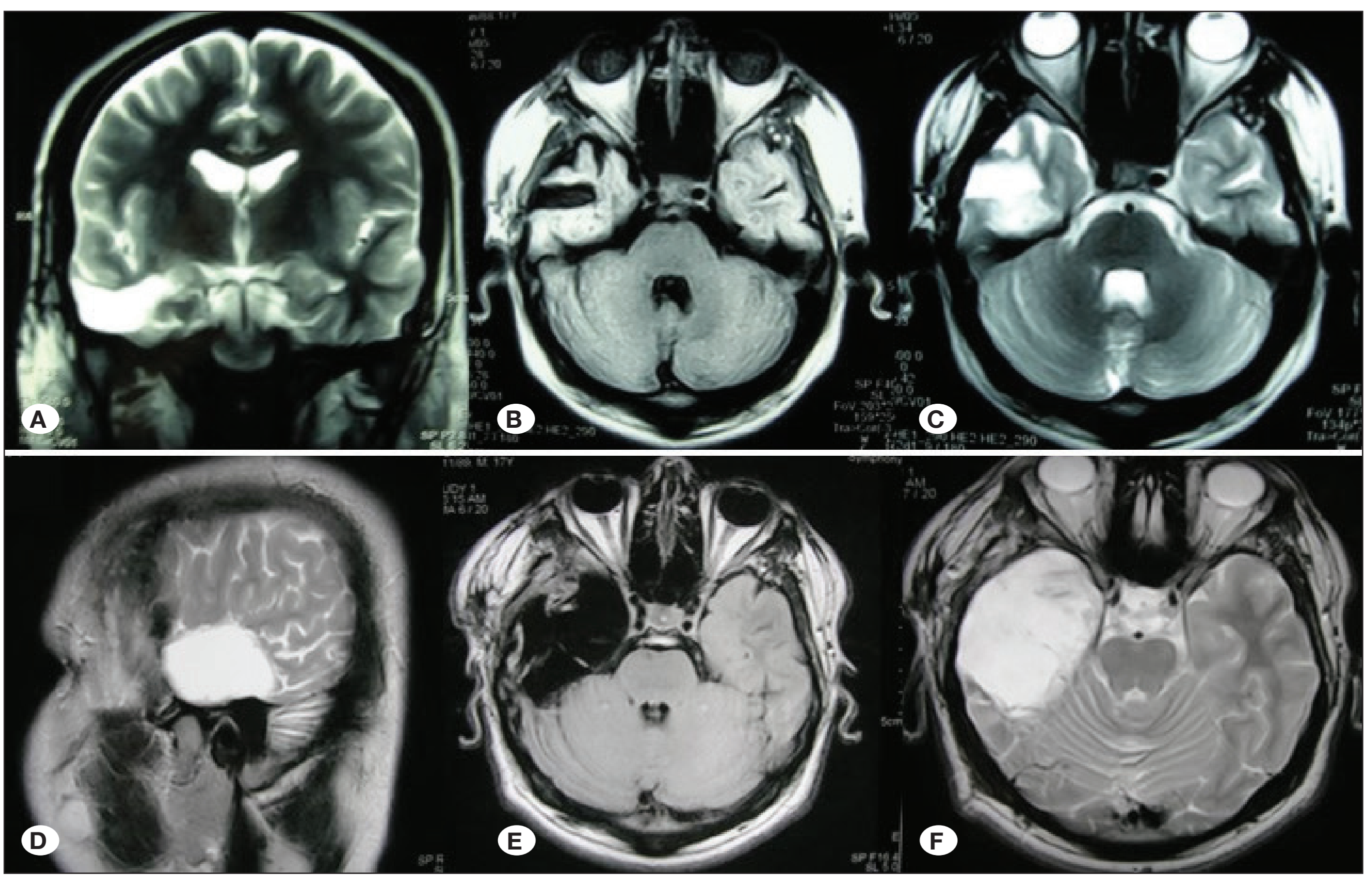

Figure 2: A-C) Preoperative brain magnetic resonance imaging (MRI) sections of patient #2; **D-F)** brain MRIs (**D:** T2W coronal, **E:** T1W axial, **F:** T2W axial) after the second surgical treatment of the patient.

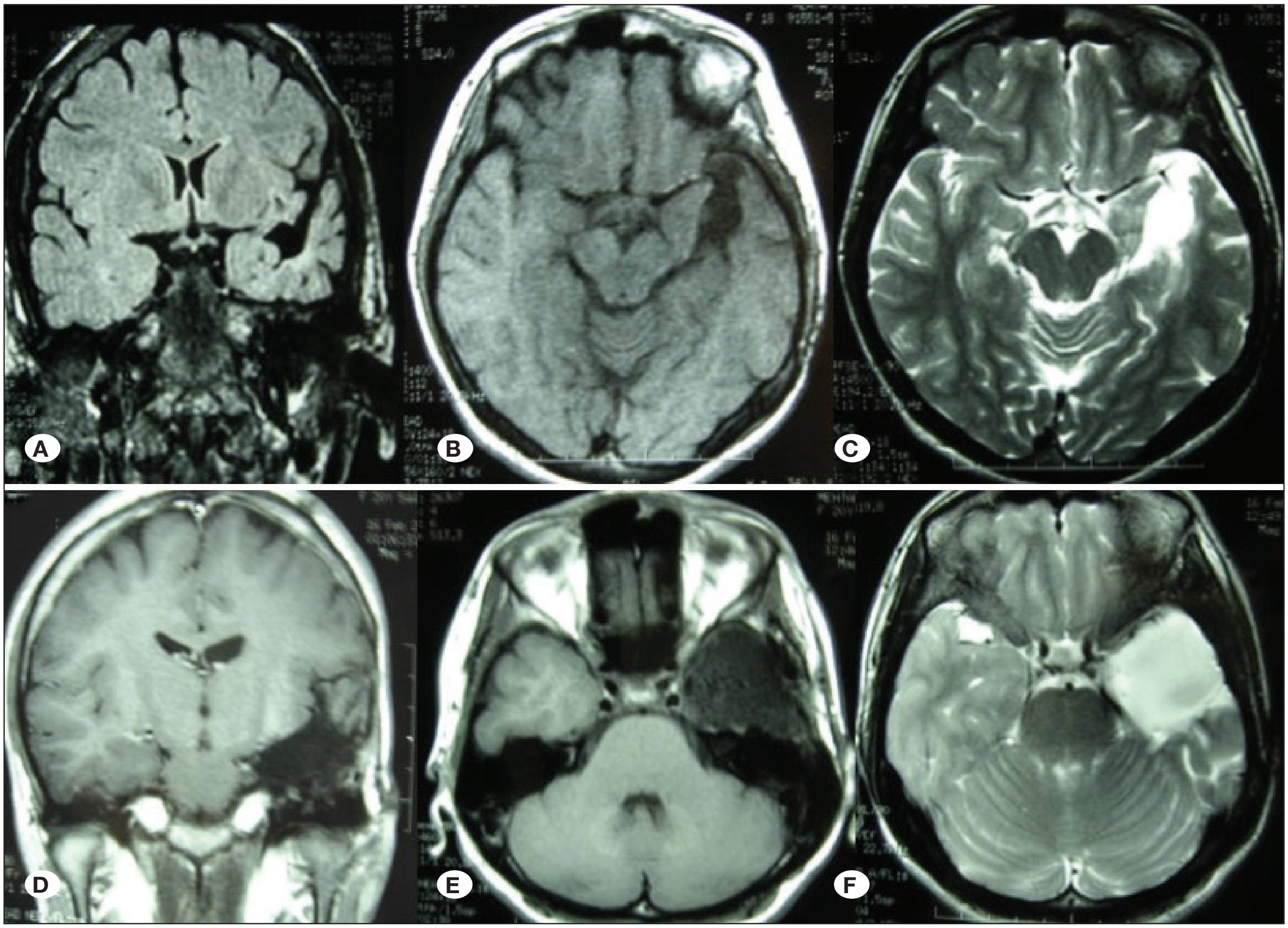

Figure 3: A-C) Preoperative brain magnetic resonance imaging (MRI) sections (**A:** T1W coronal, **B:** T1W axial, **C:** T2W axial) of patient #3; **D-F)** Postoperative MRI sections (**D:** T1W coronal, **E:** T1W axial, **F:** T2W axial) of patient #3.

three FIASs (two with right temporal and one with left temporal onset) were recorded. Remnant tissue was identified in the right temporal region on brain MRI (Figure 4A). After discussing all the risks with the patient, including the possibility of not achieving seizure freedom after an additional surgery, and with the patient's consent, the third surgery was performed. Right ATL, including the resection of the residual tissue in the right mesial temporal region, was performed (Figure 4B). The histopathological findings indicated hippocampal sclerosis. In the postoperative follow-up, the patient has been seizure-free for 21 years.

Patient #5

The fifth case is that of a 49-year-old female with a 22-year history of FIAS. She was diagnosed with right MTLE because of an extensive mass lesion involving the mesial temporal structures seen on MRI (Figure 5A). Therefore, the patient underwent surgery due to intractable seizures at 33 years of age at another hospital. However, in the postoperative period, the patient continued to have frequent seizures, which were semiologically identical to the preoperative seizures. The mass lesion similar to the one seen in the previous MRI was detected in the mesial temporal region (Figure 5A). The patient underwent right ATL with resection of the neoplastic tissue (Figure 5B). The specimen was identified as a low-grade mixed glioneuronal tumor. In the postoperative follow-up, the patient has been seizure-free for 10 years.

Patient #6

The last patient was a 59-year-old male with a history of left MTLE for more than 40 years. He was diagnosed with medically refractory MTLE and evaluated for surgical treatment. Brain MRI findings supported left mesial temporal sclerosis. The interictal and ictal EEG findings also pointed to the left mesial temporal region. Therefore, the patient underwent ATL at the age of 39 years. Six months after the surgery, the patient had his typical seizure once. No change was made to the medical treatment. However, 30 months after the surgery, he started to have recurrent seizures. The frequency of the seizures increased over time, despite adjustments to drug treatments. The seizures were the same as before the first surgery, including the aura. The patient asked for a second surgical treatment if possible. The interictal and ictal EEG findings pointed to the left temporal region. The neuropsychological

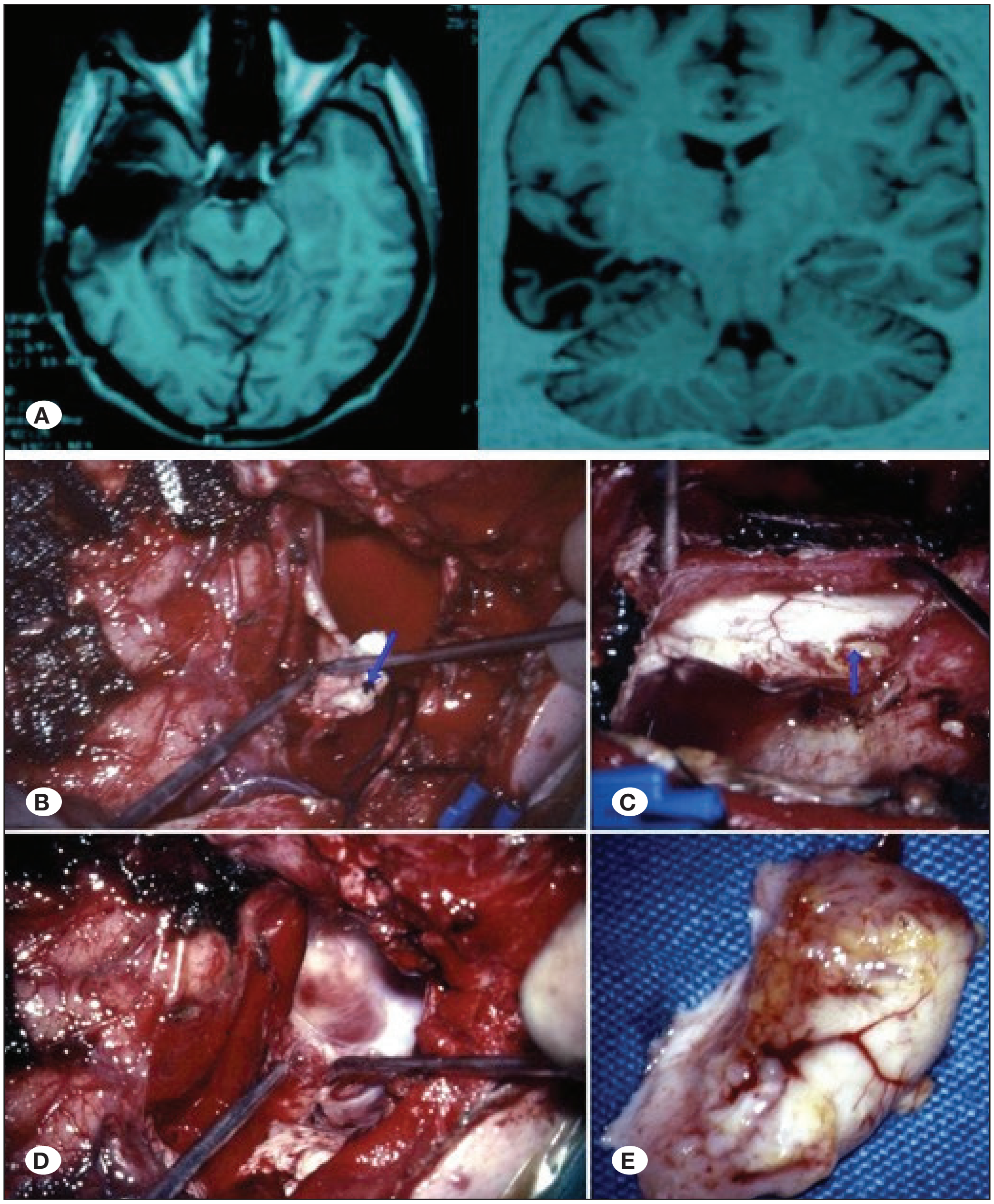

Figure 4: A) Preoperative brain magnetic resonance imaging (MRI) sections (left: T1W axial, right: double inversion recovery coronal) of patient #4; **B-E)** Intraoperative surgical view and remnant tissue (blue arrow) in mesial temporal region **(B, C)**, surgical view of mesial temporal region after resection **(D)**, and hippocampal remnant **(E)**.

tests revealed a mild verbal memory deficit. Remnant tissues were identified in the left temporal region on MRI (Figure 6). The patient underwent a second surgery involving resection of residual structures 4 years ago. He has been seizure-free ever since the second surgery, and the neuropsychological assessment performed at the first-year follow-up showed no changes compared to the preoperative evaluation.

■ DISCUSSION

The first randomized controlled trial of surgical treatment for epilepsy in 2001 showed the superiority of surgical treatment over optimal medical treatment in patients with refractory TLE (21). However, 20%–30% of medically refractory TLE patients who undergo surgical treatment might continue to have seizures. There may be multiple factors contributing to surgical failure. Najm et al. pointed to the possible relationship between the timing of seizure recurrence and the cause of surgical failure (16). The authors emphasized the importance of distinction between "early" and "late" failures. Various studies, have shown that there is an initial period in which seizure recurrence is common, and the relapse rate is 2%–5% per year for 5 years after TLE surgery (15,16). Therefore, 6–12 postop-

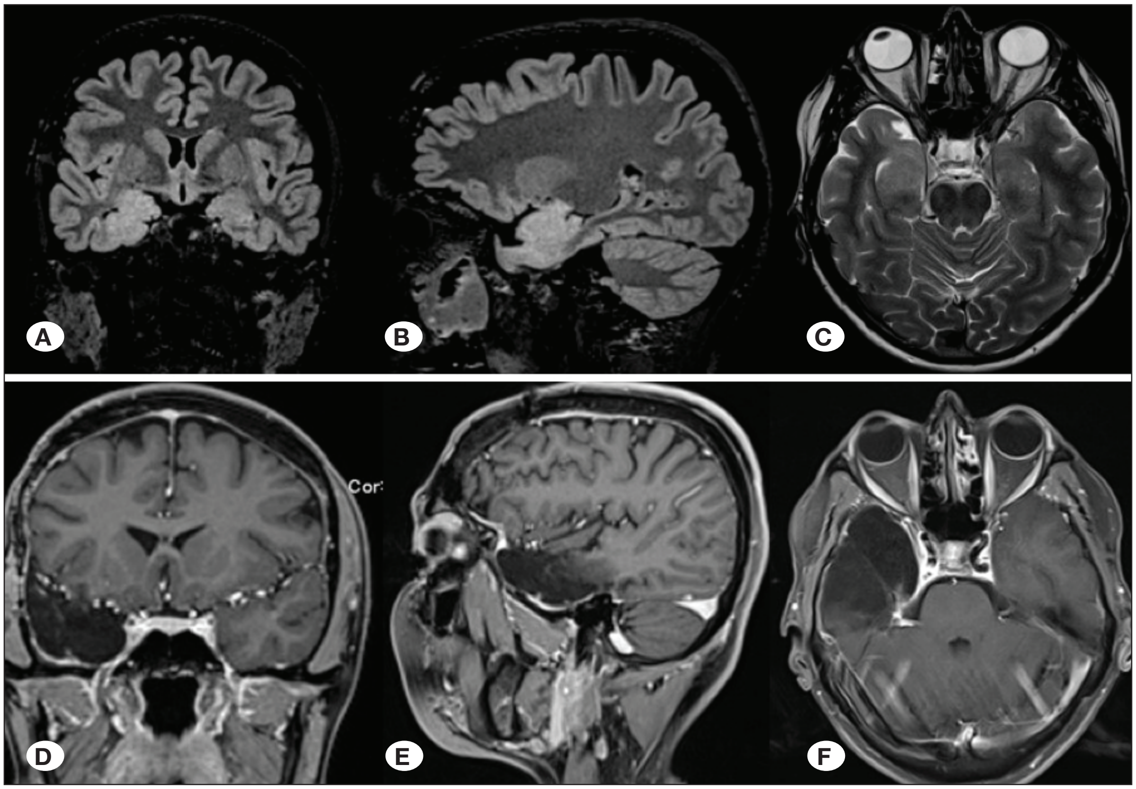

Figure 5: A-C) Preoperative brain magnetic resonance imaging (MRI) sections (**A:** double inversion recovery coronal, **B:** double inversion recovery sagittal, **C:** T2W axial) of patient #5; **D-F)** Postoperative T1-weighted contrast-enhanced MRIs (**D:** coronal, **E:** sagittal, **F:** axial) of patient #5.

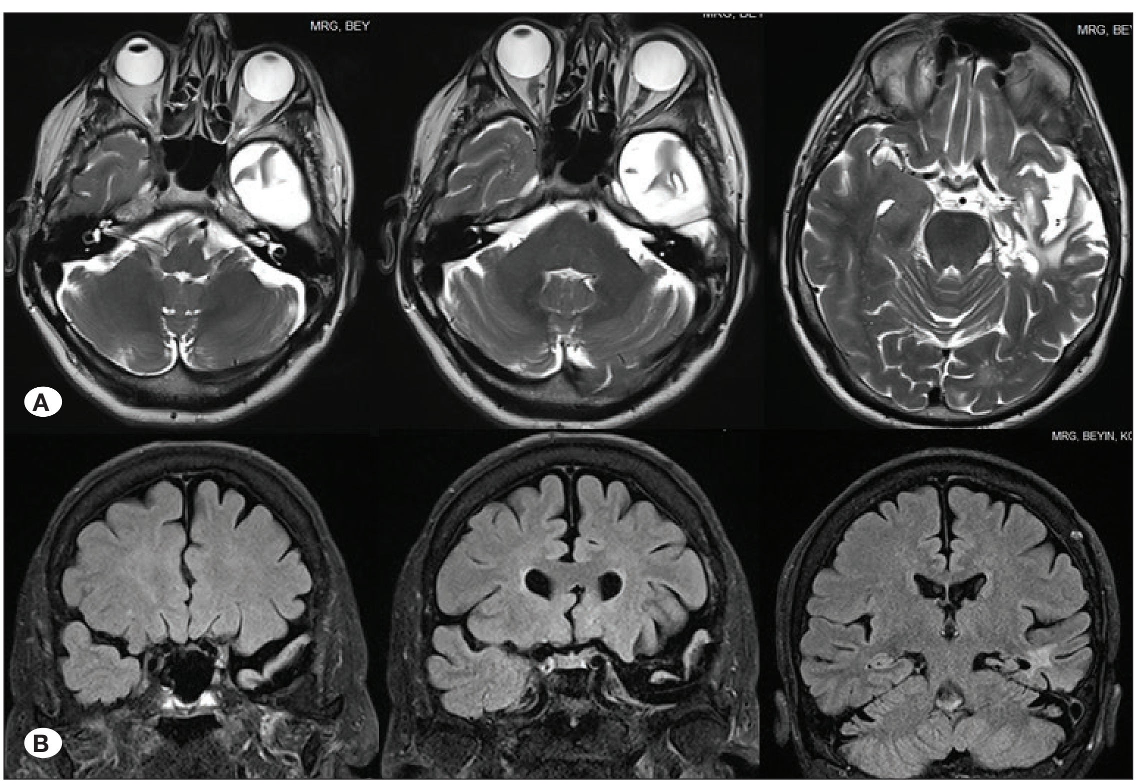

Figure 6: A) Preoperative axial T2-weighted magnetic resonance imaging (MRI) sections of patient #6; **B)** Preoperative T1-weighted coronal MRI sections of patient #6.

erative months are suggested as the cutoff for the distinction between early and late seizure recurrence. For late recurrence, the semiology of recurrent seizures is likely to be different from that of previous seizures, suggesting “new” epilepsy, and they are easier to control with ASDs and have a location contiguous to the resection bed (13,16). The existing clinical and animal data point to “de novo” epileptogenesis as the potential mechanism of late recurrence (16).

Early recurrent seizures are more similar to previous seizures, and are unfortunately more likely to be resistant to medical treatment. The location of recurrence may be distant or contiguous to the resection bed. Thus, the proposed mechanism for early recurrence is mainly incomplete resection, which may be caused by mislocation of the epileptogenic area, multiple epileptogenic lesions, and overlap of the functional cortex with the epileptic focus (16). When examined specifically for TLE surgery, the causes of recurrence include insufficient resection of mesial structures, insufficient resection of the temporal neocortex, dual pathology (coexistence of mesial temporal sclerosis and a neocortical lesion), relapse at the contralateral mesial temporal lobe, and extratemporal or temporal plus epilepsy (10,11,15,16).

In this study, all patients, except one (patient #6), had “early” seizure recurrence within the first 6 months postoperatively.

The recurrent seizures were at least as frequent as those in the preoperative period in our patients and could not be controlled with medical treatment. Patient #6 had a single seizure at 6 months after the first surgery and was seizure-free for about 2 years; however, medically intractable seizures subsequently occurred, and we may need to question the timing of recurrence. The patient’s recurrent seizures were identical to the seizures prior to the initial surgery, a finding consistent with all of our patients. Additionally, brain MRI showed remnant tissues in the mesial temporal region, and the interictal and ictal EEG findings were concordant in all our reoperated patients. Therefore, we believe that the reason for surgical failure in our patients was insufficient resection. Indeed, the most common cause of surgical failure in TLE was thought to be insufficient resection (9). Although dual pathology, underlying pathology, and extratemporal epileptogenic zones have recently gained importance among the causes of surgical failure in TLE, inadequate resection is still one of the major causes (11). A recent study analyzed the outcomes of patients who had undergone a second resection surgery for intractable epilepsy (10). Most of the patients (77%) had TLE, and the most common cause of failure was incomplete resection (59%). Freedom from seizures was achieved in 70% of the reoperated patients. One of the most striking results of this study was the neuropsychological outcome after the second surgery. Repeated losses in the same cognitive domain were rare, and if they occurred, improvement was noted with time, likely as a consequence of the successful seizure outcome. Nevertheless, the risk of permanent postoperative neurological deficit should be considered when consulting for reoperation.

We included 240 patients who underwent ATL for medically refractory MTLE at our institution. Of these patients, 12 (5%) had undergone surgery previously on the same side at least once for the same indication. We presented six of the 12 reoperated patients whose data regarding the seizure outcome was available. In all of our patients, the reason for seizure recurrence was insufficient resection, and further resection provided a good seizure outcome. In our observation, patients experiencing frequent seizures tend to accept the risk of a second or even third resection surgery. The age of the patient may not make a difference in this regard. Our oldest patient was 59 years, and this patient requested a second surgery to treat his frequent seizures. Another noteworthy point is the long duration before patients are evaluated for a second surgery after a failed surgical treatment. After seizure recurrence, our patients continued to experience frequent seizures for up to 20 years. The literature highlights the delay in referring patients with medically refractory epilepsy to epilepsy centers for evaluation regarding surgical treatment. Nevertheless, the same situation appears also to apply to patients who experience surgical failure.

In our opinion, the favorable outcome in our patient series is due to the surgical technique and extensive resection adopted (6). The main reason for surgical failure was the remnant tissue specifically in the mesial temporal region in our patients. The anatomy of the mesial temporal region is inherently complex, and neurosurgeons will need to face a more complex anatomy in previously operated patients. Microanatomical knowledge of the region and the surgical technique may determine the clinical outcome (8). Surgical techniques may vary across institutions; for example, in patient #2, stereotactic technology was utilized. We explained the surgical technique, which we apply in detail, in a previous publication, which can be broadly summarized as follows (6):

1. Anterior temporal pole resection is performed while leaving the residual tissue of the superior temporal gyrus medially.
2. Subpial removal of the superior temporal gyrus remnant is performed, and it is used as a guide to reach the inferolateral part of the circular sulcus of the insula.
3. Incision of the circular sulcus is performed just lateral to the M2 segment of the middle cerebral artery and the circular sulcus vein. This incision is extended anteriorly to complete the cutting of the temporal stem and to enter the temporal horn of the lateral ventricle. Moreover, the uncus is removed subpially and posteriorly to gain access to the collateral trigone in order to remove the hippocampal tail.
4. The choroid plexus is reflected upward, and the tenia fimbriae are opened in order to enter the ambient cistern.
5. The uncal sulcus is opened anteriorly, and the hippocampal sulcus is opened posteriorly. The hippocampal feeding arteries and drainage veins are coagulated within these sulci while staying away from the parent vessels.
6. The hippocampal head and body, anterior part of the hippocampal tail, and subiculum remnant are removed.
7. The amygdala is a nuclear complex composed of six different nuclei (lateral, basal, accessory basal, cortical, medial, and central nuclei), and total resection is not possible.

Its medial components are not included in the resection as they are located inferior to the basal ganglia.

The limitations of our study include its single-center and retrospective nature, as well as the small sample size. In addition, the study has the possibility of bias owing to the single center, and the same surgical procedure.

CONCLUSION

Surgical failure remains common among patients with MTLE, with inadequate resection often being the primary cause. However, failure after the initial surgery does not necessarily mark the end of the road for these patients. The opportunity for a second surgical treatment should not be delayed. When given a second chance, many patients may choose to take the risk of reoperation rather than continue living with frequent seizures. This opportunity for seizure freedom can be realized through the expertise and awareness of neurologists and neurosurgeons who manage epilepsy patients.

Declarations

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Availability of data and materials: The datasets generated and/or analyzed during the current study are available from the corresponding author by reasonable request.

Disclosure: The authors declare no competing interests.

AUTHORSHIP CONTRIBUTION

Study conception and design: SS, AE
Data collection: SE, SS, MZ
Analysis and interpretation of results: SE, SS, MZ, AE
Draft manuscript preparation: SE, SS
Critical revision of the article: SE, SS, AE
Other (study supervision, fundings, materials, etc...): SE, AE
All authors (SE, SS, MZ, AE) reviewed the results and approved the final version of the manuscript.

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