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Original Article

Are low-grade gliomas of mesial temporal area alone?

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ABSTRACT

Background: Temporal neocortex which appears normal on magnetic resonance imaging (MRI) may have pathological tissues in low-grade gliomas (LGG) of pure mesial temporal area. Resection of the cortex may be required together with mesial temporal glioma for satisfactory seizure and oncological outcome. The aim of this study was to explore the presence of any pathological tissue on the temporal cortex that appeared normal on preoperative MRI in patients with pure mesial temporal LGGs.

Methods: This prospective study included 10 patients who underwent surgical resection of temporal lobe for LGG of mesial temporal area. The temporal neocortex with normal appearance on MRI and mesial temporal area were resected separately, and histopathological diagnosis was performed.

Results: LGGs of the mesial temporal area were diagnosed with glioneuronal tumors in 7 (70%) and low-grade astrocytoma in 2 (20%) patients. Regarding the temporal cortex, gliosis and focal cortical dysplasia were found in 7 (70%) and 2 (20%) patients. In one patient temporal cortex did not contain any pathological tissue. All were seizure-free and no tumor recurrence was noted at the last follow-up.

Conclusion: Mesial temporal LGGs are not alone and a high proportion of temporal neocortex appeared normal on preoperative MRI, may contain dual pathology. Thus, anterior temporal resection should be performed to have satisfactory seizure and oncological outcomes.

Keywords: Epilepsy, Glioneuronal tumor, Low-grade glioma, Seizure, Temporal lobe

INTRODUCTION

Temporal lobe, particularly mesial temporal area, is the most epileptogenic lobe in the brain and any lesion in the temporal lobe may cause seizure because mainly of lower seizure threshold and if uncontrolled by medication, diagnosis of epilepsy becomes inevitable. The most common pathological entity causing epilepsy is mesial temporal lobe epilepsy (MTLE) caused by hippocampal sclerosis (HS) (MTLE-HS).[4] Another common pathological entity causing medically-intractable seizure is low-grade glioma, which especially prefers to locate temporal lobe, particularly mesial temporal area.[4,8,14] The most common low-grade tumors in the temporal lobe are glioneuronal tumors, mainly represented by gangliogliomas (GG) and dysembryoplastic tumors (DNET), and are generally cause of focal epilepsies in children and young adults.[1,3] The representative symptom of low-grade tumors, in general, is seizure and appears to be associated with an increased incidence of dual pathology, especially focal cortical dysplasia or other neuronal migration abnormalities.[12,17]

Presence of dual pathology in the temporal cortex that invisible on preoperative magnetic resonance imaging (MRI) in patients with pure mesial temporal low-grade tumors may put patients in risk of seizure continuation and tumor recurrence after resective surgery. Thus, any surgeon dealing with epilepsy has to consider both oncological and seizure outcome in patients with mesial temporal area low-grade tumors in planning surgical strategy. The surgical approach to mesial temporal area in case of a low-grade tumor is still challenging, and the data are very limited. Some investigators consider lesionectomy or resection of the tumor alone sufficient for seizure control[5,7,22] but others advocate additional resection of epileptogenic zone around the tumor or standard anterior temporal resection to optimize seizure control.[12,15,17,18] Depending on our own experience from epilepsy surgery and the current literature, we changed our surgical strategy to standard temporal resection as in temporal lobe epilepsy (TLE)-HS in patients with pure mesial temporal tumors, especially mesial temporal low-grade gliomas (LGG) during the past 10 years.[17] This shift mainly depends on pathological tissues found in temporal cortex of patients who had undergone standard temporal resection in patients with MTLE-HS.[2,16] Furthermore, in some reports that dual pathology was found in temporal cortex which appeared normal on preoperative MRI in patients with mesial temporal LGG after surgery.[16] They underlined that continuation of seizure after lesionectomy alone in patients with mesial temporal lobe LGG after surgery may be due to the existence of cortical pathology and suggested tailored resection with the guidance of electrophysiological studies.[2,12,16,17]

With this respect, we conducted a prospective study of patients with pure mesial temporal LGG treated by surgery: all underwent standard anterior temporal resection to see whether temporal cortex which was normal on preoperative MRI has any pathological tissue in addition to mesial temporal LGG.

PATIENTS AND METHODS

This study consisted of 10 patients who had undergone surgical removal of pure mesial temporal LGG associated with epilepsy at the Division of Neurosurgery, Cerrahpasa Medical Faculty, Istanbul University, Cerrahpasa, and Istanbul, Turkey, during the period between February 2016 and April 2019. This study was approved by the Local Ethics Committee. Our strict inclusion criteria were as follows: the tumors which had (1) the features that suggestive of LGG on preoperative MRI, (2) should be in pure mesial temporal area (should be located medial to the rhinal and collateral sulci or at the level of uncus-entorhinal area-amygdala-hippocampal/parahippocampal complex), and (3) no previous surgery. Since pure mesial temporal LGGs are uncommon and we had strict criteria for the study, we were able to include only 10 patients.

All patients were hospitalized for resective surgery, and medical history, symptoms and/or signs were noted. All had head MRI with epilepsy protocol and the images reviewed and noted carefully. With respect to seizure, seizure semiology and routine scalp electroencephalography (EEG), to confirm diagnosis of epilepsy topographically related to the side of the lesion, were obtained and evaluated by an epileptologist. After completion of preoperative workup and obtained permission from the patients, anterior temporal resection including temporal cortex and mesial temporal area was performed. On the dominant side, temporal cortex was removed 3.5–4 cm from the temporal pole and on the non-dominant side it was 4.5–5 cm, which we routinely are performing in patients with MTLE-HS. Within 24 h of surgery, all patients had MRI to evaluate any tumor tissue left. During the surgery, two tissues were sent separately for histopathological diagnosis: temporal cortex and mesial temporal area (tumor).

After discharge from the hospital, clinical, seizure, and radiological outcomes were followed up with regular intervals, generally every 3 months within a year, then every 6 months. Telephone interviews with patients and/or their next of kin were also used. Seizure outcome was assessed by seizure outcome scale of Engel.[10]

Statistical analysis

Results are given as mean ± standard deviations for continuous variables. Chi-square test was used inappropriate comparisons. All statistical analyses were performed with the SPSS computer software, version 20.0 for Windows (SPSS, Chicago, USA). Values of ($P < 0.05$) were considered as statistically significant.

RESULTS

Clinical and histopathological diagnosis of the 10 patients is summarized in Tables 1 and 2. The half (50%) was female and the mean age was 33.4 ± 12.6 years. All were presented with the complex-partial seizure of temporal origin and mean duration of seizure was 29.2 ± 34.9 months. Mean seizure frequency at the time of admission was 6.8 ± 5.5/month which ranged from 1 to 16/month. The neurological examination before surgery showed nothing abnormal. All had scalp EEG to lateralize seizure and findings from scalp EEG confirmed the lateralization of the tumor on the temporal lobe. All patients had head MRI with contrast agent and showed the features of LGG on the pure mesial temporal area. The tumor was localized on the right and left temporal lobes in 4 and 6, respectively. Involvement of uncus and amygdala only (anterior location) was noted in three patients, and the

Table 1: Summary of clinical characteristics of the patients.

No	Age	Sex	*Symptom	†Duration	Side	Site	‡Follow-up
1	41	F	Seizure	10 years	Left	U, A	36
2	18	M	Seizure	1 year	Left	U, A	36
3	33	F	Seizure	4 years	Left	U, A, H, PH	36
4	23	M	Seizure	2 years	Right	U, A, H, PH	36
5	56	M	Seizure	6 months	Left	U, A, H, PH	4
6	44	M	Seizure	10 months	Right	U, A, H, PH	12
7	25	F	Seizure	3 years	Right	U, A, H, PH	36
8	20	F	Seizure	2 years	Left	U, A, H, PH	12
9	29	F	Seizure	6 months	Right	U, A	12
10	45	M	Seizure	6 months	Left	U, A, H, PH	36

A: Amygdala; H: Hippocampus; U: Uncus; PH: Parahippocampus. †Duration: Seizure duration; ‡Follow-up: Months; *Symptom: Presenting symptom

Table 2: A summary of the surgical results of the patients.

No	*Seizure frequency		†Antiepileptic drug		Pathological diagnosis		Head MRI
	Preoperative	Postoperative	Preoperative	Postoperative	Mesial	Cortex	Recurrence
1	12	None	3	1	‡DNET	FCD-Ib	None
2	4	None	1	None	DNET	Gliosis	None
3	16	None	2	None	DNET	Gliosis	None
4	12	None	3	None	GG	FCD-IIIb	None
5	1	None	1	1	LGA	Gliosis	None
6	1	None	1	None	GG	Gliosis	None
7	2	None	1	None	DNET	Gliosis	None
8	12	None	1	1	LGA	Gliosis	None
9	4	None	1	1	DNET	Gliosis	None
10	4	None	1	None	LGA	Normal	None

DNET: Dysembryoplastic tumor; GG: Ganglioglioma; LGA: Low-grade astrocytoma; MRI: Magnetic resonance imaging; Preop: Preoperative; Postop: Postoperative. †Number of antiepileptic drug; *Seizure frequency/month; ‡Histopathological diagnosis form the hippocampus was hippocampal sclerosis ILAE type-I

whole mesial temporal area including amygdala and uncus was involved in the rest. All were using anti-epileptic drug (AED) which ranged from 1 to 3 with a mean number of AED was 3 ± 1.5. The mean follow-up was 25.6 ± 13.6 months. Neuropsychological tests were also completed, but the results were not analyzed in this study because we consider both oncological and seizure outcomes in mesial temporal located LGG and furthermore we want to draw attention to the temporal cortex which appears normal on preoperative MRI in patients with pure mesial temporal area.

Histopathological diagnosis regarding mesial temporal area showed DNET in 5 (50%), LGG (low-grade astrocytoma grade-II) in 3 (30%), and GG in 2 (20%) patients. On the other hand, temporal cortices, which appeared normal on preoperative MRI showed gliosis in 7 (70%) and FCD in 2 (20%) patients [Figure 1]. In one patient with LGG on the mesial temporal area, the temporal cortex was normal. In one patient (patient no 1) with uncus and amygdala involvement only, hippocampal and parahippocampal complex showed HS (ILAE type-I) [Figure 2].

At the past follow-up examinations, all patients were seizure-free even without aura (Engel Ia) and six (60%) were drug free. Remaining four patients were on monotherapy. The difference regarding the number of AED before and after surgery was significant (P = 0.04). In three patients who were still on monotherapy, we have to complete two seizure-free years according to the law before we stop AED. In one (patient no 1), we could not stop AED although the patient was seizure-free after 36 months because of the fear of patients to have seizure again. The last head MRI showed no residue and/or recurrence of the tumor because mainly of supra-total resection.

No death was noted during surgery or in the postoperative period. Only one patient had transitory third nerve palsy. Visual field defects are expected complications after temporal resections so that we do not routinely perform ophthalmological examinations after surgery.

DISCUSSION

The answer to the title of this paper is "yes." Any neurosurgeon or epileptologist dealing with epilepsy surgery or treatment of

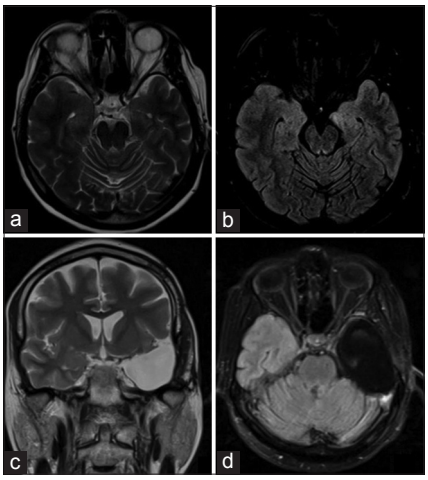

Figure 1: A 23-year-old male who presented with complex-partial seizure had right-sided mesial temporal lesion on axial T2-weighted (a) and fluid-attenuated inversion recovery (FLAIR) magnetic resonance images (b). The temporal cortex appeared normal. The radiological examination at the last follow-up showed no tumor recurrence on coronal T2-weighted (c) and axial FLAIR images (d) and the patient was seizure-free.

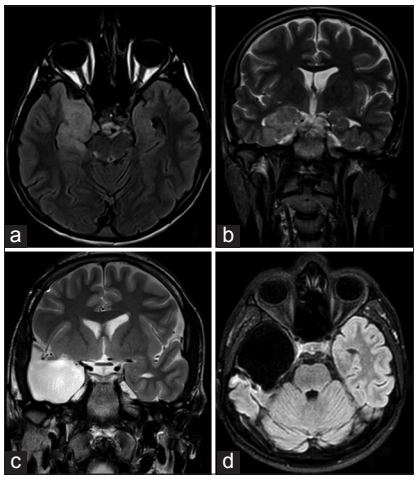

Figure 2: A 41-year-old female with dysembryoplastic tumor on the left mesial temporal area. The tumor had involved uncus and amygdala on axial fluid-attenuated inversion recovery (FLAIR) image (a) and coronal T2-weighted images (b). Temporal neocortex and the hippocampal + parahippocampal complex appeared normal. Radiological examinations at the last follow-up showed no tumor recurrence on coronal T2-weighted (c) and axial FLAIR (d) images and the patient was seizure-free.

epilepsy knows very well the coexistence of dual pathology in the temporal neocortex in patients with MTLE-HS and even in patients with LGG in the pure mesial temporal area. The most common symptom in LGG, especially in temporal lobe is drug-resistant epilepsy, and surgery has been proven to be the most effective treatment modality in both terms of seizure and oncological outcome.[7,12,17] Pure mesial temporal LGG is uncommon and previously published series are composed generally of heterogeneous group of patients.[7,15,19,20,22] Among LGGs of temporal lobe, particularly mesial temporal area, glioneuronal tumors, namely, DNET and GGs are more common.[12,14,17] As in this paper with limited number of patients, glioneuronal tumors are more common and only two patients were diagnosed with low-grade astrocytoma. Glioneuronal tumors are epileptogenic compared with other low-grade astrocytoma because mainly of having both glial and neuronal components.

It has been shown that temporal neocortex even appeared normal on preoperative MRI may show pathological tissues.[16] Experience from TLE surgery has proven dual pathology, especially FCD, on the temporal neocortex in patients with pure HS[2,17] and it has been claimed that continuation of seizure after selective resection of mesial temporal area may be due to the presence of dual pathology on the unresected temporal neocortex. With the same sense, dual pathology has been found in the temporal neocortex in patients who had undergone resection of glioneuronal tumors from the mesial temporal area[12] suggesting that epileptogenic zone in these kinds of tumors is more extensive than appeared on preoperative MRI.

Temporal lobe, especially hippocampal and parahippocampal complex, is one of the most important parts of limbic and paralimbic systems and has important neuropsychological functions. Anatomical proximity of vital neurovascular structures to the temporal lobe such as common carotid, middle cerebral, and anterior choroidal arteries, and midbrain make surgical resection challenging so that several surgical approaches have been proposed.[13,23] Unfortunately, the best surgical strategy to the temporal lobe, especially to the mesial temporal area in patients with MTLE-HS or tumor-related epilepsy remains controversial and is still one of the contemporary issues in epilepsy surgery although we have now contemporary tools using in operating room such as neuronavigation. The main teaching from our masters all over the world is the "maximum resection with minimal neurological or neuropsychological deficits." As a neurosurgeon, we are always following this teaching and trying to do our best to have optimum results.

Our patient group showed that pure mesial temporal LGGs are not alone, and resection of temporal neocortex even appears normal on preoperative MRI should be resected together with mesial temporal area. Seven patients showed gliosis, two showed FCD and only one patient showed normal tissue on the temporal neocortex. Furthermore, in one patient with anteriorly located tumor (uncus and amygdala) without HS on the preoperative MRI, the resected hippocampal and parahippocampal complex

were diagnosed with HS. Gliosis is a pathological tissue and also now accepted as a different entity in TLE and the term "hippocampal gliosis only" has been introduced into the diagnosis of TLE. These findings suggest that anterior temporal resection may eliminate epileptogenic tissues since results from the tailored resections in patients with mesial temporal LGGs showed the presence of architectural or cytoarchitectural abnormalities mainly in the temporal pole and anterior lateral neocortex.[21] Furthermore, the importance of temporal pole in patients with MTLE-HS has been demonstrated in TLE evaluated by invasive depth electrode studies.[6]

The authors of the current paper do not aim to compare seizure and oncological and even neuropsychological results from anterior temporal resection with selective resections. Rather the aim of this paper is to show whether temporal neocortex which appears normal on the preoperative MRI has pathological tissues in patients with pure mesial temporal LGG since histopathological studies proved the dual pathology on the temporal neocortex in patients with MTLE-HS[2,16] and LGG of mesial temporal area.[12] All patients included here were seizure-free, and no recurrence was noted because of supra-total resection (anterior temporal resection).

We do not have a chance to compare anterior temporal resection with lesionectomy alone in this paper; however, we have a chance to discuss previously published studies. We have to underline that favorable seizure and oncological outcomes have been reported after lesionectomy alone,[7,9,11,22] tailored resection, and temporal lobectomies.[12,15,17] The common notion is that lesionectomy alone is inadequate to obtain optimal seizure control in mesial temporal LGGs and resection of epileptogenic zone (or tailored temporal resection) under the guidance of neurophysiological and neuropsychological tests appears to offer the best results with respect to seizure control. We suggest that not only seizure control but also tumor control is important for the patients.

There is a lack of prospective randomized comparative studies with respect to seizure or oncological outcome in patients who had lesionectomy alone or tailored resection and/or temporal lobectomy in LGG of mesial temporal area. Our experience largely depends on very limited number of retrospective comparative clinical studies. A retrospective series of 30 patients with temporal mass lesions by Jooma *et al*.[15] was divided into two groups: first group was treated by lesionectomy only (16 patients) and second groups were treated by temporal lobectomy (14 patients). Seven and nine tumors were located in the mesial temporal area in the first and second group, respectively. The authors reported that 19% in the first and 93% in the second groups were seizure free at the last follow-up. In five patients of the first group, lesionectomy failed to control seizures and they had temporal lobectomy as a second procedure and become seizure-free. However, this study included heterogeneous group of patients. Giulioni *et al*.[12] reported 28 patients with mesial temporal glioneuronal tumors treated by lesionectomy alone or selective lesionectomy (14 patients) and tailored temporal or anterior temporal resection (14 patients). They reported that gross-total removal of the tumor was achieved in 11 patients (78.6%) and six patients (42.8%) were seizure-free (Engel I) and 8 (57.1%) had rare disabling seizure, almost seizure-free (Engel II) in lesionectomy only group. On the other hand, gross-total removal of the tumor was achieved in all patients, and 13 patients (93%) were seizure-free (Engel I), and 1 (7.1%) had rare seizure (Engel II) in anterior temporal resection group. More importantly, the authors reported that non-neoplastic temporopolar cortex and hippocampal specimens in a total of 6 cases (42. 8%) of those who had anterior temporal resection showed FCD, HS, or both associated with the neoplastic lesions.

Our study does not compare seizure and oncological outcomes of different surgical techniques applied in patients with mesial temporal LGGs but rather simply provided that mesial temporal LGGs are not alone and anterior temporal resection seems to be feasible to have a good seizure and oncological outcome. All patients in the current study were seizure-free and no tumor recurrence was noted. The majority of temporal neocortex or non-neoplastic cortex showed several pathological entities including FCD and gliosis. Depending on our results with limited number of patients and experience from the limited number of retrospective comparative studies,[12,15] findings support the concept that epileptogenic zone is larger and can be extended to the extrahippocampal region or temporal neocortex in patients with mesial temporal LGGs and lesionectomy alone may be inadequate for optimal seizure control.

Limitations

The authors want to acknowledge the limitation of the study. The first limitation in this study is that we were able to include less number of patients with LGG of mesial temporal area. However, given that the current literature does have a very small number of patients with LGG of mesial temporal area, this limitation can be greeted with understanding. The second limitation is that our study had short-term follow-up and the last limitation is that the study is retrospective. Future studies should be prospective randomized and include larger cohort of patients with LGG of mesial temporal area to have optimal and common surgical strategy to the temporal lobe, especially to mesial temporal area.

CONCLUSION

Only one conclusion should be underlined depending on the current study. Mesial temporal LGGs, especially glioneuronal tumors, are not alone and anterior temporal resection including temporal neocortex and hippocampus even they appear normal on preoperative MRI, should be resected to have favorable seizure and tumor control.

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Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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