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Risk factors for preoperative and postoperative late seizure in supratentorial Meningiomas. A retrospective analysis of 63 patients

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ABSTRACT

Introduction. Seizure following meningioma surgery is common and management may be challenging. Identifying risk factors may help physicians to initiate optimal medical management. The aim of this study is to report seizure outcome and risk factors for perioperative seizure.

Materials and Methods. Sixty-three adult patients who underwent supratentorial meningioma resection were included, and perioperative data and long-term follow-up were provided in this retrospective study. Binary logistic regression analysis was used to identify the risk factors for perioperative seizure and postoperative late seizure.

Results. The results showed that 20 (37.1 %) patients had preoperative seizure and 10 (50 %) patients were seizure free at the long-term follow-up. Absence of headache was associated with preoperative seizure (p=0.002) while presence of early seizure was significant predictor for postoperative late seizure (p=0.03). Although not significant, occurrence of surgical complications (p=0.08) and non-skull base location (p=0.06) tended toward being a significant risk factor for postoperative late seizure.

Conclusion. Presence of early seizures, surgical complications and locations out of skull base may direct postoperative anti-epileptic treatment to decrease seizure incidence which, indeed, increases quality of life for patients with meningioma.

INTRODUCTION

Meningioma is the most common form of benign intracranial neoplasms and surgery is the first-line treatment. Epileptic seizure, as the first symptom, is one of the most common manifestations of supratentorial meningiomas, occurring up to 60% (5, 14). Surgical resection results in complete cessation of seizure in the majority of patients, but new-onset seizures can develop following surgery in the patients who are seizure free preoperatively.

Leaving a proportion of patients with seizure even after total tumor removal significantly decreases quality of life and patients have to use

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anti-epileptic drugs (AED) for long-term, which also affects patients' life adversely (8). Predicting preoperative and postoperative risk factors for seizures in patients with meningioma have become the focus of recent studies and accumulating evidence showed that younger age, presence of preoperative peritumoral edema, and tumour location are the strongest predictors for either preoperative or postoperative seizure (3, 9, 10, 13). Prediction of risk factors is of utmost importance which guides physicians to decide whether or not AED should be started (1, 4, 12, 15, 16). More importantly, informing patients or next of their kin about seizure outcome makes the follow-up period easier for both patients and treating physicians.

In this paper, we aimed to share our experience related to preoperative and postoperative seizures in patients who underwent meningioma resection and to find out which patients are under risk of seizure after surgery.

Material and Methods

Patient selection

This retrospective study included the patients operated on supratentorial meningiomas between 2010 and 2017. Patients who had infratentorial meningioma, multiple meningioma, and previous intracranial meningioma surgery were excluded from the study. To provide a homogeneous population, patients who were younger than 18 were excluded from the study. The remaining 63 patients were enrolled in this study. The research was conducted in accordance with the principles of Helsinki Declaration.

Data retrieval

Perioperative clinical, radiological, and pathological data were retrieved from the patients' files. All patients were followed-up clinically and radiologically at regular intervals. Clinical, radiological, seizure and AED outcomes were noted.

Statistical analysis

Statistical analysis was performed by using SPSS, version 22.0 (IBM, Chicago, IL). Independent sample t test and chi-square test were used in appropriate comparisons. Binary logistic regression analysis was used for multivariate testing of factors associated with preoperative and postoperative seizures. The differences were accepted significant if p value was < 0.05.

Results

Demographic and clinical characteristics

45 (71.4%) females and 18 (28.6%) males were enrolled in the study with a mean age of 51.9±14.2 years (range: 20-76 years). Headache was found in 35 (55.6%) patients at admission and 20 patients (31.7%) suffered from preoperative seizure. Of the 20 patients with preoperative seizure, 10 had single (50%) and the other 10 had multiple seizures. The majority of seizure type was generalized tonic-clonic (n=12; 60%), followed by focal motor (n=5; 25%) and focal sensory (n=3; 15%) seizures. Neurological examination demonstrated that 22 patients (34.9%) had neurological deficit ranging from cranial nerve dysfunction to paresis. Before surgery, 24 patients (38.1%) were on AED monotherapy. Nineteen patients with preoperative seizure (19/20; 95 %) and 5 patients with no seizure (5/43; 11.6%) were on AED. The difference regarding use of AED between patients with and without preoperative seizure was significant (p=0.00001). Demographic features of the patients are presented in Table 1.

Table 1. Demographic and radiological characteristics. GTC: generalized tonic-clonic, R: right, L: left, M: male, F: female.

	Patient number	(%)
Sex (M/F)	18/45	28.6%/71.4%
Age	51.9±14.2 years	-
Preoperative seizure	20	31.7%
GTC	12	60%
Focal motor	5	25%
Focal sensory	3	15%
Preoperative AED therapy		
with seizure	19/20	95%
without seizure	5/43	11.6%
Tumour side (R/L/midline)	24/36/3	38/57.1/4.7
Tumour location		

Skull-base	15	23.8%
Non-skull base	48	76.2%

Radiological characteristics

All patients were evaluated by cranial magnetic resonance imaging (MRI). Peritumoral edema (PTE) was determined on T_2-weighted images. Anterior-posterior diameter was measured on post-contrast axial MR images. The location was divided into 2 groups: skull base and non-skull base. Non-skull base group included tumors located on convexity or parasagittal/falx region. MRI showed that 36 patients (57.1%) had tumor on the left side, followed by the right side (n=24; 38.1%) and midline (n=3; 4.8%). The difference with respect to the side of location was significant (p=0.00001). But side was not significant between the patients with and without preoperative seizure (p=0.41). Skull base and non-skull base location were noted in 15 (23.8%) and 48 (76.2%) patients respectively. The difference was significant (p=0.00001). However, the difference did not reach a significant level between patients with and without preoperative seizure related to skull base and non-skull base location (p=0.62). Convexity was significantly the most common location (30 patients; 47.6%) (p=0.00001). Second common location was the parasagittal/falx region (18; 28.6%). Six patients (9.5%) had anterior clinoid and 4 patients (6.3%) had sphenoid wing meningiomas. Two olfactory groove, 2 tuberculum sellae, and 1 petroclival meningioma were observed. Comparing patients with and without preoperative seizures, no significant difference was found regarding the site (p=0.60). PTE on preoperative MRI was present in 37 (58.7%) patients. The difference between presence or absence of PTE was insignificant in the whole group (p=0.16). Fifteen out of 20 patients (75%) with preoperative seizures and 22 of 43 patients (51.16%) without preoperative seizure had PTE on preoperative MRI and the difference was not significant (p=0.07). None of the 12 patients diagnosed with atypical meningioma showed PTE. The mean anterior-posterior (A-P) diameter was found to be 37.6 ± 14.4 mm (range: 10-72 mm). Twenty patients with and 38 patients without preoperative seizure had a mean A-P diameter of 40.8 ± 10.5 mm and 36.2 ± 15.7 mm, respectively. The difference was not significant (p=0.17).

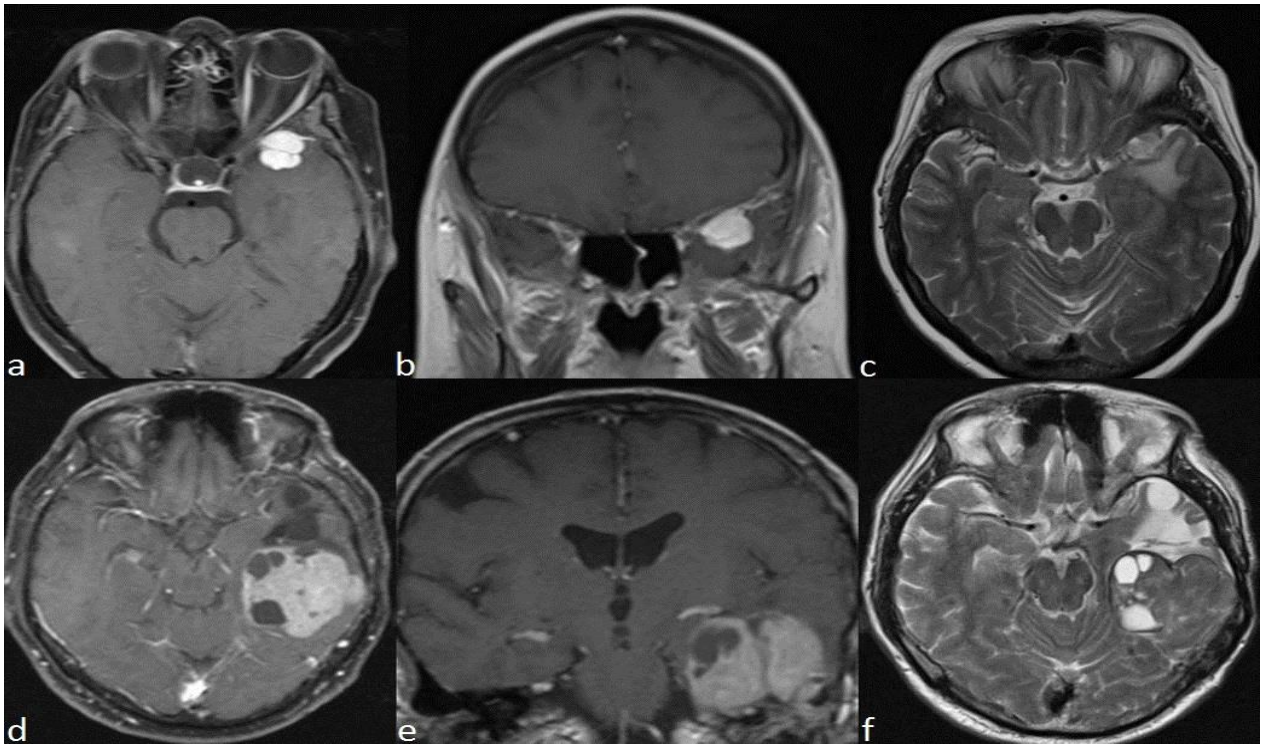

Figure 1. A left temporal Grade 1 secretory meningioma presenting with seizure shows homogeneous contrast enhancement (**a** and **b**) and PTE on T2 weighted (**c**) MR images. A Grade 1 fibrous meningioma which also shows contrast enhancement with cyst formation (**d** and **e**) and PTE on T2 weighted images (**f**) without preoperative epileptic seizure. PTE: peritumoral edema.

Surgical and histopathological characteristics

Informed consent form was obtained from all patients undergoing surgical resection. Extent of surgery was categorized as gross total resection (GTR) and subtotal resection (STR) depending on the findings on postoperative MRI. GTR was defined as absence of contrast enhancement on postoperative MRI. GTR was achieved in 54 (85.7%) patients and STR in 9 (14.3%) patients. Histopathological diagnosis was grade-I in 51 (81%) and grade-II (atypical) in 12 (16.9%) patients. GTR was achieved in all grade-I meningiomas, and all STRs were noted in the atypical group. Considering grade-I meningiomas, transitional type was the most common subtype (n=24; 38.1%).

Follow-up

The mean follow-up period was 46.87 ± 29.4 months (range: 12-96 months). No new neurological deficit was noted early after surgery. Nonetheless, 16 patients (25.4%) in the whole group continued to have neurological deficits. Of the 22 patients with preoperative neurological deficit, 6 patients recovered after surgery (27.2%). Postoperative seizures were divided into two groups: 1) Early seizure and 2) late seizure were defined as a seizure occurring within 7 days and after 7 days following surgery respectively. Five (7.9%) patients in the whole group showed early seizures and 10 (15.9%) exhibited late seizures. Two (4.65%) and 5 patients (11.62%) without seizure before surgery had early and late seizures respectively. Three patients who showed early seizure had late seizure at the last follow-up. Of the 10 patients with late seizure, 5 (50%) had single and the rest had multiple seizures. Focal motor, generalized tonic-clonic, and focal sensory seizures were seen in 5 (50%), 3 (30%), and 2 (20%) patients, respectively. Eight patients (8/10; 80%) with persistent seizure at the last follow-up had convexity meningiomas. Interestingly most of the patients with late seizure (8/10) had GTR. Although the number of patients with seizure decreased from 20 (31.7%) to 10 (15.9%) at the last follow-up, the difference was not significant (p=0.26). Overall, seizure free rate of patients with preoperative seizure was 50% at the last follow-up.

Five patients (7.9%) showed surgery-related complications. Two had hematoma within the resection cavity. Two other patients developed hydrocephalus which required ventriculo-peritoneal shunting. All patients were put on AED therapy after surgery. At the last follow-up, 10 patients (15.9%) with late seizure were still using AED monotherapy. Comparing the number of patients who were on AED before surgery (n=24; 38.1%) and at the last follow-up showed no significant difference although there was a trend to decrease in the number of patients using AED (p=0.48). The continuation of AED in these 10 patients depended on the clinical and electrophysiological findings.

Early MRI was obtained from all patients during their stay in the hospital. The first follow-up MRI was obtained at the 3rd month of surgery. Patients with atypical meningioma had MRI every 3 months. In contrast, it was performed in patients with grade-1 meningiomas at the 1st year, then every 2 years until 5 years after surgery. No patient showed new tumor formation or progression of residual tumor on the follow-up MRIs.

Predictors of preoperative seizure

In this study, 6 categorical risk factors were introduced in logistic regression analysis to find out predictors for preoperative seizure. The risk factors included *gender* (female/male), *edema* on MRI (present/absent), *headache* (present/absent), *neurological deficit* (present/absent), *location* (skull base/non-skull base), and *side* (right/left/midline). Binary logistic regression analysis (log likelihood=60.697; chi square=18.045; p=0.012) showed that among the 6 risk factors, only absence of *headache* (OR 8.295, 95% CI 2.105-32.68, p=0.002)) was found to be a significant and strong predictor for preoperative seizure.

Predictors of postoperative late seizure

For identification of risk factors for late seizure, 10 categorical variables were analyzed. The factors included *gender* (female/male), *preoperative seizure* (yes/no), use of *preoperative AED* (yes/no), *postoperative early seizure* (yes/no), *side* (right/left/midline), *edema* on preoperative MRI (present/absent), *location* (skull base/non-skull base), *extent of resection* (gross total/subtotal), *surgical complication* (present/absent), *pathological grade* (grade-I/grade-II). Binary logistic regression analysis (log likelihood = 36.571; chi square = 18.561; p=0.06) showed that among the variables above, presence of postoperative *early seizure* (OR 0.045; 95% CI 0.009-0.864; p=0.03) was a risk factor for postoperative late seizures. Although regression analysis did not show non-skull base location (p=0.06) and occurrence of

surgical complication (p=0.08) to be a significant risk factor postoperative late seizure, they tended toward.

Discussion

Seizure is a common symptom adversely affecting the quality of life after intracranial tumor surgery (8). In case of meningiomas, seizure even after total removal of the tumor may require collaboration of epileptologists to figure out the epileptogenic area. Preoperative and postoperative seizure outcomes after glioma surgery have been studied extensively and risk factors have been defined (6, 11). However, this issue has not been well-studied for meningioma.

Depending on the limited number of studies, it was shown that nearly 30% of patients present with seizure in supratentorial meningioma (1, 3, 4, 9, 10, 12, 13, 15, 16). However, type of seizure differs among the papers so that either generalized tonic-clonic seizures (GTC) or focal tonic seizures can be encountered as the most common type (1, 4, 13, 16). In fact, GTC seizure is expected to be more common given that meningioma generally presents with seizure after reaching a certain size compressing larger cortical zone.

Following surgery, about 50 to 70% of patients become seizure free but new seizures can be seen in almost 12% (9, 14). Previous studies suggested that prophylactic AEDs should be used depending on the risk factors which are associated with seizures (8, 12, 15). The rate with respect to prophylactic AED use in the present paper is comparable to previous studies which do not support routine use of prophylaxis without seizure despite of peritumoral edema (5, 14).

Almost all previous studies showed that the left side was more commonly involved similar to our findings (1, 4, 9,13, 15). Different from other series, non-skull base location was more common in the present paper which may be due to smaller number of patients (3, 10, 13). Convexity region is noted as the most common site besides the other frequent locations such as tuberculum sellae, sphenoid wing or parasagittal/falx region (3, 4, 10, 12, 13, 16). In the current literature, convexity meningiomas have been shown to be more epileptogenic (3, 9), nevertheless some authors found that parasagittal/falx meningiomas present with seizure more common than other locations (1). Side and site of locations were not different between the patients with and without preoperative/postoperative seizures in our study.

Atypical and malignant meningiomas are generally associated with PTE which may explain higher occurrence of seizure in these types. Glutamate, an amino acid which decreases electrical threshold of surrounding cortex and aggravate seizure, has been found to be higher in peritumoral edematous tissue (2). Furthermore, PTE is shown to be related to angiogenesis, increased pial blood supply, and increased vascular endothelial growth factor (7). All these factors give PTE an epileptogenic potential and AED is preferred to start upon detection of edema on MRI. We found PTE in 58.7% of the patients. However, no difference was found regarding presence of PTE and preoperative seizure. Interestingly, no PTE was detected on MRI in 12 patients with atypical meningioma. Concerning the size of tumor, >3-3.5 cm diameter was associated with either preoperative or postoperative seizure (3, 13). Mean diameter did not show difference between the patients with and without preoperative seizure in our study suggesting that location and/or size of PTE may be more important than size of meningioma itself.

Our overall seizure free rate at the last follow-up was 50% similar to previous reports (50-70%; 5, 14). Besides, our early and late seizure rates are comparable with the current literature (3, 10, 16) so that 50% of patients with preoperative seizure have become seizure free after surgery. Complex-partial seizure is the seizure type that responds to surgery well. Almost 80% of patients with late seizure had surgery on convexity meningiomas and again majority had GTR. Concerning these results, we support the notion that GTR may result in seizure more commonly due to increased damage to surrounding cortex.

Predictors of preoperative and postoperative late seizures

When the limited number of retrospective studies are reviewed, only the number of variables included in statistical analysis differs while the negative and/or positive predictors before and after surgery are almost similar (5, 14). Male gender, convexity or falx location, absence of headache, tumor diameter >3-3.5 cm, presence of peritumoral edema, younger age were found to be predictors of preoperative seizures. On the other hand, male gender, convexity or falx location, tumor size >3- 3.5 cm diameter,

presence of edema, presence of preoperative seizure, use of postoperative AED, location of the left side and higher grade were associated with postoperative seizure (4, 12, 15, 16).

The present study demonstrated that among the variables which we introduced into regression analysis, occurrence of postoperative early seizure was a significant risk factor for postoperative seizure. Existence of postoperative surgical complications and non-skull base location showed a tendency to be postoperative late risk factor.

Study Limitations

The small patient group and retrospective nature of our study are two major limitations.

Conclusion

Depending on our results, absence of headache in the preoperative period and presence of postoperative early seizure are associated with seizure outcome. Occurrence of surgical complication(s) and non-skull base locations tend toward to be a predictor for postoperative late seizure. Identifying risk factors in the perioperative period may lead treating physician to start timely AED and decrease seizure incidence which, indeed, improves quality of life in patients with meningiomas.

Conflicts of Interest The authors inform that there is no conflict of interest in this study.

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