Assessment of Risk Factors for Early Seizures Following Surgery for Meningiomas Using Logistic Regression Analysis

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This study analysed the influence of clinical factors on early postoperative seizures in patients with meningiomas and constructed a logistic regression equation for assessing risk factors. Clinical data from 222 patients with meningiomas were collected. The odds ratios (ORs) for independent variables were determined: the ORs for preoperative seizure history and movement disorder were > 1, whereas the OR for prophylactic therapy was < 1. A logistic regression analysis was then performed to select potential risk factors for early postoperative seizures. Five variables (preoperative seizure history, movement disorder, tumour location, primary location of initial tumour and prophylactic therapy) were introduced into the regression model. A logistic regression equation was then constructed that had a positive predictive value of 66.65% and a negative predictive value of 84.95%. This suggested that the five variables introduced in the equation were closely associated with early postoperative seizures, with preoperative seizure history and movement disorder as potential risk factors and prophylactic therapy as a protective factor.

KEY WORDS: Meningioma; Seizures; Risk factors; Logistic regression analysis

Introduction

Seizures are a frequent presenting symptom in patients with meningiomas.¹,² Although seizures may be early or late complications of meningiomas, the majority of postoperative seizures occur within the first week after surgical tumour removal and are termed ‘early postoperative seizures’.³,⁴ The first week following surgery is the peak period for brain oedema⁵ and early postoperative seizures during this period aggravate brain oedema, as well as intracranial haematoma, frequently resulting in poor prognosis.⁶ Thus, identification of risk factors for early postoperative seizures is important for the selection of treatment and prediction of prognosis. According to the literature, postoperative seizures are associated with a number of risk factors and a higher incidence occurs in patients with a previous preoperative seizure history, peritumoral brain oedema, meningiomas near functional...

¹B Zhang, H-F Yang and D Wang contributed equally to this work.
brain areas, and movement disorder before surgery.\(^7\) Perioperative prophylaxis with antiepileptic drugs can decrease the incidence of early postoperative seizures and is considered to be a protective factor.\(^8\) Although the contribution of these clinical factors to the onset of postoperative seizures has generally been agreed, to date how individual factors interact has not been investigated.

Based on a cohort of patients with meningiomas, the present study analysed a number of clinical factors in a multiple logistic regression model in an attempt to understand the influence of these factors on the onset of early postoperative seizures, and to construct a regression equation for predicting and preventing the occurrence of early postoperative seizures.

**Patients and methods**

**STUDY POPULATION**

This retrospective study included patients with meningiomas who underwent surgery at the Department of Neurosurgery, First Affiliated Hospital of Jilin University between March 2006 and March 2007. There were no other specific inclusion/exclusion criteria for this study.

The study protocol was approved by the Ethics Committee of the First Affiliated Hospital of Jilin University and verbal informed consent was obtained from all patients for the use of their clinical data.

**COLLECTION OF CLINICAL DATA**

General clinical data, including details of the meningioma and preoperative seizure history, were collected prospectively for all patients on admission. Neurological examinations were performed to determine whether the patients had preoperative seizures, dysphasia and/or movement disorder. Brain imaging, including 16-slice computed tomography or 1.5 T magnetic resonance imaging, was used to detect the maximum tumour diameter, the tumour location and to examine whether the patients had peritumoral brain oedema. All patients underwent a craniotomy to remove the tumour.

Some patients received prophylactic therapy with antiepileptic drugs during the perioperative period. Phenytoin sodium 5 mg/kg per day or sodium valproate 15 mg/kg per day were administered for 3 – 7 days before surgery and for > 7 days after surgery to patients whom the investigators expected to have early seizures following surgery to remove their meningiomas.

**STATISTICAL ANALYSES**

Odds ratios (ORs) were calculated to measure the association between binary outcome variables and early postoperative seizures. The independent variables were stratified and sorted in ascending order according to their ORs.

The ORs of individual variables were determined and patients were stratified into the following different numbered subgroups: patient age – (1) 30 – 39 years; (2) 40 – 69 years; (3) 10 – 29 years; and (4) > 70 years; maximum tumour diameter – (1) 3 – 5 cm; (2) < 3 cm; and (3) > 5 cm; length of operation – (1) > 4 h; (2) 2 – 4 h; and (3) < 2 h; tumour location – (1) spine of sphenoid bone, parieto-occipital, posterior fossa, occipitotemporal area, occiput, cerebellopontine angle, cerebellar hemisphere; (2) frontotemporal, middle cranial fossa, petroclival; (3) paracele, anterior cranial fossa, forehead, saddle region; and (4) temporoparietal region, tempora, parietal lobe, frontal and parietal lobes; primary location of initial tumour – (1) posterior fossa, optic nerve, middle cranial fossa, brainstem, tentorium cerebella, petroclival; (2) spine of sphenoid bone, anterior cranial fossa, convex; (3) choroid
plexuses, tuberculum sellae, cerebral falx; and (4) olfactory sulcus, sagittal sinus; brain zone of located tumour – (1) left hemisphere; (2) middle zone; (3) right hemisphere; and (4) bilateral brain; prophylactic therapy (excluding intramuscular injection of phenobarbital sodium 30 min before surgery) – (1) receiving postoperative but not preoperative treatment; (2) receiving preoperative but not postoperative treatment; (3) receiving pre- and postoperative combination treatment; and (4) no treatment.

These variables were incorporated into a logistic regression model and were selected using a forward stepwise method and processed using the SPSS® statistical package, version 15.0 (SPSS Inc, Chicago, IL, USA) for Windows®. A multiple logistic regression analysis was used to predict the risk factors associated with early postoperative seizures. The regression equation was derived by the forward stepwise selection of variables using the likelihood ratio test to determine which variables should be included in the model. A P-value < 0.05 was considered to be statistically significant.

Results

PATIENTS AND TREATMENT

In total, 222 patients with meningiomas were included in the study: 52 patients (14 males, 38 females, aged 15 – 79 years [mean 51.7 years]) had early epileptic seizures after surgery; and the remaining 170 patients (58 males, 112 females, aged 15 – 75 years [mean 50.6 years]) had no early epileptic seizures following surgery. Phenytoin sodium 5 mg/kg per day or sodium valproate 15 mg/kg per day were administered for 3 – 7 days before surgery to 117 patients and for > 7 days following surgery to a further 75 patients who were expected to have early seizures following surgery.

LOGISTIC REGRESSION MODEL

The logistic regression model with selection by a forward stepwise method identified five statistically significant (P < 0.05) variables for early postoperative seizures, namely preoperative seizure history (PS), movement disorder (MD), tumour location (TL), primary location of initial tumour (TI) and prophylactic therapy (PT).

The five variables were introduced into the regression equation (Formula 1) to estimate the likelihood of occurrence of early postoperative seizures. Application of the regression equation to data from each patient produced a number ranging from 0 to 1; the definitive cut-off value was 0.5. A value of \( P_{\text{outcome}=1} (\text{seizures}) \geq 0.5 \) (close to 1) indicated a high chance of early postoperative seizures and a value < 0.5 (close to zero) indicated a low chance of early postoperative seizures. This logistic regression equation was tested with a \( \chi^2 \) goodness of fit test to indicate how closely the observed and predicted probabilities matched; the null hypothesis predicted that the model will fit with \( P > 0.05 \) expected. The \( \chi^2 \) goodness of fit test gave results of \( P = 0.877 \), sensitivity of 46.2%, specificity of 92.9%, positive predictive value of 66.65% and negative predictive value of 84.95%.

\[
\begin{align*}
P_{\text{outcome}=1} (\text{seizures}) &= \frac{e^{0.685+0.944PS+1.102MD–2.455TL(1)–0.268TL(2)–0.229TL(3)–2.555TI(1)–1.290TI(2)–0.869TI(3)–1.932PT(1)–1.334PT(2)–2.008PT(3)}}{1+e^{0.685+0.944PS+1.102MD–2.455TL(1)–0.268TL(2)–0.229TL(3)–2.555TI(1)–1.290TI(2)–0.869TI(3)–1.932PT(1)–1.334PT(2)–2.008PT(3)}},
\end{align*}
\]

FORMULA 1: Regression equation used to estimate the possible occurrence of early postoperative seizures (PS, preoperative seizure history; MD, movement disorder; TL, tumour location; TI, primary location of initial tumour; PT, prophylactic therapy)
The ORs for PS and MD were both > 1 so were considered to be risk factors for early postoperative seizures (Table 1). The OR of PT was < 1 and so was considered to be a protective factor for early postoperative seizures (Table 1). The three variables TL, TI and PT were analysed as dummy variables, quantified qualitative variables given a value of either 0 or 1 derived from the ORs of potential risk factors for early postoperative seizures and the results of this analysis are shown in Table 2.

Discussion

Seizures are one of the most severe complications following meningioma surgery. The majority occur within the first week after surgery, and are often life-threatening for patients with meningiomas and frequently lead to a poor prognosis. There are a number of likely causes of early postoperative seizures after meningioma surgery, including compression beneath the cortex, local oedema, tumour invasion and local cortical irritability. The occurrence of seizures is associated with tumour location and probably also with tumour pathology.

The association of early postoperative seizures with several clinical factors (patient age, preoperative seizure history, dysphasia and movement disorder, tumour location, maximum tumour diameter, length of the operation, location of the initial tumour and use of prophylactic therapy) were analysed in the present study using multiple regression analysis in a cohort of 222 patients. The ORs for PS and MD were both > 1 so were considered to be risk factors for early postoperative seizures (Table 1). The OR of PT was < 1 and so was considered to be a protective factor for early postoperative seizures (Table 1). The three variables TL, TI and PT were analysed as dummy variables, quantified qualitative variables given a value of either 0 or 1 derived from the ORs of potential risk factors for early postoperative seizures and the results of this analysis are shown in Table 2.

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**TABLE 1:**

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>B</th>
<th>χ²</th>
<th>d.f.</th>
<th>P-value</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>PS</td>
<td>0.944</td>
<td>4.465</td>
<td>1</td>
<td>0.035</td>
<td>2.570</td>
<td>1.071, 6.170</td>
</tr>
<tr>
<td>MD</td>
<td>1.102</td>
<td>5.431</td>
<td>1</td>
<td>0.020</td>
<td>3.012</td>
<td>1.192, 7.612</td>
</tr>
<tr>
<td>TL (1)</td>
<td>-2.455</td>
<td>8.443</td>
<td>1</td>
<td>0.004</td>
<td>0.086</td>
<td>0.016, 0.450</td>
</tr>
<tr>
<td>TL (2)</td>
<td>-0.268</td>
<td>0.073</td>
<td>1</td>
<td>NS</td>
<td>0.765</td>
<td>0.110, 5.326</td>
</tr>
<tr>
<td>TL (3)</td>
<td>-0.229</td>
<td>0.237</td>
<td>1</td>
<td>NS</td>
<td>0.795</td>
<td>0.316, 2.000</td>
</tr>
<tr>
<td>TI (1)</td>
<td>-2.555</td>
<td>6.601</td>
<td>1</td>
<td>0.010</td>
<td>0.078</td>
<td>0.011, 0.546</td>
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<tr>
<td>TI (2)</td>
<td>-1.290</td>
<td>6.249</td>
<td>1</td>
<td>0.012</td>
<td>0.275</td>
<td>0.100, 0.757</td>
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<tr>
<td>TI (3)</td>
<td>-0.869</td>
<td>3.045</td>
<td>1</td>
<td>NS</td>
<td>0.419</td>
<td>0.158, 1.113</td>
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<tr>
<td>PT (1)</td>
<td>-1.932</td>
<td>11.416</td>
<td>1</td>
<td>0.001</td>
<td>0.145</td>
<td>0.047, 0.444</td>
</tr>
<tr>
<td>PT (2)</td>
<td>-1.334</td>
<td>7.844</td>
<td>1</td>
<td>0.005</td>
<td>0.263</td>
<td>0.103, 0.670</td>
</tr>
<tr>
<td>PT (3)</td>
<td>-2.008</td>
<td>7.601</td>
<td>1</td>
<td>0.006</td>
<td>0.134</td>
<td>0.032, 0.560</td>
</tr>
<tr>
<td>Constant</td>
<td>0.685</td>
<td>1.452</td>
<td>1</td>
<td>NS</td>
<td>1.983</td>
<td>–</td>
</tr>
</tbody>
</table>

B, estimated value of regression coefficient; d.f., degrees of freedom; CI, confidence intervals; PS, preoperative seizure history; MD, movement disorder; TL, tumour location – (1) spine of sphenoid bone, parieto-occipital, posterior fossa, occipitotemporal area, occiput, cerebellopontine angle or cerebellar hemisphere with that of temporoparietal region, tempora, parietal lobe or frontal and parietal lobes, (2) frontotemporal, middle cranial fossa or petroclival with that of temporoparietal region, tempora, parietal lobe or frontal and parietal lobes, and (3) paracentral, anterior cranial fossa, forehead or saddle region with that of temporoparietal region, tempora, parietal lobe or frontal and parietal lobes; TI, location of initial tumour – (1) posterior fossa, optic nerve, middle cranial fossa, brainstem, tentorium cerebellum or petroclival with that of olfactory sulcus or sagittal, (2) spine of sphenoid bone, anterior cranial fossa, convex with that of olfactory sulcus or sagittal sinus, and (3) choroid plexuses, tuberculum sellae or cerebral falx with that of olfactory sulcus or sagittal sinus; PT prophylactic therapy – (1) receiving postoperative but not preoperative treatment with that of no prophylactic therapy, (2) receiving preoperative but not postoperative treatment with that of no prophylactic therapy, and (3) receiving pre- and postoperative combination treatment with that of no prophylactic therapy.
patients who underwent meningioma surgery. Patients with a preoperative seizure history had a 2.570 times higher risk of having postoperative seizures than those without a preoperative seizure history. This was consistent with previous reports showing that 32.7 – 50.8% of patients with prior seizures had epileptic seizures following surgery, whilst only 17.3 – 30.6% of patients without prior seizures had postoperative seizures, and suggests that the occurrence of postoperative seizures is closely associated with preoperative seizure history.

Meningiomas can arise from almost everywhere in the dura, most commonly in the skull vault, the base of the skull (planum sphenoidal, sphenoid wing, petrous ridge, cavernous sinus and perisellar region, and clivus) and dural reflections (falk cerebri, tentorium cerebelli and dura of the adjacent venous sinuses). The optic nerve sheath and the choroid plexus are less commonly involved. Previous studies suggest that the occurrence of seizures is closely associated with tumour location. Patients with meningioma in the frontal, parietal and temporal lobes are more likely to develop seizures than those with meningiomas at other locations. Tumours in the paracentral lobule are most frequently associated with epilepsy. A retrospective study by Penfield in 1952 found that the incidence of seizures is about 50% in patients with supratentorial meningioma, 5.7% in saddle region meningioma and 2.5% in infratentorial meningioma. Other studies have revealed that seizures are closely associated with supratentorial and cerebral

<table>
<thead>
<tr>
<th>Group</th>
<th>Subgroup</th>
<th>Frequency (n)</th>
<th>Parameter coding</th>
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</thead>
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<tr>
<td></td>
<td></td>
<td>(1)</td>
<td>(2)</td>
</tr>
<tr>
<td>PT</td>
<td>1</td>
<td>45</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>72</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>3</td>
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</tr>
<tr>
<td></td>
<td>4</td>
<td>75</td>
<td>0</td>
</tr>
<tr>
<td>TI</td>
<td>1</td>
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<td>1</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>69</td>
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</tr>
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<td></td>
<td>4</td>
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<tr>
<td>TL</td>
<td>1</td>
<td>61</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>20</td>
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<td>0</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>64</td>
<td>0</td>
</tr>
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</table>

TL 1, spine of sphenoid bone, parieta occipital, posterior fossa, occipitotemporal area, occiput, cerebellopontine angle or cerebellar hemisphere; TL 2, frontotemporal, middle cranial fossa or petroclival; TL 3, paracfrone, anterior cranial fossa, forehead or saddle region; TL 4, temporooparietal region, tempora, parietal lobes or frontal and parietal lobes; TI 1, posterior fossa, optic nerve, middle cranial fossa, brainstem, tentorium cerebelli or petroclival; TI 2, spine of sphenoid bone, anterior cranial fossa, convex PT or prophylactic therapy; TI 3, choroid plexuses, tuberculum sellae or cerebral falx; TI 4, olfactory sulcus or sagittal sinus; PT 1, receiving postoperative but not preoperative treatment; PT 2, receiving preoperative but not postoperative treatment; PT 3, receiving pre- and postoperative combination treatment; PT 4, no prophylactic therapy.
convexity meningioma.² The highest frequency of seizures is found in frontal lobe meningioma, followed by frontoparietal, temporal and parietal lobe meningioma.² A high incidence of postoperative seizures has also been found in patients with parasagittal meningioma irrespective of whether or not they have had a history of preoperative seizure.²⁴ Tumour location was also significantly associated with early onset postoperative seizures in the present study – cortical sites and sites beneath the cortex or near functional brain regions posed the greatest risk factors for early postoperative seizures.

Comprehensive therapy for meningioma using surgery and drugs could significantly decrease the onset of preoperative seizures.²,²⁵ Valproate, phenobarbital and phenytoin sodium are widely used as antiepileptic drugs with broad spectra of activity.²⁶ – ³⁰ Treatment with antiepileptic drugs during the perioperative period can prevent epilepsy gravior, focal seizures or partial seizures from progressing to generalized seizures, decrease the incidence of early postoperative seizures and relieve brain injuries.³¹,³² As the prophylactic use of valproate sodium and phenytoin sodium can reduce the incidence of postoperative seizures,³³ – ³⁵ they were selected as a possible variable that may be associated with the incidence of postoperative seizures. The ORs of postoperative prophylaxis, preoperative prophylaxis and combined pre- and postoperative prophylaxis were 0.145, 0.263 and 0.134, respectively. Thus, prophylaxis was protective against early postoperative seizures and combination treatment had the greatest effect.

In summary, to construct a simple, objective assessment method to predict postoperative seizures without the interference of superfluous factors, several clinical factors (patient age, gender, history of meningioma and preoperative seizures, dysphasia, movement disorder, tumour location, the maximum tumour diameter, peritumoral brain oedema, prophylactic therapy, length of operation, and extent of tumour resection) were investigated and analysed in a multiple logistic regression model. Five variables and their dummy variables were included in the equation and the results were statistically significant for predicting early postoperative seizures. When the value of \( P_{\text{outcome} = 1 (\text{seizure})} \) was \( \geq 0.5 \), the possibility of early postoperative seizure occurrence was 66.65%. When the value of \( P_{\text{outcome} = 1 (\text{seizure})} \) was \(< 0.5\), the possibility of no early postoperative seizures was 84.95%. This equation could, therefore, potentially be used to predict early postoperative seizures, estimate the prognosis of patients, direct treatment strategies and play a significant role in future investigations.

**Conflicts of interest**
The authors had no conflicts of interest to declare in relation to this article.

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