EDITORIAL

Seizures with meningioma

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NEARLY every neurosurgeon has faced seizures associated with meningioma, either before or after resection. As one of the most common brain tumors, meningioma has become recognized for its high predilection for inciting seizure and even chronic epilepsy. Despite the frequency of meningioma occurrence, the prophylaxis and management of associated or potential seizures remains inconsistent. In fact, an epilepsy colleague once joked that “the best way to provoke a seizure from a meningioma is to operate on it.” The management of meningioma-associated seizures is debated and warrants further investigation.

In their manuscript “Seizures in supratentorial meningioma: favorable surgical outcomes and association with peritumoral edema,” Englot et al. have pooled cases from the world’s literature to probe the incidence and occurrence of seizures from these extrinsic tumors.⁵ Briefly, they performed a systematic review of pre- and postoperative seizures from supratentorial meningiomas occurring between 1980 and 2014. Sadly, there are no controlled studies to examine this topic. From 39 observational studies with 4709 patients, seizures occurred in 29.2% of the preoperative patients, whereas 12.3% of postoperative patients without prior seizures developed them. A meta-analysis was performed and identified preoperative factors for seizure occurrence as male sex, the absence of headache, peritumoral edema, and non–skull base tumor location. The factors statistically associated with postoperative seizures included peritumoral edema, tumor location, and tumor progression.

There are several key observations gained from this comprehensive analysis. First, nearly 70% of patients became seizure free with resection of the tumor. The new development of seizures after surgery was associated with a history of radiation therapy and gross-total resection (unlike intrinsic gliomas); however, anticonvulsant prophylaxis did not affect the development of new post-

operative seizures. Importantly, peritumoral edema was the variable most strongly associated with preoperative (OR 7.48, 95% CI 6.13–9.47) and continued postoperative seizures. In fact, the rate of seizures regardless of pre- or postoperative status was more than double for tumors with peritumoral edema.

As with any meta-analysis, however, the data must be interpreted with the understanding that the overall results are subject to bias and the fact that errors reported in the compiled original studies may be additive. Despite this inevitable bias, one cannot discount the lengths to which the authors sought to minimize error, including the use of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standards for data reporting, and significant credit should be given to their consolidation and analysis of outcomes on more than 4000 cases.⁷ What this comprehensive study cannot answer, however, is why do certain individuals with meningiomas develop seizures in the first place? The authors discuss the fact that the presence of peritumoral edema significantly increases the risk for the development of seizures. Despite this, approximately two-thirds of patients with tumor-related edema did not develop seizures.⁵ Thus, although recognizing that peritumoral edema may be an important component of epileptogenesis in certain individuals, it does not tell the entire story; further investigation into this topic is warranted.

This study is also unable to answer why the presence of peritumoral edema contributes to the development of seizures. To answer this question, one must first understand how cerebral edema paradoxically forms in the presence of an extra-axial lesion. Several studies have investigated this, but controversy still exists on this matter. Previous studies have shown an association with increased expression of vascular endothelial growth factor (VEGF) and the development of peritumoral edema with meningiomas.^{6,10–13} Others have postulated that brain invasion simi-

larly can lead to the formation of peritumoral edema.^{8,9} Certainly more than one etiology is probably responsible, but understanding if one or more of these pathophysiological mechanisms actually plays a role in the epileptogenesis of meningiomas is important. For instance, one can imagine that brain invasion by meningioma could plausibly be epileptogenic within itself while simultaneously causing cerebral edema. If this is the case, then the current study's finding that peritumoral edema represents a significant risk factor for tumor-related epilepsy may be a confounder. Unfortunately, the manuscripts compiled for analysis in this study did not report the presence or absence of brain invasion, and thus this question remains unanswered. If, however, the development of peritumoral edema proves to be epileptogenic, then certainly one could consider the use of VEGF inhibitors, such as bevacizumab, in the treatment of medically and surgically refractory epilepsy related to meningiomas.

More than 3 decades of data related to meningioma-related seizures are compiled in this report. Given that one-third of all patients who harbor meningiomas present with or develop seizures during their diagnostic and treatment course, it is unsettling that a problem so common in neurosurgery has met with so little attention until now. Indeed, it is quite amazing to think that there have been no prospective studies examining this topic. Englot et al. are truly experts in the study of tumor-related epilepsy, including glioneuronal low-grade and high-grade glioma; and fortunately they have set their sights on meningioma and its many unanswered questions.^{1–5} For instance: is peritumoral edema causative or correlative with the development of meningioma-related epilepsy; does the presence or absence of brain invasion change the natural history of meningioma-related epilepsy; and can factors that reduce VEGF expression curtail the frequency of seizures in those with meningioma-related epilepsy?

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Response

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We sincerely appreciate the thoughtful editorial provided by Shepard and Elias regarding our manuscript on seizures in patients with supratentorial meningioma. First, we agree that the results of any meta-analysis must be interpreted with caution, given both the inherent limitations of the technique, and the fact that many studies presented as “meta-analyses” in the literature fall far short of PRISMA standards. The need for strict adherence to PRISMA guidelines has been eloquently described recently in the *Journal* by Sampson and Barker,¹ and we did adhere to these standards in our present study, as highlighted by Shepard and Elias.

We agree with the authors of the editorial that it is not entirely clear why the presence of peritumoral edema in meningioma dramatically increases the risk of both pre- and postoperative seizures. However, given that several studies have identified increased expression of VEGF in meningiomas associated with edema, we concur that future studies should consider the potential effects of VEGF inhibitors on epileptogenicity in meningioma.

Next, we share the frustration of Shepard and Elias that so little work has been done in this field, given the high rate of seizures in patients with meningioma, and

the significant effects of epilepsy on quality of life. Even compared to other brain tumor types, we have less understanding of the rates, predictors, and need for prophylaxis of seizures in meningioma. Although we did identify several studies to examine in our meta-analysis, this required analysis extending over a 30-year period. Furthermore, all of the studies we examined represented observational case series—many of them relatively small in size—and no controlled studies have ever investigated these topics in meningioma.

One critical question that remains unanswered is whether perioperative prophylaxis with antiepileptic drugs (AEDs) is indicated in meningioma surgery, and practice patterns differ wildly between brain tumor surgeons. If perioperative AEDs do reduce seizures significantly, then the prescription duration can potentially be standardized and health care dollars can be saved by shorter courses

of drugs and reduced readmission rates. If perioperative AEDs do not prevent seizures in patients with no seizure history, there is an extraordinary potential to save substantial costs and prevent the risk of side effects in these patients. Therefore, our center is in the early stages of planning a multicenter prospective trial examining this issue in supratentorial meningioma surgeries. Again, we sincerely appreciate the commentary and support of Shepard and Elias, and we hope their center will consider joining us in exploring these important questions regarding seizures in meningioma.

Reference

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