Neuro-Oncology Advances
5(S1), i49–i57, 2023 | https://doi.org/10.1093/noajnl/vdac110

The clinical and genomic features of seizures in meningiomas

Alper Dincer, Muhammad I. Jalal, Trisha P. Gupte, Shaurey Vetsa, Sagar Vasandani, Kanat Yalcin, Neelan Marianayagam, Nicholas Blondin, Zachary Corbin, Declan McGuone, Robert K. Fulbright, Zeynep Erson-Omay, Murat Günel, and Jennifer Moliterno

Department of Neurosurgery, Tufts Medical Center, Boston, Massachusetts, USA (A.D.); Department of Neurosurgery, Yale School of Medicine, New Haven, Connecticut, USA (M.I.J., T.P.G., S.Ve., S.Va. K.Y., N.M., Z.E.-O., M.G., J.M.); Chenevert Family Brain Tumor Center, Yale Cancer Center, Smilow Cancer Hospital, New Haven, Connecticut, USA (M.I.J., T.P.G., S.Ve., S.Va. K.Y., N.M., N.B., Z.C., D.M., R.K.F., Z.E.-O., M.G., J.M.); Department of Neurology, Yale School of Medicine, New Haven, Connecticut, USA (N.B., Z.C.); Department of Pathology, Yale School of Medicine, New Haven, Connecticut, USA (D.M.); Department of Radiology and Biomedical Imaging, Yale School of Medicine, New Haven, Connecticut, USA (R.K.F); Department of Genetics, Yale School of Medicine, New Haven, Connecticut, USA (M.G.)

Corresponding Author: Jennifer Moliterno, MD, Department of Neurosurgery, Yale School of Medicine, 15 York Street, LLCI 810, New Haven, CT 06510, USA (jennifer.moliternogunel@yale.edu).

Abstract

Meningiomas are the most common central nervous system tumors. Although these tumors are extra-axial, a relatively high proportion (10%–50%) of meningioma patients have seizures that can substantially impact the quality of life. Meningiomas are believed to cause seizures by inducing cortical hyperexcitability that results from mass effect and cortical irritation, brain invasion, or peritumoral brain edema. In general, meningiomas that are associated with seizures have aggressive features, with risk factors including atypical histology, brain invasion, and higher tumor grade. Somatic *NF2* mutated meningiomas are associated with preoperative seizures, but the effect of the driver mutation is mediated through atypical features. While surgical resection is effective in controlling seizures in most patients with meningioma-related epilepsy, a history of seizures and uncontrolled seizures prior to surgery is the most significant predisposing factor for persistent postoperative seizures. Subtotal resection (STR) and relatively larger residual tumor volume are positive predictors of postoperative seizures. Other factors, including higher WHO grade, peritumoral brain edema, and brain invasion, are inconsistently associated with postoperative seizures, suggesting they might be crucial in the development of an epileptogenic focus, but do not appear to play a substantial role after seizure activity has been established. Herein, we review and summarize the current literature surrounding meningioma-related epilepsy and underscore the interaction of multiple factors that relate to seizures in patients with meningioma.

Key Points

- Preoperative seizures are associated with *NF2* and aggressive tumor features.
- Resection of the meningioma is effective in controlling seizures in most patients.
- Preoperative and uncontrolled seizures increase risk of postoperative seizures.

Meningiomas are the most common central nervous system tumors, accounting for 36% of all brain tumors overall with an incidence of 4.2 and 8.6 per 100,000 individuals.[1,2] While many meningiomas are asymptomatic and incidentally found, overall, anywhere between 10% and50% of meningioma patients have seizures[3–8] and therefore represent a large portion

of brain tumor-related epilepsy.[9,10] Meningioma-related epilepsy is a significant cause of morbidity, including cognitive deficits, depression, and impaired ability to drive and perform other tasks of daily living, substantially decreasing the quality of life.[11] Indeed, Gupte et al. showed patients with meningiomas who present with seizures suffer significantly worse progression-free survival compared to those who do not, suggesting that meningioma-related epilepsy portends a more aggressive underlying tumor.[12]

Symptomatic meningiomas are typically amenable to and treated with surgical resection. Tumor removal results in seizure freedom in 53%–90% of meningioma patients with preoperative seizures, rendering seizure freedom a primary goal of surgery.[13,14] However, postoperative seizure rates still range from 26% to 60% in the literature, which includes patients who do not obtain seizure freedom, as well as those who are seizure naïve and develop seizures postoperatively.[15–18] Thus, improving our understanding of the pathophysiology underlying meningioma-related epilepsy and identifying risk factors for preoperative and postoperative seizure occurrence is a priority.

Herein, we review the recent literature surrounding the topic of meningioma-related epilepsy. We underscore the relationships and overlap of several associated factors, which together, more commonly signify a more aggressive, higher grade underlying meningioma.

Current Theories on the Mechanism of Epileptogenesis in Meningiomas

In general, epileptogenic activity arises due to an overall shift in excitatory and inhibitory balance, leading to cortical hyperexcitability.[19] The incidence of seizures in patients with meningiomas is surprisingly high, given these tumors are extra-axial and typically slow-growing lesions. In terms of seizure frequency, intra-axial, slow-growing tumors are the most epileptogenic and include dysembryoblastic neuroepithelial tumors, gangliogliomas, and low-grade gliomas with seizure frequencies of 100%, 80%–90%, and 75%, respectively.[20]

Meningiomas are thought to cause cortical hyperexcitability through cortical irritation due to mass effect, brain invasion, and/or peritumoral brain edema (PBTE).[5,6,8,21,22] While cortical irritation due to the mass effect of meningiomas is speculated as an etiology of seizures, the mechanism is not well studied or understood. Compression of the cortex by an extra-axial mass can lead to focal ischemic changes, gliosis, and ion channel disruption.[20] The location and extent of cortical irritation, particularly in epileptogenic regions overlying the convexities, could affect the risk of seizure development.

Brain invasion as a cause of meningioma-related epilepsy, on the other hand, is better elucidated and intuitively logical as it is similar to that of intra-axial tumors. When meningiomas invade brain parenchyma, they do so as finger-like projections of tumor cells and lead to disruption of the pial–glial basement membrane.[22] This can induce a strong astrocytic response[23,24] leading to changes in the microenvironment and epileptogenesis. Indeed, brain invasion is an independent grading criterion for CNS WHO grade 2 meningiomas, suggesting that patients with higher grade tumors are at greater risk for seizures. Brain invasion is also strongly correlated with PBTE, which further contributes to epileptogenicity.[12,25] Although PBTE can develop in the absence of brain invasion, increasing volume of edema is associated with increased risk of brain invasion and seizures.[25]

Peritumoral brain edema has been extensively demonstrated in association with meningioma-related epilepsy and is thought to be a surrogate marker for peritumoral changes that drive epileptogenesis.[8,21,26,27] In meningiomas, brain edema is vasogenic in origin and associated with increased expression of vascular endothelial growth factor (VEGF), metalloproteinases 2 and 9, and aquaporins 4 and 5.[28–30] VEGF secreted by meningioma cells induces the proliferation of pial and tumor vessels, resulting in increased vascularity and blood supply and subsequent edema to the surrounding brain.[31] Brain edema results in neurotransmitter alterations, ionic channel changes, and blood–brain barrier disruption, all of which have been shown to induce epileptogenicity.[27,32–34]

However, it should be noted that not all cases of meningioma with mass effect, invasion, and/or PBTE lead to seizure formation, and thus further work is needed to better understand this observation.

Preoperative Associations with Seizures

Incidence

Seizures are one of the most common manifestations of intracranial meningiomas. The reported incidence of preoperative seizures in the literature is quite variable ranging from 13% to 60%.[5] In one meta-analysis of 39 studies and a total of 4,709 patients with supratentorial meningiomas, preoperative seizures were present in 29.2% of patients.[13] Seizures are the initial presenting symptom in 20%–50% of patients.[5]

Age and Sex

Although meningiomas are more common in adults, younger patients (<18 years old) have a higher risk of developing seizures.[13] The basis of this age-dependent vulnerability is unknown, but is likely due to an increased prevalence of atypical and aggressive meningioma subtypes amongst the pediatric population.[35] Seizure rates in children range from 26% to 79% compared to 13%–51% of the adult population.[6] While no direct comparisons exist, one meta-analysis found a statistically significant difference of 42% versus 23.7% for preoperative seizures in the pediatric and adult populations, respectively.[13]

Similarly, whereas meningiomas are more common overall in females, males are almost twice as likely to experience preoperative seizures.[13] Male gender is associated with an increased frequency of atypical and anaplastic meningiomas.[22] Additionally, one study by Spille et al. found a male predilection for a specific type of brain invasion involving finger-like projections of tumor cells into the brain parenchyma, while in females, the pattern is predominantly cluster-like infiltrative growth.[22] Differences in histologic brain invasion may contribute to the gender

difference in seizures, but further investigations are necessary to determine if an association exists. Taken together, these variables likely influence the significantly increased incidence of preoperative seizures seen amongst male patients (Figure 1).[36]

Brain Invasion and Peritumoral Brain Edema

Invasion of a meningioma into the brain parenchyma is one independent criterion for diagnosis of a CNS WHO grade 2 atypical meningioma.[37,38] Hess et Al. demonstrated a 5-fold increase in the risk of preoperative seizures associated with brain invasion independent of age, sex, tumor location, and PBTE (Figure 1).[39] In patients with preoperative seizures, the probability of detecting brain invasion was increased more than 2-fold compared to patients without seizures.[39] Brain invasion is also closely associated with PBTE.[12,25] Brain edema is reported in 38%–67% cases of all meningiomas[31] and has been extensively demonstrated as a primary risk factor and predictive value for seizures (Figure 1). Mantle et al. found a 20% increase in the incidence of brain invasion for each 1-cm increase in edema and mean edema volume was 5-fold higher with brain-invasive tumors compared to noninvasive tumors.[40] Those with preoperative PBTE are up to 3 times more likely to have preoperative seizures than those without.[15]

The association of an extra-axial tumor and PBTE has been an area of interest, given that the cerebrospinal fluid space and arachnoid membrane should separate the tumor from the brain parenchyma. Brain invasion disrupts the intervening leptomeninges, perhaps contributing to the pathophysiology of edema formation. However, edema caused by brain invasion is likely a distinct entity from vasogenic edema, which can occur without brain invasion. The association between PBTE and other factors, such as age, sex, tumor location, tumor volume, histologic subtypes, and expression of sex hormones and receptors, has been contradictory and inconclusive.[41]

CNS WHO Grade and Histologic Subtype

Certain subtypes of CNS grade 1 meningiomas, including secretory, angiomatous/microcystic, and lymphoplasmacyte-rich tumors, are associated with up to 10–100 times larger PBTE compared to other subtypes, but only the secretory subtype is associated with increased risk of preoperative seizures.[42] Secretory meningiomas are uncommon CNS WHO grade 1 tumors characterized by focal gland-like differentiation with secretory droplets, increased brain edema risk, and are almost 3 times more likely to present with seizures as an initial symptom on admission.[42] Underlying somatic *KLF4* mutations drive the formation of secretory meningiomas and regulate angiogenesis through the activation of VEGF.[31,42–44] These observations suggest secretory meningiomas may be an alternative mechanism leading to epileptogenesis.

CNS WHO grade 2 meningiomas inconsistently demonstrate a higher risk of seizures depending on the histologic subtype (Figure 1).[12,25,45] Histologically atypical WHO grade 2 meningiomas are defined by brain invasion, or a mitotic count greater than 4 mitotic figures per 10 higher power

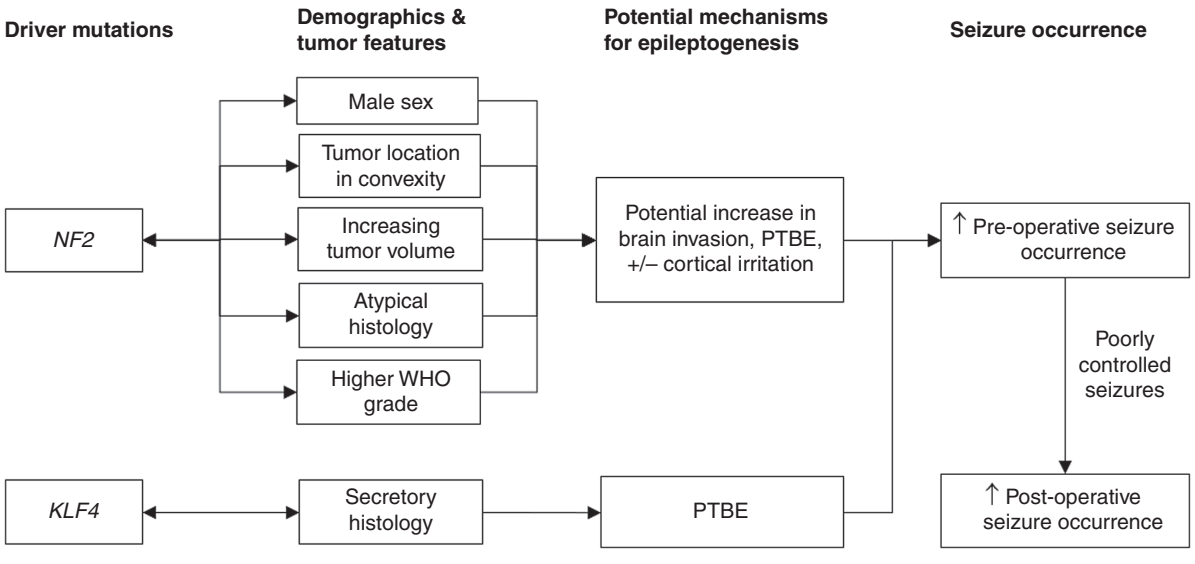

Figure 1. Proposed relationships between driver mutations, demographics, tumor characteristics, mechanisms of epileptogenesis, and seizure occurrence. *NF2* and *KL4* are driver mutations related to demographics and tumor factors that increase preoperative seizure occurrence. *KL4* is a driver mutation for secretory histologic subtypes that produce peritumoral brain edema and increase risk of preoperative seizures. *NF2* is related to male sex, tumor location in convexity, increasing tumor volume, atypical histology, and higher WHO grade. These factors increase risk of preoperative seizures through brain invasion, peritumoral brain edema, and cortical irritation. The primary risk factor for postoperative seizures is poorly controlled preoperative seizures.

fields, or at least 3 of 5 morphologic criteria including high cellularity, small cells with enlarged nuclei, prominent nucleoli, loss of architecture, or necrosis. Atypical WHO grade 2 meningiomas are directly associated with preoperative seizures, increasing the odds of preoperative seizures 2-fold compared to grade 1 meningiomas with no atypical features.[12] Other CNS WHO grade 2 meningiomas, including clear cell and chordoid meningiomas, have not been shown to be significantly associated with preoperative seizures.

Given the low incidence of anaplastic CNS WHO grade 3 meningiomas, most studies, including systemic reviews and meta-analyses, either combine grade 2 and 3 meningiomas together or do not investigate grade 3 meningiomas as a potential factor associated with seizures. Further investigation is needed to determine if an association exists.

Tumor Size and Location

The association and clinical relevance of tumor volume with preoperative seizures remain unclear with conflicting results.[13,39,45] Several studies have shown up to a 2-fold increased risk in seizures with increasing tumor size.[12,27,46,47] Several studies demonstrate a significance in univariate analysis that is lost in multivariate analysis, suggesting confounding variables are at play (Figure 1). A recent meta-analysis of 5 studies found no association between tumor volume and preoperative seizures.[13]

For instance, relatively larger meningiomas, depending on the intracranial location, can more commonly harbor an underlying somatic *NF2* mutation.[48] This driver mutation has also been associated with more aggressive tumor characteristics, including high grade, PBTE and brain invasion, which in turn can be associated with preoperative seizures.[49] When controlling for brain invasion and PBTE, Gupte et al. found no association between tumor volume and preoperative seizures.[12] Tumors of large volume may, therefore, reflect a tumor with features more likely to be associated with an increased risk of seizures.

Tumor location may also confound the effects of tumor size. Certain intracranial locations, such as the convexity, allow for larger tumor size prior to the development of neurologic sequela. Indeed, meningiomas arising from non-skull base locations are more likely to be associated with preoperative seizures (Figure 1).[8,16,50–52] The increased risk of seizures in non-skull base locations may reflect intrinsic region-dependent vulnerability, or it may relate to increased mass effect on cortical regions susceptible to epileptogenesis, underscoring cortical irritation as a potential mechanism increasing the risk of preoperative seizures in larger volume tumors.

Studies have inconsistently identified specific regions within the supratentorial region to be associated with preoperative seizures.[8,53–55] *NF2* mutations may also explain these inconsistent results. Meningiomas with this driver mutation tend to occur along the convexities and have a laterality preference along the skull base. Thus, the aggressive tumor features associated with this molecular subtype may be contributing to seizure formation, rather than the location itself.

Molecular Basis and Associations of Seizures

The last decade has afforded an in-depth understanding of the genomic and epigenomic landscapes of meningiomas. Greater than 80% of sporadic meningiomas have been classified into at least 7 distinct genomic subgroups based on somatic driver mutations with specific clinical and prognostic implications: *NF2*, *POLR2A*, *SMARCB1*, *TRAF7*, *KLF4*, molecules involved in the Hedgehog (HH) (ie SMO, SUFU), and PI3K (ie *AKT1*^{E17K}) signaling pathways.[56]

One study to date has revealed an association of meningioma driver mutation with increased seizure risk.[12] Gupte et al. demonstrated a significant relationship between *NF2* mutation and preoperative seizures. However, the driver mutation itself was found to be insufficient to cause preoperative seizures. Rather, its effect is thought to mediate through atypical histology and its association with PBTE (Figure 2). Apart from brain invasion, it is not known which atypical histological features, either independently or in combination, are responsible for increased seizure risk. An alternative pathway involved atypical histology and brain invasion, but this mediation was not significant (Figure 2).[12]

Somatic *NF2* driver mutations in meningiomas are strongly correlated with higher grade meningiomas and aggressive features such as elevated proliferation indices, brain invasion, and PBTE, as well as location.[8,16,50–52] Interestingly, Gupte et al. did not find an association between *KLF4* mutant meningiomas and preoperative seizures, despite these driver mutations being associated with secretory histology.[48] Therefore, the presentation of a patient with a meningioma and seizure may indicate an underlying *NF2* mutation and more aggressive tumor behavior. Further work is needed to elucidate the main molecular drivers and points of convergence and divergence in cellular pathways responsible for epileptogenesis in association with brain edema.

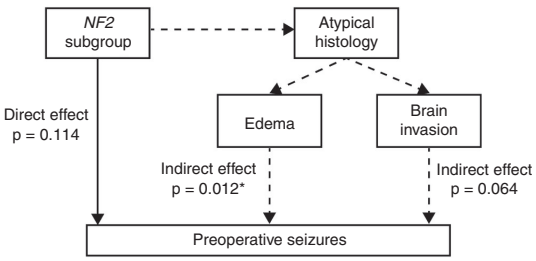

Figure 2. Mediation analysis investigating the causal pathways between genomic subgroups and preoperative seizures. A significant indirect effect instead of a direct effect of the NF2 subgroup on preoperative seizures through the sequential mediators of atypical histology and peritumoral brain edema was revealed. An indirect effect of the NF2 subgroup on preoperative seizures through the sequential mediators of atypical histology and brain invasion was suggested, but not significant. Figure reproduced from Gupte et al. (2020) with permission from *Journal of Neurosurgery*.

Overall, no associations between meningioma somatic driver mutations and postoperative seizures have been reported. However, when analyses are confined to CNS WHO grade 1 meningiomas, tumors with mutations involving the HH signaling pathway were associated with postoperative seizures. These tumors are more likely to occur along the olfactory groove and can often be of relatively larger volume and associated with bilateral frontal edema.[48,56]

The association between meningioma driver mutations and seizures remains in its early stages of investigation, and while it is appreciated, the driver mutation itself cannot induce epileptogenesis, the exact underlying mechanisms remain unclear. Further research should be conducted in this area to gain a further understanding of the genetic and molecular mechanistic underpinnings of seizure etiology in meningiomas.

Role of Surgery in Achieving Seizure Freedom

Surgical resection is highly effective in drastically decreasing seizure occurrence in patients with meningioma-related epilepsy, with reports of seizure freedom in 69%–90% of patients experiencing preoperative seizures.[13] In a recent meta-analysis, Englot et al. found the average rates of seizure freedom postoperatively were 69%.[13] Additionally, seizure freedom appears long term following surgery in the majority of meningioma patients at subsequent follow-ups ranging from 1 to 5 years.[14]

Postoperative Associations with Seizures

Given the incidence of postoperative seizures is comparatively much smaller than preoperative seizures, the identification of risk factors for postoperative seizures has been largely inconsistent and overall does not demonstrate strong epidemiologic associations.[18,45,57]

Preoperative Seizures

A history of meningioma-related epilepsy prior to surgery is the most significant predisposing factor for postoperative seizures, with studies demonstrating almost a 6-fold increased risk in patients with postoperative seizures (Figure 1).[16,46,58] For patients with and without preoperative seizures, the 5-year seizure-free status is 60% and 90%, respectively.[16–18,46] Patients with uncontrolled preoperative seizures have decreased incidence of seizure freedom postoperatively and are more than 2 times more likely to have seizure recurrence after surgery.[46,51,59] Patients with seizures prior to surgery also have an increased risk of poorly controlled and refractory seizures postoperatively.[16–18] Focal versus generalized seizures have not been shown to affect the risk of postoperative seizures.[13]

These findings suggest that seizure foci, once formed, have a propensity to persist postoperatively. The difference between controlled and uncontrolled preoperative seizures may also imply differences in the pathophysiology of epileptogenesis, rendering an overall lowered seizure threshold. If patients continue to experience seizures following tumor resection, further workup and consideration of removal of the cortical epileptogenic focus may be warranted.[16]

Age and Sex

Age and sex are unlikely to be associated with postoperative seizures. One literature review in 2018 by Baumgaurten et al. found that 1 in 6 studies demonstrated an increased risk of seizures in a slightly younger adult patient population.[50,60] Similarly, gender does not appear to play a significant role in postoperative seizures. The observation that males had twice the risk of developing postoperative seizures on a univariate analysis in the Baumgaurten review is undermined by a failure to support an association between age group or gender and postoperative seizures in the majority of other studies.[50]

Tumor Characteristics

CNS WHO grade 2 and 3 meningiomas have an increased risk of postoperative seizures on univariate statistical analysis.[16,47,57,61] Anaplastic or malignant (ie CNS WHO grade 3) tumor trend toward worse seizure outcomes compared to lower grade tumors, but without statistical significance.[62] Although it would be intuitive that higher grade meningiomas may indirectly increase the risk of postoperative seizures through increased PBTE and brain invasion, these associations have not been found to be as strong as the preoperative ones.

How PBTE influences the risk of postoperative seizures remains unclear.[16,27,50,63] Chen et al. demonstrated that postoperative PBTE >1 cm was associated with seizures; however, this significant effect was lost on multivariate analysis when including patients with a history of preoperative seizure. Likewise, brain invasion does not appear to directly influence postoperative seizures.[39] These findings suggest that preoperative PBTE and brain invasion may be sufficient to induce epileptogenesis but are not necessary once an epileptogenic area within the cortex is formed.[64]

Extent of resection plays a significant role in achieving seizure freedom and is likely related to other factors, including residual tumor volume and tumor location. Gross total resection (GTR) has been shown to significantly reduce seizure rate postoperatively.[50] However, certain tumor locations hinder GTR, rendering residual tumor volume. Indeed, extent of resection, preoperative tumor volume. and residual tumor volume are predicators of postoperative seizures.[39,61] In seizure-naïve patients, STR was associated with an increased risk of postoperative seizures. Additionally, residual tumor size greater than 3–4 cm in diameter is associated with postoperative seizures.[16,46,65]

Tumor location is an important risk factor for postoperative seizures. Patients with convexity/parasagittal/parafalcine tumors have 3- to 6-fold increase in postoperative seizures.[8,46,58,61] Interestingly, in contrast to preoperative seizures, Englot et al. found postoperative seizures occurred commonly with skull base tumors,[21] likely due to the difficult location of

these tumors and critical surrounding neurovascular structures, thereby limiting the extent of resection.

The risk of residual tumor in postoperative seizures likely reflects direct and indirect associations with postoperative seizures. Residual tumor may directly increase the risk of postoperative seizures through cortical irritation as intuitively, a relatively larger residual tumor volume could perhaps worsen the effect on the cortex and may be associated with other surgical risk factors, such as increased brain manipulation or retraction, that lead to ischemia and influence postoperative epileptogenicity as well.

Several factors related to surgery are associated with increased risk of postoperative seizures. Postoperative ischemia, new postoperative neurological deficits, or a Karnofsky Performance Score score ≤70 has been associated with increased risk of seizures.[16,57,62,64] Patients who have a postoperative medical or surgical complication, such as new weakness, pneumonia, stroke, or intracranial hemorrhage, are at 3 times increased risk of having a postoperative seizure while in the hospital and after discharge.[16] Indeed, patients who experience postoperative seizures seemingly have a more complicated postoperative clinical course.

Tumor Recurrence/Progression and Adjuvant Therapy

Rarely, patients present with new-onset postoperative seizures, and this often occur years after surgical resection. In these circumstances, seizures may indicate tumor recurrence.[51,57,58] Indeed, tumor recurrence has been shown to be a risk factor for seizure recurrence as well.[8,12,16,21,52] In cases where tumor recurrence is not present, the etiology of seizure is often unclear. Tumor progression is also a risk factor for seizure recurrence in patients both with and without preoperative seizures.[13]

Likewise, patients with postoperative seizures are also more likely to undergo postoperative radiation[12] and underscore the association of seizures with higher grade meningiomas. The role of radiation-induced vasculopathy as a potential mechanism for epileptogenesis is unknown, although there does not appear to be an association between postoperative radiation itself and increased seizure occurrence.[7,16,61] Gupte et al. did note an increased risk of seizures in meningioma patients receiving radiation before the initiation of radiation, and thus the seizures were unlikely to be the effect of radiation, but rather more likely due to the history of seizures, underlying higher grade and residual tumor in some circumstances.[12]

Role of Anti-Epileptic Drugs in Meningiomas

Given that seizures are one of the most common presenting symptoms of meningiomas, many patients with meningiomas are started on antiepileptic agents (AEDs). First-line therapy typically consists of a single agent, particularly for simple partial seizures.[66] Levetiracetam has been extensively studied in tumoral epilepsy and therefore become most commonly used for meningioma associated epilepsy.[12,21] Less commonly used agents include valproate acid, carbamazepine, lamotrigine, phenytoin, and lacosamide.[6,12,20,21]

Careful consideration of AED risk profile, side effects, and metabolic pathway must be taken into account when choosing an AED, given many AEDs and other drugs (including chemotherapies) share common metabolic pathways via the hepatic cytochrome p450 enzyme.[20]

Although surgical resection of the meningioma has been shown to drastically reduce the incidence of postoperative seizures, current data suggests the continuation of AEDs in patients with preoperative seizures given the relatively high risk that seizures can continue postoperatively.[54]

A titrated approach to wean AEDs is advised, with discontinuation when the patient is seizure free for a certain period. For patients with preoperative seizures, AEDs were stopped less than 12 months after surgery in the majority of patients (65%) whereas a minority (35%) continued with lifelong AED treatment.[54] If seizures persist beyond 12-month period postoperatively, the likelihood of seizure freedom becomes less likely.[54] Further investigation is needed to determine the rate and risk factors of patients that meet the criteria of drug-resistant epilepsy.

In patients with refractory seizures, referral to an epilepsy specialist is appropriate. Likewise, in certain circumstances, consideration of more of an "epilepsy"-focused surgical procedure may be favored over the removal of the meningioma.[67] For example, meningiomas causing compression of the temporal lobe may induce gliosis, resulting in a dual pathology driving epilepsy. Even after GTR, continued seizures may persist. Some authors have advocated for further resection of temporal lobe lesions to improve seizure control postoperatively.[6]

The role of AEDs for seizure prophylaxis has been more recently been addressed with the 2021 guidelines published by the Society of Neuro Oncology and European Association of Neuro Oncology which suggest against the use of AEDs in patients with newly diagnosed tumors who have not had a seizure.[13,68] Islim et al., however, suggest that in certain seizure-naïve patients who may be at higher risk for seizure, initiation of prophylactic AEDs may be warranted. High-risk factors include tumor location in the convexity, frontoparietal location, or midline shift on preoperative imaging.[54] Further randomized controlled studies, if feasible, are needed.

Case Illustration

To illustrate the above associations, we present a case of a 48-year-old male who presented with new-onset seizure managed with levetiracetam. On magnetic resonance imaging (MRI), he was found to have a relatively large right frontal extra-axial mass, consistent with a convexity meningioma (Figure 3a) with surrounding PBTE (Figure 3b). He was lost to follow-up for nearly a year and was subsequently referred to the senior author after he underwent reimaging that showed both the tumor volume and peritumoral edema had increased. He underwent a right craniotomy for GTR (Figure 3c). The final integrated diagnosis was a CNS WHO grade 2 meningioma (atypical

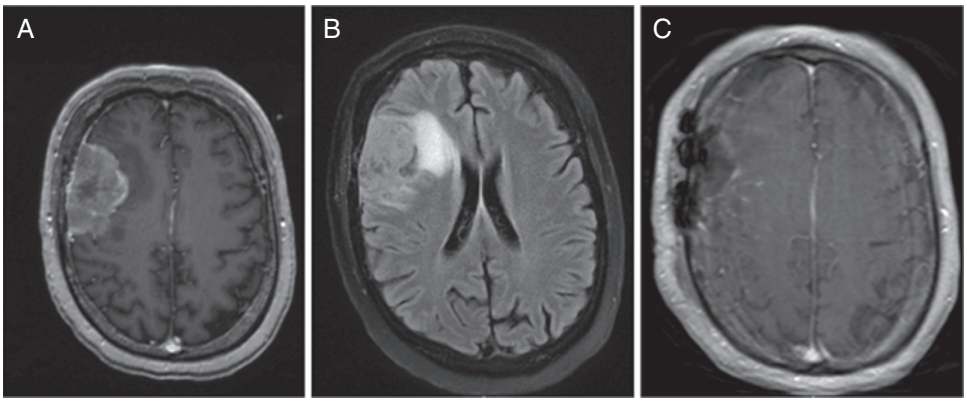

Figure 3. Magnetic Resonance Imaging of WHO grade 2 meningioma *NF2* mutation in a patient who presented with seizure. T1-weighted image with contrast demonstrating an extra-axial lesion causing compression and mass effect of underlying cortex (a). Fluid Attenuated Inversion Recovery (FLAIR) MRI demonstrating peritumoral brain edema (b). Postresection T1-weighted MRI with contrast, without evidence of residual tumor (c).

histology) with an underlying *NF2* driver mutation, chromosomal instability, and copy number variations including loss of heterozygosity of chromosomes 1, 10, 14, 16, 18, and 22. He subsequently underwent fractionated radiotherapy. Four years later, he experienced left-sided weakness with corresponding tumor recurrence for which he underwent an uncomplicated re-resection. He has remained seizure free and is currently off AEDs.

This case underscores certain risk factors, such as male sex, high tumor grade, convexity location, PBTE, chromosomal instability, and underlying *NF2* mutation, all of which have been described with seizure in meningioma patients. Seizure freedom was achieved after GTR.

Conclusion

Meningioma-related epilepsy is relatively common, and perhaps surprisingly so given the extra-axial location of these tumors. Factors that impact the cortical microenvironment and create an intra-axial epileptogenic focus, such as tumor invasion of the brain and/or associated intraparenchymal edema, are associated with seizures in meningioma patients. While the tumor biology does not have a direct effect on producing meningioma-related epilepsy, the more common underlying *NF2* driver mutation associated with meningiomas in this particular subpopulation of patients, is likely a strong contributing factor and is likely mediated through atypical histology and PBTE. Furthermore, an underlying NF2 mutation is associated with other variables relevant to seizure occurrence in meningioma patients, such as convexity, non-skull base location, volume, histology, and sex. Surgical resection affords high rates of seizure freedom and allows patients to be weaned from AEDs. Preoperative seizures, and particularly those that are poorly controlled, are the most significant factors for the occurrence of postoperative seizures in meningioma patients. A patient presenting with seizure appears to signify a potentially more aggressive underlying meningioma.

Keywords

meningioma | NF2 | seizures

Funding

None.

Conflict of interest statement. The authors report no conflict of interest.

Supplement sponsorship. This supplement was sponsored by a generous donation from Mr. Paul Mielnik and his family to help raise awareness and advance the care of patients with meningiomas worldwide.

Authorship statement. Concept and design: AD, MJ, JM. Drafting and revising the article: AD, MJ, TG, SVe, SVa, KY, NM, NB, ZC, DM, RF, ZE, MG, JM. Final approval: AD, MJ, TG, S.Vetsa, S.Vasandani, KY, NM, NB, ZC, DM, RF, ZE, MG, JM

References

1. Dolecek TA, Propp JM, Stroup NE, Kruchko C. CBTRUS statistical report: primary brain and central nervous system tumors diagnosed in the United States in 2005-2009. *Neuro Oncol.* 2012;14(Suppl 5):v1–49.
2. Epidemiology of meningioma in the United Kingdom. PubMed. Accessed February 19, 2022. https://pubmed.ncbi.nlm.nih.gov/22777495/

3. Annegers JF, Schoenberg BS, Okazaki H, Kurland LT. Epidemiologic study of primary intracranial neoplasms. *Arch Neurol.* 1981;38(4):217–219.
4. Vernooij MW, Ikram MA, Tanghe HL, et al. Incidental findings on brain MRI in the general population. *N Engl J Med.* 2007;357(18):1821–1828.
5. Xue H, Sveinsson O, Tomson T, Mathiesen T. Intracranial meningiomas and seizures: a review of the literature. *Acta Neurochir.* 2015;157(9):1541–1548.
6. Englot DJ, Chang EF, Vecht CJ. Chapter 16 - Epilepsy and brain tumors. In: Berger MS, Weller M, eds. *Handbook of Clinical Neurology. Vol* 134. *Gliomas*. Elsevier; 2016:267–285. doi:10.1016/B978-0-12-802997-8.00016-5
7. Chozick BS, Reinert SE, Greenblatt SH. Incidence of seizures after surgery for supratentorial meningiomas: a modern analysis. *J Neurosurg.* 1996;84(3):382–386.
8. Lieu AS, Howng SL. Intracranial meningiomas and epilepsy: incidence, prognosis and influencing factors. *Epilepsy Res.* 2000;38(1):45–52.
9. Davis FG, Kupelian V, Freels S, McCarthy B, Surawicz T. Prevalence estimates for primary brain tumors in the United States by behavior and major histology groups. *Neuro Oncol.* 2001;3(3):152–158.
10. Wiemels J, Wrensch M, Claus EB. Epidemiology and etiology of meningioma. *J Neurooncol.* 2010;99(3):307–314.
11. Waagemans ML, van Nieuwenhuizen D, Dijkstra M, et al. Long-term impact of cognitive deficits and epilepsy on quality of life in patients with low-grade meningiomas. *Neurosurgery* 2011;69(1):72–78. discussion 78–79.
12. Gupte TP, Li C, Jin L, et al. Clinical and genomic factors associated with seizures in meningiomas. *J Neurosurg.* 2020;1(aop):1–10.
13. Englot DJ, Magill ST, Han SJ, et al. Seizures in supratentorial meningioma: a systematic review and meta-analysis. *J Neurosurg.* 2016;124(6):1552–1561.
14. Whittle IR, Smith C, Navoo P, Collie D. Meningiomas. *The Lancet* 2004;363(9420):1535–1543.
15. Chaichana KL, Pendleton C, Zaidi H, et al. Seizure control for patients undergoing meningioma surgery. *World Neurosurg.* 2013;79(3):515–524.
16. Chen WC, Magill ST, Englot DJ, et al. Factors associated with pre- and postoperative seizures in 1033 patients undergoing supratentorial meningioma resection. *Neurosurgery* 2017;81(2):297–306.
17. Sughrue ME, Rutkowski MJ, Chang EF, et al. Postoperative seizures following the resection of convexity meningiomas: are prophylactic anticonvulsants indicated? Clinical article. *J Neurosurg.* 2011;114(3):705–709.
18. Li X, Wang C, Lin Z, et al. Risk factors and control of seizures in 778 Chinese patients undergoing initial resection of supratentorial meningiomas. *Neurosurg Rev.* 2020;43(2):597–608.
19. Schaller B. Influences of brain tumor-associated pH changes and hypoxia on epileptogenesis. *Acta Neurol Scand.* 2005;111(2):75–83.
20. van Breemen MSM, Wilms EB, Vecht CJ. Epilepsy in patients with brain tumours: epidemiology, mechanisms, and management. *Lancet Neurol.* 2007;6(5):421–430.
21. Harward SC, Rolston JD, Englot DJ. Chapter 18 - Seizures in meningioma. In: McDermott MW, ed. *Handbook of Clinical Neurology. Vol 170. Meningiomas, Part II*. Elsevier; 2020:187–200.
22. Spille DC, Heß K, Sauerland C, et al. Brain invasion in meningiomas: incidence and correlations with clinical variables and prognosis. *World Neurosurg* 2016;93:346–354.
23. Zeltner L, Schittenhelm J, Mittelbronn M, et al. The astrocytic response towards invasive meningiomas. *Neuropathol Appl Neurobiol.* 2007;33(2):163–168.
24. Fritz J, Roser F, Tatagiba M, Bornemann A. The basement membrane at the tumour-brain interface of brain-invasive grade I meningiomas. *Neuropathol Appl Neurobiol.* 2005;31(3):339–342.
25. Hess K, Spille DC, Adeli A, et al. Brain invasion and the risk of seizures in patients with meningioma. *J Neurosurg.* 2018;130(3):789–796.
26. de Vries J, Wakhloo AK. Cerebral oedema associated with WHO-I, WHO-II, and WHO-III-meningiomas: correlation of clinical, computed tomographic, operative and histological findings. *Acta Neurochir (Wien)* 1993;125(1-4):34–40.
27. Kawaguchi T, Kameyama S, Tanaka R. Peritumoral edema and seizure in patients with cerebral convexity and parasagittal meningiomas. *Neurol Med Chir (Tokyo).* 1996;36(8):568–574.
28. Iwado E, Ichikawa T, Kosaka H, et al. Role of VEGF and matrix metalloproteinase-9 in peritumoral brain edema associated with supratentorial benign meningiomas. *Neuropathology* 2012;32(6):638–646.
29. Lambertz N, Hindy NE, Adler C, et al. Expression of aquaporin 5 and the AQP5 polymorphism A(-1364)C in association with peritumoral brain edema in meningioma patients. *J Neurooncol.* 2013;112(2):297–305.
30. Ng WH, Hy JW, Tan WL, et al. Aquaporin-4 expression is increased in edematous meningiomas. *J Clin Neurosci.* 2009;16(3):441–443.
31. Osawa T, Tosaka M, Nagaishi M, Yoshimoto Y. Factors affecting peritumoral brain edema in meningioma: special histological subtypes with prominently extensive edema. *J Neurooncol.* 2013;111(1):49–57.
32. Haglund MM, Berger MS, Kunkel DD, et al. Changes in gamma-aminobutyric acid and somatostatin in epileptic cortex associated with low-grade gliomas. *J Neurosurg.* 1992;77(2):209–216.
33. Lobato RD, Alday R, Gómez PA, et al. Brain oedema in patients with intracranial meningioma. *Acta Neurochir.* 1996;138(5):485–494.
34. Shamji MF, Fric-Shamji EC, Benoit BG. Brain tumors and epilepsy: pathophysiology of peritumoral changes. *Neurosurg Rev.* 2009;32(3):275–284; discussion 284.
35. Kotsopoulos IAW, Van Merode T, Kessels FGH, De Krom MCTFM, Knottnerus JA. Systematic review and meta-analysis of incidence studies of epilepsy and unprovoked seizures. *Epilepsia* 2002;43(11):1402–1409.
36. Mehta N, Bhagwati S, Parulekar G. Meningiomas in children: a study of 18 cases. *J Pediatr Neurosci.* 2009;4(2):61–65.
37. Brokinkel B, Hess K, Mawrin C. Brain invasion in meningiomas—clinical considerations and impact of neuropathological evaluation: a systematic review. *Neuro-Oncology* 2017;19(10):1298–1307.
38. Louis DN, Perry A, Wesseling P, et al. The 2021 WHO classification of tumors of the central nervous system: a summary. *Neuro-Oncology* 2021;23(8):1231–1251.
39. Hess K, Spille DC, Adeli A, et al. Brain invasion and the risk of seizures in patients with meningioma. *J Neurosurg.* 2018;130(3):789–796.
40. Mantle RE, Lach B, Delgado MR, Baeesa S, Bélanger G. Predicting the probability of meningioma recurrence based on the quantity of peritumoral brain edema on computerized tomography scanning. *J Neurosurg.* 1999;91(3):375–383.
41. Hou J, Kshettry VR, Selman WR, Bambakidis NC. Peritumoral brain edema in intracranial meningiomas: the emergence of vascular endothelial growth factor–directed therapy. *Neurosurg Focus.* 2013;35(6):E2E2.
42. Mohme M, Emami P, Regelsberger J, et al. Secretory meningiomas: increased prevalence of seizures secondary to edema formation in a rare histologic subtype. *World Neurosurg.* 2016;92:418–425.
43. Wang Y, Yang C, Gu Q, et al. KLF4 promotes angiogenesis by activating VEGF signaling in human retinal microvascular endothelial cells. *PLoS One.* 2015;10(6):e0130341e0130341.
44. Acker T, Diez-Juan A, Aragones J, et al. Genetic evidence for a tumor suppressor role of HIF-2alpha. *Cancer Cell* 2005;8(2):131–141.
45. Skardelly M, Rother C, Noell S, et al. Risk factors of preoperative and early postoperative seizures in patients with meningioma: a retrospective single-center cohort study. *World Neurosurg.* 2017;97:538–546.
46. Chaichana KL, Pendleton C, Zaidi H, et al. Seizure control for patients undergoing meningioma surgery. *World Neurosurg.* 2013;79(3-4):515–524.
47. Islim AI, Mohan M, Moon RDC, et al. Incidental intracranial meningiomas: a systematic review and meta-analysis of prognostic factors and outcomes. *J Neurooncol.* 2019;142(2):211–221.

48. Youngblood MW, Duran D, Montejo JD, et al. Correlations between genomic subgroup and clinical features in a cohort of more than 3000 meningiomas. *J Neurosurg.* 2019;133(5):1345–1354.
49. Harmancı AS, Youngblood MW, Clark VE, et al. Integrated genomic analyses of de novo pathways underlying atypical meningiomas. *Nat Commun.* 2017;8(1):14433.
50. Baumgarten P, Sarlak M, Baumgarten G, et al. Focused review on seizures caused by meningiomas. *Epilepsy Behav.* 2018;88:146–151.
51. Chozick BS, Reinert SE, Greenblatt SH. Incidence of seizures after surgery for supratentorial meningiomas: a modern analysis. *J Neurosurg.* 1996;84(3):382–386.
52. Chow SY, Hsi MS, Tang LM, Fong VH. Epilepsy and intracranial meningiomas. *Zhonghua Yi Xue Za Zhi (Taipei)* 1995;55(2):151–155.
53. Das RR, Artsy E, Hurwitz S, et al. Outcomes after discontinuation of antiepileptic drugs after surgery in patients with low grade brain tumors and meningiomas. *J Neurooncol.* 2012;107(3):565–570.
54. Islim AI, Ali A, Bagchi A, et al. Postoperative seizures in meningioma patients: improving patient selection for antiepileptic drug therapy. *J Neurooncol.* 2018;140(1):123–134.
55. Ramamurthi B, Ravi B, Ramachandran V. Convulsions with meningiomas: incidence and significance. *Surg Neurol.* 1980;14(6):415–416.
56. Clark VE, Erson-Omay EZ, Serin A, et al. Genomic analysis of non-NF2 meningiomas reveals mutations in TRAF7, KLF4, AKT1, and SMO. *Science* 2013;339(6123):1077–1080.
57. Zheng Z, Chen P, Fu W, et al. Early and late postoperative seizure outcome in 97 patients with supratentorial meningioma and preoperative seizures: a retrospective study. *J Neurooncol.* 2013;114(1):101–109.
58. Das RR, Artsy E, Hurwitz S, et al. Outcomes after discontinuation of antiepileptic drugs after surgery in patients with low grade brain tumors and meningiomas. *J Neurooncol.* 2012;107(3):565–570.
59. Ramamurthi B, Ravi B, Ramachandran V. Convulsions with meningiomas: incidence and significance. *Surg Neurol.* 1980;14(6):415–416.
60. Wirsching HG, Morel C, Gmür C, et al. Predicting outcome of epilepsy after meningioma resection. *Neuro-Oncol.* 2016;18(7):1002–1010.
61. Schneider M, Güresir A, Borger V, et al. Preoperative tumor-associated epilepsy in patients with supratentorial meningioma: factors influencing seizure outcome after meningioma surgery. *J Neurosurg.* 2019;1(aop):1–7.
62. Gadot R, Khan AB, Patel R, et al. Predictors of postoperative seizure outcome in supratentorial meningioma. *J Neurosurg.* 2021;1(aop):1–10.
63. Lieu AS, Howng SL. Intracranial meningiomas and epilepsy: incidence, prognosis and influencing factors. *Epilepsy Res.* 1999;38(1):45–52.
64. Chan RC, Thompson GB. Morbidity, mortality, and quality of life following surgery for intracranial meningiomas. A retrospective study in 257 cases. *J Neurosurg.* 1984;60(1):52–60.
65. Zhang B, Zhao G, Yang HF, et al. Assessment of risk factors for early seizures following surgery for meningiomas using logistic regression analysis. *J Int Med Res.* 2011;39(5):1728–1735.
66. Glauser T, Ben-Menachem E, Bourgeois B, et al. Updated ILAE evidence review of antiepileptic drug efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes. *Epilepsia* 2013;54(3):551–563.
67. Blumcke I, Aronica E, Urbach H, Alexopoulos A, Gonzalez-Martinez JA. A neuropathology-based approach to epilepsy surgery in brain tumors and proposal for a new terminology use for long-term epilepsy-associated brain tumors. *Acta Neuropathol.* 2014;128(1):39–54.
68. Greenhalgh J, Weston J, Dundar Y, Nevitt SJ, Marson AG. Antiepileptic drugs as prophylaxis for postcraniotomy seizures. *Cochrane Database Syst Rev.* 2020(4).