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Clinical management of seizures in patients with meningiomas: Efficacy of surgical resection for seizure control and patient-tailored postoperative anti-epileptic drug management

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Abstract

Meningiomas are the most common primary intracranial tumor. They are slow growing and often incidentally found tumors that arise from the arachnoid villi. As they grow, they have a greater likelihood of becoming symptomatic with seizures being one of the most clinically significant symptoms. Seizures are more likely to present as a symptom of larger meningiomas and meningiomas that compress cortical areas particularly those in non-skull base locations. These seizures are often managed medically, utilizing the same anti-seizure medications that are used to treat other causes of epilepsy. We discuss common anti-seizure medications used including valproate, phenobarbital, carbamazepine, phenytoin, lacosamide, lamotrigine, levetiracetam and topiramate and their common adverse effects. The goal of pharmacotherapy for seizure control is to maximize seizure control while minimizing the adverse effects of the medication. The decision to provide medical management is dependent on individual seizure history and plans for surgical treatment. Patients who did not require seizure prophylaxis before surgery are commonly prescribed seizure prophylaxis postoperatively. Symptomatic meningiomas not controlled by medical management alone are commonly evaluated for surgical resection. The efficacy of surgical resection in providing seizure freedom is dependent on several features of the tumor including tumor size, the extent of the peritumoral edema, the number of tumors, sinus infiltration and the degree of resection.

Keywords

anti-seizure medications | meningioma | peritumoral edema | seizure

Meningiomas are tumors derived from arachnoid cap cells within arachnoid villi. These tumors are often discovered incidentally because they are slow growing but, as they become larger, they begin to cause symptoms as a direct result of their mass effect as well as their area of surrounding edema, termed peritumoral edema (PTE). Significant PTE is

rare but commonly seen in association with higher grade meningiomas and secretory meningiomas.[1] Seizures are one of the most clinically significant symptoms caused by meningiomas, occurring in roughly 30% of patients.[2] Meningiomas compressing cortical areas, as well as larger meningiomas, have a greater propensity to cause either focal or generalized seizures.[3] Furthermore, literature has shown that the risk for seizure is increased in tumors that grow along the brain's surface as opposed to the skull base because these tumors are more often located in a region where they can compress cortical tissue that is susceptible to epileptogenesis (Table 1).[4,5] Other individual characteristics that increase the likelihood of seizure in patients diagnosed with meningiomas include age less than 18 years and male gender.[6] Tumor characteristics that increase the likelihood of seizure being WHO grade 2–3, larger than 3.5 cm in diameter and parasagittal or falcine in location[7–9] (Table 2). Without intervention, roughly one-third of patients with meningiomas will have a seizure.[2,10] For these patients, healthcare providers may opt for either surgical intervention as a means of removing the mass and potentially alleviating seizure burden, or medical intervention to lessen the frequency of seizures and potentially improve the patient's quality of life. In this review we will discuss the efficacy of surgical intervention in controlling seizures that occur due to meningioma as well as the utility of anti-seizure medication (ASMs) in individuals preoperatively and postoperatively, weighing the potential risks and benefits of commonly used ASMs.

Risk Factors

The majority of meningiomas occur sporadically with no identifiable cause.[11] The incidence of meningiomas is greater in familial syndromes including neurofibromatosis type 2 (NF2), an autosomal dominant disorder that is caused by a loss-of-function mutation in a tumor-suppressor protein. Meningiomas are also associated with Li-Fraumeni syndrome, Gorlin syndrome, multiple endocrine neoplasia (MEN) type 1, multiple meningiomatosis and Cowden disease. Additional risk factors increasing the incidence of meningiomas include prior ionizing radiation to the skull as well as lifestyle factors such as obesity.[12] Conversely, numerous epidemiological associations including cigarette smoking, history of head trauma, and cell phone usage have not been definitively linked to an increased risk in meningiomas, though this may be data may be confounded by biases such as poor recall.[13]

Table 1. Features of Meningiomas Associated with High Risk for Preoperative, Perioperative, and Postoperative Seizures: Male Gender, Size > 8 cm, Cortical Location (tumor shown in green along the falx), Peritumoral Edema (depicted in red), and Prior Seizure

Features of that increase seizure risk in meningioma patients
Male gender
Size greater than 8 cm
Parasagittal/falcine location
Significant PTE
History of prior seizure

Epidemiology

Meningiomas are the most common primary intracranial tumor making up approximately one-third of all primary brain tumors. It is estimated that there are approximately 29,000 newly diagnosed meningiomas in the United States yearly with Black Americans having a 1.2-fold greater incidence than White Americans and a 2:1 female to male predominance. The reason for this female to male bias partially correlates to an increased level of endogenous sex hormone levels as the bias increases to approximately 3:1 during childbearing years.[14] This connection between hormone levels and meningioma incidence is due to the expression of estrogen and progesterone receptors by meningiomas. Estrogen and progesterone have proven not to be tumorigenic, rather their presence allows for increased growth of meningiomas when the tumors are present.[15] The incidence of meningioma also increases with age, with an incidence of 0.14 per 100,000 in individuals 0–19 years of age and 37.75 per 100,000 in individuals 75–84 years of age, with 65 being the median age of diagnosis for meningiomas occurring sporadically.

Efficacy of Surgical Resection on Seizure Control

Upon initial diagnosis of small, asymptomatic meningiomas, many patients undergo observation including routine surveillance imaging. However, once a tumor becomes symptomatic, particularly from seizures, surgical resection has become the standard of care when there is confidence that full resection can be accomplished, and that the patient's surgical risk is reasonable. It is imperative to note that the seizures that occur in the setting of meningiomas occur as a result of mass effect caused by the tumor. These tumors are typically only removed when presenting with symptoms which are commonly due to mass effect. Factors that affect the decision to offer surgical resection include tumor location, as well as involvement

Table 2. Factors Associated with Increased Risk of Seizure in Patients Diagnosed with Meningioma in the Preoperative Setting

Factors increasing the rate of seizure in meningioma
Male gender[6]
< 18 years of age[6]
No neurological deficit[4]
The presence of PTE[4]
WHO Grade 2–3[7]
Parasagittal/falcine location[8]
Diameter > 3.5 cm[9]

Table 3. Efficacy of Surgical Resection or Radiosurgery for Meningioma in Seizure Control

Efficacy of surgery and radiotherapy in seizure control	
Study	Factors that influence surgical seizure control
Gadot et al. [17]	Seizure freedom was attained in 74% of patients following meningioma resection with a median follow up period of 17 months. Resolution of seizure postoperatively was associated with lack of postresection ischemia, lack of recurrent disease, lower WHO grade and lower MIB-1 index
Chaichana et al. [18]	In this cohort, 90% of patients remained seizure-free in a 48-month period following primary resection of WHO grade 1 meningioma
Schneider et al. [19]	In 187 patients with meningioma who had seizures preoperatively, 169 (90%) achieved seizure freedom following surgical resection of meningioma. Predictors for continuation of seizures postoperatively included low extent of resection, larger PTE diameter and greater WHO grade
Xue et al. [9]	In 21 patients with meningioma who had seizures preoperatively, 8 (38.1%) achieved seizure freedom following surgical resection of the meningioma
El-Khatib et al. [20]	129 patients were followed for a median of 12 years following stereotactic linear accelerator radiosurgery for meningioma. In this cohort, 77 patients (59.7%) displayed neurological improvement or decreased seizure burden
Englot et al. 2016[2]	69.3% of 703 patients diagnosed with preoperative seizures became seizure-free post-resection of meningioma. Seizure postoperatively was twice as likely in patients with PTE
Hwang et al. 2019[21]	The most significant predictors of seizure following radiosurgery were peritumoral edema (odds ratio, 53.99; 95% confidence interval, 5.214–559.1; $P = .001$) and brain tumor contact-surface index (odds ratio, 2.466; 95% confidence interval, 1.183–5.138; $P = .016$)
El-Khatib et al. 2011[22]	Of 129 participants, the neurological symptoms existing before SRS improved in 77 patients (59.7 %), remained unchanged in 42 (32.6 %), and deteriorated in 10 (7.8 %) patients

of nearby intracranial structures such as dural venous sinuses, arteries, and cranial nerves. In a case where a patient is not an optimal surgical candidate, surgeons will often continue interval imaging surveillance while seizures are medically managed utilizing ASMs. Surgical management is more urgent when seizures become refractory to two or more anti-seizure medications, often with contributing cortical irritation from the tumor or peritumoral edema (PTE). The goal of surgical resection, even if subtotal, is to improve seizure control or clinical symptoms. Unfortunately, due to risk of eloquent structures, total surgical resection is not always possible and even if achieved, the cortical irritation may persist.[16] Thus, resolution of seizures postoperatively is not always attained.

Several studies have compared the efficacy of surgical resection and radiosurgery in decreasing the number of seizures in postoperatively (Table 3). Gadot et al.[17] reviewed 384 patients with meningiomas of whom 59 had preoperative seizures. Seizure freedom was attained in 74% of patients. In multivariable analysis, absence of postresection ischemia ($P = .012$), WHO grade 1 tumor histology ($P = .022$), lack of residual disease ($P = .038$), and low MIB-1 index ($P = .002$) were all predictive of favorable seizure outcome. Regarding tumor location, Chaichana et al. reviewed 626 patients with supratentorial meningiomas, of whom 84 had preoperative seizures. In this cohort, 90% of patients achieved seizure freedom compared to patients with parasagittal tumors ($P = .03$) and sphenoid wing ($P = .05$) who had greater risk for postoperative seizures.[18] Schneider et al.[19] reviewed 187 patients who had preoperative seizures and remarkably, 90% of patients experienced seizure freedom after tumor resection. Factors associated with failure to achieve seizure freedom included tumor size > 4 cm ($P = .02$), significant PTE ($P = .007$), multiple tumors ($P = .02$), WHO Grade 2 or 3 ($P = .02$), sinus infiltration ($P = .03$), incomplete resection ($P = .004$), and tumor progression ($P = .02$). These findings are supported in a retrospective analysis by Conti et al.[23] which ultimately concluded that the degree of PTE that occurs following stereotactic radiosurgery (SRS) is dependent on characteristics of the meningioma such as tumor volume greater than 4.5 mL, non-basal location, and atypical histology rather than the method of treatment that is used. However, there appears the be a lack of consensus regarding the correlation between the presence of preoperative seizures and likelihood of postoperative seizures. In a retrospective study by Xue et al., 113 adults with meningioma were assessed for seizure occurrence postoperatively. Of this cohort of patients 21 of the 113 (18.6%) experienced seizure preoperatively. Following surgery, 8 of the 21 (38.1%) demonstrated absence of seizures in the seven-year period they were followed. Utilizing regression analysis, this study demonstrated that history of preoperative seizure is associated with the persistence of postoperative seizure (OR 3.50, 95% CI 1.55–7.90).[9]

SRS also lessens the seizure burden on patients diagnosed with meningioma, but perhaps to a lesser degree than surgical resection. El-Khatib et al. followed 129 patients for a median of 12 years (range 1.1–21.6 years) following stereotactic linear accelerator radiosurgery for meningioma. They found that 77 patients (59.7%) displayed neurological improvement or decreased seizure burden. However, 42 patients (32.6%) had no change in their seizure frequency, and 15 (11.7%) developed new neurological symptoms including seizure following treatment.[20]

In a large meta-analysis summarizing the findings on this topic, Englot et al. identified 4709 patients with supratentorial meningiomas of whom 69.3% of patients became seizure-free post-resection. Among patients with preoperative seizures, presence of peritumoral edema ($P < .001$), sphenoid wing location ($P = .05$), and tumor

progression ($P < .05$) were associated with ongoing postoperative seizures. Amongst patients without preoperative seizures, previous radiation treatment for the meningioma ($P < .01$), sub-total resection ($P = .02$), and tumor progression ($P < .05$) were associated with the development of postoperative seizures. Recognizing which patients are at greatest risk for postoperative seizures (Table 1) is important in managing ASMs during this timeframe.

Seizure Prophylaxis with Anti-Seizure Medications in Patients with Meningiomas

The symptomatic seizures occurring in patients with meningiomas are typically responsive to anti-seizure medication. To lessen the seizure burden in patients with meningiomas, commonly used broad spectrum anti-seizure medications are typically the first-line of therapy. Guidelines built from numerous studies including a large meta-analysis have stated there is no benefit to ASM prophylaxis for seizure-naïve patients with brain tumors. Nonetheless, many providers still opt to utilize these medications.[24–26] Clinicians should separate adverse effects of medication from adverse effects of surgery/radiation/tumor. The cost of anti-seizure medication can be substantial and should be considered while planning outpatient therapy. The data regarding seizure prophylaxis for seizure-naïve patients and patients with prior seizure will be reviewed at three time points in patient care: prior to or in the absence of surgery, peri-operatively, and postoperatively.

Nonoperative and Preoperative Seizure Prophylaxis

The guidelines from the American Academy of Neurology and the Congress of Neurological Surgeons regarding ASM prophylaxis in seizure-naïve patients with brain tumors who are not undergoing surgery are clear: ASMs offer no benefit and should not be used.[25,26] Real world practice is inconsistent and treatment decisions are made on a case-by-case basis.[24] Factors may include tumor size, location, and the extent of PTE.[27] Despite several studies, there is no current evidence to support seizure prophylaxis with ASMs in patients who have not yet had a seizure. There have been studies that concluded the rate of seizure postoperatively is not high enough to outweigh potential ASM adverse effects. Thus, they should not be used if not absolutely implicated. A randomized trial conducted by Wu et al., observed the rate of postoperative seizure in patients undergoing craniotomy for tumor resection who had not had any seizure preoperatively. They were randomized to receive phenytoin for 7 days postoperatively or no seizure prophylaxis. Incidence of early seizure (less than 30 days after surgery) was 8% in those without prophylaxis and 10% with prophylaxis ($P = 1.0$).[28] Based on the literature, there appears to be support for withholding seizure prophylaxis in patients who have not yet had a seizure is reasonable, even if they are going to undergo surgery for tumor removal based upon the small difference in seizure incidence in those who receive prophylaxis versus those who do not receive prophylaxis.

On the other hand, there is literature recommending prophylaxis in seizure-naive patients who display one or more risk factors for increased peri-operative seizure including the absence of focal neurological deficit, the presence of peri-tumoral vasogenic edema, and non-skull base location of tumor origin.[3,4]

In patients with symptomatic epilepsy from meningiomas, most healthcare providers and care guidelines affirm ASMs are appropriate therapy. Symptomatic epilepsy is often responsive to ASMs. Medication choice is based upon seizure type, and any comorbidities such as headache, mood disorders, metabolic disease, etc. Medications should be titrated to efficacy or toxicity prior to adding a second ASM (either in combination or substituted for the first).[6]

Postoperative Seizure Prophylaxis

ASMs are a mainstay in peri-operative neurosurgical care except in rare circumstances, but the duration of peri-operative therapy is highly variable in the absence of defined guidelines. Such practice is based upon historically high incidence of postoperative seizures and several nonrandomized studies have suggested efficacy; however, none have provided Level 1 evidence.[29] Youngerman et al.[29] suggests that this variation may also be dependent upon geographic variation, availability of post-discharge services, and electronic prescribing defaults that provide predetermined number of doses and refills when a drug is being prescribed. As with preoperative decision making, there is a lack of clear consensus regarding whether the benefits outweigh the risks in patients who have not had a seizure previously. Additionally, the decision to begin seizure prophylaxis with ASMs is guided by the presence of key risk factors that make the development of seizures more likely (Table 1). In the absence of these risk factors, data suggests that the incidence of seizures is not significant and thus the adverse effects inherent to ASMs[30,31] outweigh the seizure-associated risks. According to Scarcely et al., seizure prophylaxis can be considered in patients who are at high risk of developing seizures [male gender (odds ratio [OR], 2.06; $P = .009$), a non-skull base location (OR, 4.43; $P < .001$), and a tumor volume of > 8 cm^3 (OR, 3.05; $P = .002$)], There was no reduction in the frequency of early postoperative seizure despite peri-operative ASMs being given. Of the 537 patients observed, 23 (5%) without preoperative seizure received peri-operative ASMs. An increased rate of seizure was observed in those that received levetiracetam compared to no medication (OR, 2.69; 95% CI 1.14–5.81) and an even higher rate of seizure was observed in those receiving a combination of other ASMs (OR, 8.57; 95% CI 3.43–20.2).[30] Additionally the findings of Sugrue et al., suggest that the rate of postoperative seizure following resection of meningioma is low enough that the costs of prophylactic ASM use outweigh the benefits. Of the 180 patients they observed, 129 received ASMs and 51 did not. The rate of new onset seizure in those not on ASM was 1 out of 129 (1.9%) compared to the rate of 0% in the group receiving seizure prophylaxis.[31] These findings are supported by a large meta-analysis by Sirven et al.[24] which analyzed five studies. This included 403 patients with brain tumors including meningiomas, gliomas, metastases,

and other less common pathologies. The ASMs utilized were phenobarbital, phenytoin, and valproic acid; all patients had confirmed serum-drug levels. The findings demonstrated a lack of efficacy for early (OR = 0.91; 95% CI 0.45–1.83) and late (OR = 1.01; 95% CI 0.51–1.98) seizure prophylaxis. In this study, early prophylaxis was ASM therapy in a patient less than 2 years seizure-free and late prophylaxis was ASM therapy in a patient more than 2 years seizure-free. The authors summarize that in the lack of clear benefit, these drugs, which have significant side-effects, are not clearly beneficial to patients. Furthermore, a recent randomized control trial by Rahman et al.[32] demonstrated that in patients who underwent craniotomy for supratentorial brain tumor, the incidence of seizures is unchanged by duration of prophylactic levetiracetam (either 1 or 6 weeks) but the rate of mood complications was higher is the group of patients with longer therapy duration.

Conversely, there is compelling evidence for postoperative ASM use in patients with preoperative seizures as this is the greatest predictor of postoperative seizures.[23] ASMs trials in patients with preoperative seizures significantly lower the risk of postoperative seizures compared with the expected rate observed in patients who did not receive seizure prophylaxis. In this population, ASMs are typically started peri-operatively and their duration is tailored to the individual patient. The duration that the patient should remain on an ASM is dependent on the length of time that the patient is seizure-free but research on the subject is limited.[3] However, the existing research supports continuing seizure prophylaxis for 1 year following surgery if the patient remains seizure-free in this time. This is supported by the findings of Lieu and Howng[33] in a clinical trial where it was demonstrated that of a group of 52 patients who had postoperative seizures, 71.2% displayed were seizure-free for 1 year while on ASMs and were successfully tapered off. Islim et al.[34] demonstrated similar findings noting that within the 1st year postoperatively by approximately 40%, although this did not meet statistical significance. This data is different from the suggestions made by Beghi et al., who determined that seizure prophylaxis should be continued for at least 2 years following seizure freedom. This data was observed in a mixed cohort assessing seizure presence on both adults as well as children.[35]

Patient-Oriented Selection of Anti-Seizure Medication

Symptomatic epilepsy from meningiomas should be treated the same as other localization related seizure disorders. ASMs work by raising the seizure threshold, reducing the risk of seizures while also actively suppressing the seizures that do occur.[36] Monotherapy is preferred for seizure prevention and approximately two-thirds of patients that suffer from epileptic seizures are seizure-free with one medication.[37] In cases where this fails, providers may opt to place the patient on a combination regimen taking into consideration the drug-drug interactions as well as mechanism of action.[38] The addition of a third ASM should only be considered after maximizing dosages of a dual therapy ASM regimen. If a patient is already on a combination of two or three ASMs, addition of ASMs to the regimen is less likely to result in seizure freedom and the epilepsy is considered drug resistant.[39] Consultation with an epileptologist or comprehensive epilepsy program is recommended for drug-resistant epilepsy. Initially, healthcare providers s typically begin seizure prevention and prophylaxis with a broad spectrum ASM that protects against generalized seizures but this approach has begun to fall out of favor as the evidence supporting it was deemed to be largely anecdotal.[36] ASMs vary in their mechanism of action, dosing regimen, and adverse effects (Table 4). Due to the severity of many of their adverse effects, individuals taking ASMs may need regular monitoring of their medication levels. Currently, with the myriad of newer ASMs (termed second-generation anticonvulsants) approved for use in seizure prophylaxis, physicians have a wide array of medications to choose from with broader therapeutic ranges, fewer drug–drug interactions, and fewer adverse effects. This has made it easier for healthcare providers to both maximize the efficacy of the drug while minimizing the burden of adverse effects on the patient.[36] In general, the newer medications are more expensive, and patients may have higher co-pays or share of cost, which can be burdensome.

Levetiracetam is the most prescribed second generations ASM. It theorized to inhibit calcium release from intra-neuronal stores, thus opposing the activity of negative modulators of GABA and lessening the excessive synchronized activity between neurons that contributes to seizure activity.

Levetiracetam is generally chosen as a first-line agent for seizure control. Though its mechanism is not thoroughly understood, it is known to bind to synaptic vesicle protein 2A (SV2A), a protein involved in calcium dependent neurotransmitter release. Its binding to this protein ultimately decreases the rate of vesicle release. This drug has shown both greater efficacy and tolerability than other ASMs, when used for the prophylaxis and treatment of focal seizures. Additionally levetiracetam is the favored drug for seizure control as it demonstrates rapid and complete absorption, a high oral bioavailability, renal excretion and does not interact with cytochrome P450.[40] Adverse effects of levetiracetam include headache and lethargy and fatigue, which may be dose limiting in the brain tumor patient population. Levetiracetam displays no significant drug–drug interactions with other ASMs, and its metabolism and clearance rate may be affected in patients simultaneously taking carbamazepine, Phenobarbital, or phenytoin.

Several anti-seizure medication may decrease neuronal firing by inhibiting sodium or calcium channels while others may increase inhibition. Phenobarbital, a first-generation ASM, increases GABA levels and GABA activity with the former acting as an inhibitor of GABA transaminase and the latter directly facilitating increased GABA release. Furthermore, it functions as a form of prophylactic or preventative therapy rather than as an abortive therapy for already ongoing seizures. Valproate is another first-generation ASM frequently used and is a first-line long-term treatment for tonic-clonic generalized seizures as well as focal seizures and established status epilepticus. Valproate can be taken orally and is dosed with the goal of remaining

Table 4. Commonly Used Anti-seizure Medications (ASMs), Their Primary Mechanisms of Action, Their Typically Prescribed Dosage Range in Milligrams (mg) Per Day, Indications for Drug Level Monitoring and Common Adverse Effects Associated with These Medications

Anti-seizure medications				
ASM	Primary mechanism of action	Typical dosage in adults (in mg per day)	Drug level monitoring	Adverse effects
Levetiracetam	Binding to synaptic vesicle Protein 2[49]	1000–3000[40]	No current indication	Asthenia (15%), somnolence (15%), headache (14%)[50]
Valproate	GABA-receptor agonist Sodium-channel blocker[41]	500–2500[41]	Initial therapeutic level Instances of suspected toxicity[41]	Nausea (48%), headache (31%), somnolence (27%), dizziness (25%), flu syndrome (12%), alopecia (6%)[51]
Phenobarbital	GABA-receptor agonist[41]	30–180[41]	Serum peak levels 2–8 h after initial intake and with dose increase[41]	Sedation (74%), dizziness (60%), memory difficulty (46%)[52]
Carbamazepine	Sodium-channel blocker[41]	400–1600[41]	At short intervals (such as every 3 weeks) following initiation and can gradually increase to longer intervals (such as every 3 months) Soon after beginning a medication that interacts with cytochrome P450[42]	Drowsiness (36%), nausea (32%), weight gain (8%), tremor (8%), rash (4%)[53]
Phenytoin	Sodium-channel blocker[41]	150–400[41]	Initial therapeutic level (24 h after last oral dose)[41]	Hypotension (1–10%), nausea (13%), bruising (1–10%), nystagmus (59%), dizziness (31%)[54]
Lacosamide	Slow sodium-channel blocker [55]	200–400[55]	No current indication	Dizziness (23%), somnolence (17%), headache (14%), nausea (10%)[56]
Lamotrigine	Sodium-channel blocker[41]	200–600[44]	No current indication	Headache (29%), nausea (19%), dizziness (38%), diplopia (28%), rash (10%)[57]
Topiramate	Sodium-channel blocker GABA-receptor agonist[41]	100–500[45]	Concurrent use of another medication that interacts with cytochrome P450[45]	Fatigue (15%), dizziness (25%), ataxia (16%), nausea (10%), somnolence (29%)[58]

within the therapeutic index. To assess if an individual is within the therapeutic index for the drug serum concentration of valproate can be measured using a serum valproic acid test. It is typically ordered at the beginning of treatment with the medication, is not routinely monitored but can be assessed in the case of suspected toxicity. Valproate toxicity often presents with encephalopathy, hepatotoxicity, and electrolyte abnormalities.[41] It also carries the adverse effects of pancreatitis, alopecia, tremor, agranulocytosis, and teratogenicity as well as, inhibiting cytochrome P450 leading to increased serum levels of other drugs such as warfarin. Phenobarbital is a direct agonist of GABA by increasing the length of time that the chloride channels that facilitate GABA release are open. Phenobarbital must be dosed carefully as it has the risk of causing respiratory and cardiac depression, sedation, dependency, and tolerance. Following the initial administration or increases in dosage, the peak serum level of phenobarbital will need to be measured and is done so 2–8 h following intake. Expert judgment should be used when increasing the dose of phenobarbital as tolerance to the drug can display individuals requiring larger doses for the same degree of seizure control. As the maximum dose is approached other pharmacologic methods for seizure prophylaxis may need to be explored. Another first-generation ASM, carbamazepine, is effective as a prophylactic anti-seizure medication. Carbamazepine has two important mechanisms of action that allow it to prevent and dampen seizure activity. It impacts synaptic transmission increasing GABA release and decreasing glutamate release and reducing the high-frequency repetitive firing of action potentials that are responsible for seizure activity. Carbamazepine does this by increasing the inactivation of the sodium channels that enable action potentials.[42] Monitoring of serum levels of carbamazepine is obligated for anyone on the medication as the adverse effects of this drug directly correlate with the serum levels. The increase in serum levels will often precede the observation of the drug's adverse effects and can prompt necessary modifications to an individual's drug regimen before severe effects occur. Serum levels should be measured often and at regular intervals such as every 3 weeks following the initiation of the drug and then the interval between serum-drug level measurement can be increased to approximately every 3 months or soon after beginning a medication that induces or inhibits the cytochrome. Adverse effects of carbamazepine that can occur with a serum level elevated above the therapeutic index include rash, agranulocytosis, toxicity, ataxia, syndrome

of inappropriate antidiuretic hormone secretion, Steven-Johnson syndrome, and teratogenicity. Additionally, carbamazepine is an inducer of cytochrome P450 decreasing the serum concentration of drugs that are metabolized by this cytochrome.[43]

Second-generation ASMs that are commonly utilized in seizure prophylaxis are lamotrigine and topiramate. The mechanism by which lamotrigine works is not fully understood. Research has demonstrated that it binds to the voltage-gated sodium channels of presynaptic neurons stabilizing their membranes and subsequently inhibiting the presynaptic release of glutamate.[41] It is theorized that lamotrigine may exhibit its anti-seizure properties through additional mechanisms such as by interacting with calcium-gated channels as well. Adverse effects of lamotrigine include Stevens-Johnson syndrome, aseptic meningitis, hemophagocytic lymphohistiocytosis, and suicidal behaviors and/or ideations. It is not commonplace to regularly measure the serum levels of lamotrigine and as is the case for several of the second-generation ASMs because there is limited data supporting or refuting this practice because the relationship between serum-drug levels and efficacy of these medications is poorly understood.[44]

Topiramate causes inhibition of voltage-gated sodium channels, decreasing synaptic excitability by decreasing the frequency of action potentials that can occur. It is not commonplace for physicians to recommend that patients taking topiramate have their serum levels regularly assessed. However, research has shown that patients taking topiramate in addition to other ASMs that may increase the serum levels of the medication through inhibition of cytochrome P450 could benefit from serum testing to ensure that they remain in the therapeutic window for topiramate in the setting of altered metabolism.[45] Adverse effects of topiramate include cognitive impairment, weight loss, decreased sweating with the potential to cause heat intolerance and hyperthermia, metabolic acidosis and acute myopia, and secondary angle glaucoma.[46–48]

Conclusion

Meningiomas are common primary brain tumors with higher incidence in women and are generally associated with low morbidity and mortality. With increased tumor size, higher grade, greater area of PTE, and interaction with epileptogenic brain parenchyma foci, a significant seizure burden affects one-third of individuals diagnosed with sporadically occurring meningiomas, impacting quality of life for these patients and their families and in several cases can be debilitating. Gross total resection is the first-line treatment in patients with non-skull base meningiomas and if the entire mass can be resected, the incidence of ongoing seizures is minimized, increasing their quality of life postoperatively. The change in seizure burden is affected by a combination of preoperative factors such as the frequency of seizure, intra-operative factors such as the degree of tumor removal, and postoperative factors such as tumor recurrence.

In cases where operative intervention is not possible, either due to the characteristics of the tumor location, or the patient having contraindications to surgery such as advanced age or poor functional status, pharmacologic interventions can be utilized to lessen the incidence of seizures in these patients. ASMs can be used as monotherapy or combination therapy, but are associated with extensive side effect profile, and care must be taken to regularly follow these patients assessing for the development of these adverse effects and potentially altering their care regimen when necessary. Furthermore, expert judgment must be used to decide whether a patient truly needs to be placed on seizure prophylaxis and subject to the risks associated with these medications and cost of therapy.

Regarding the initial decision to place a patient on seizure prophylaxis, the literature supports taking a more conservative approach in patients who are seizure-naïve because the risks associated with ASMs outweigh the potential benefits. In these individuals, the incidence of seizure pre- and postoperatively is not increased enough to justify the adverse effects of ASMs. Alternatively, patients who have documented history of seizure in the setting of meningioma diagnosis are candidates for seizure prophylaxis pre- and postoperatively following the same medication regimen as those who are affected by idiopathic epilepsy. Regarding the duration of seizure prophylaxis, this is a topic that could benefit from additional research as there is a lack thereof. We discussed the existing literature on recommended ASM duration and taking this data into account, we recommend that ASMs be continued for 1 year if the patient remains seizure-free during this period. This data applies only to adults as we noted the literature recommends a longer duration of seizure treatment in children. In the incidence that the patient does have a seizure they should continue prophylaxis for a minimum of 1 year following their most recent seizure. In the rare case that a patient has a seizure after recommended ASM discontinuation, we suggest that they are restarted on an ASM which should again be continued for at least 1 year.

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