Managing Common Complex Symptomatic Epilepsies: Tumors and Trauma

Jorge G. Burneo, MD, MPH,1 Joseph I. Sirven, MD,2 Lily Wong Kiesel, MD,3 Charles J Vecht, MD,4 Lara Jehi, MD,5 Steve S. Chung, MD,6 Joon Uhm, MD,7 Jeffrey M. Politsky, MD,8 Edward F. Chang, MD,9 Aatif M. Husain, MD,10 William O. Tatum, DO,11 Kimford J. Meador, MD,12 Katherine Noe, MD, PhD,13 Dale C. Hesdorffer, MD,14 Susan T. Herman, MD,15 Samuel Wiebe, MD,16 Jerome Engel, Jr, MD, PhD,17 Sara Schrader, MD,18 Karen L. Parko, MD,19 March A. Dichter, MD, PhD,20 Patrick Kwan, MD, PhD,21 Eric Kossoff, MD,22 Michael R. Sperling, MD23

1Epilepsy Program, Western University, London, Ontario, Canada
2Departments of Neurology, Mayo Clinic in Arizona, Phoenix, AZ
3Mayo Clinic, Rochester, MN
4Medical Centre the Hague, Netherlands
5Cleveland Clinic Neuroscience Institute, OH
6Barrow Neurological Institute, Phoenix, AZ
7Mayo Clinic, Rochester, MN
8Northeast Regional Epilepsy Group, Atlantic Neurosciences Institute, Summit, NJ
9University of California, San Francisco, CA
10Duke University Medical Center, Durham, NC
11Mayo Clinic, Jacksonville, FL
12Emory University, Atlanta, GA
13Mayo Clinic, Phoenix, AZ
14Columbia University, New York, NY
15Beth Israel Deaconess Medical Center, Boston, MA
16University of Calgary, Calgary, Alberta, Canada
17University of California, Reed Neurological Research, Los Angeles, CA
18University of California, Los Angeles, CA
19United States Public Health Service, San Francisco, CA
20University of Pennsylvania
21Chinese University of Hong Kong, Prince of Wales Hospital, Hong Kong
22Johns Hopkins Hospital, Baltimore, MD
23Thomas Jefferson University, Philadelphia, PA

Address correspondence to: Joseph I. Sirven, MD, Department of Neurology, Mayo Clinic in Arizona, 5777 East Mayo Blvd, Phoenix, AZ 85054, E-mail: sirven.joseph@mayo.edu

Head trauma and brain tumors are inextricably linked to epilepsy. Both traumatic brain injury and brain tumors are overrepresented in newly diagnosed patients with epilepsy, as well as in patients with drug-resistant focal epilepsy. Indeed, chronic seizures are the most cited problem associated with either of these conditions. However, managing complex cases of postrauematic epilepsy or tumor-based epilepsy can be a challenge for many epilepsy specialists. Currently, there is no clear understanding of the basic science that underpins the mechanism for epileptogenesis in patients with tumors or trauma so at present one cannot identify appropriate targets that could help prevent seizures and epilepsy from occurring. Because of these challenges, complex lesional epilepsy was chosen as the theme for this year’s 2012 American Epilepsy Society Annual Course.

The objectives for the course included understanding models for preventing epileptogenesis, creating best evidence algorithms that describe how to best manage patients with epilepsy related to brain tumors, including novel intraoperative monitoring techniques. Risk analyses were summarized to benefit treatment decisions regarding the prophylactic use of antiepileptic drugs in patients with CNS tumors or traumatic brain injury and to present the best management options with patients with metastatic brain tumors based on current knowledge.

Throughout two half-day sessions, post-traumatic epilepsy and tumoral epilepsy were explored in detail. Each session was framed by clinical cases involving adults and children. Through a variety of learning methodologies that included lectures, debates, and panel sessions, clinical management was highlighted, illuminating basic science and practice gaps. This discussion summarizes the salient take-home points of the session that are clinically useful for the practicing clinician.

Tumor-Related Epilepsy

Brain tumors are a common cause of lesional epilepsy. The frequency of epilepsy in patients who have brain tumors is...
estimated to be 40% (1). However, there is an inverse relationship between the degree of aggressiveness of a tumor and its relationship to epilepsy; the lower the grade of brain tumor pathology, the higher the likelihood for epilepsy. This is why tumors such as dysembryoplastic neuroepithelial tumors (DNETs), gangliogliomas, and other low grade gangliogliomas are frequently associated with epilepsy in contrast to the lower incidence of epilepsy seen with more aggressive tumors (such as glioblastoma multiforme or metastatic brain tumors). Seizures that are a presenting symptom for tumors indicate a more favorable prognostic factor for survival from the tumor itself (2).

DNETs merit special attention. These lesions often have dual pathologies with major cortical dysplasias and mesial temporal sclerosis. The risk of intractability is 50%, almost twice as high as any other cause. Unfortunately, studies have shown that the longer the duration of epilepsy, the worse the chance of control of seizures for these patients.

Reflecting on the relationship between aggressiveness of tumor pathology and epilepsy, as many as 80% of patients with low-grade tumors present with seizures. The frontal lobe, temporal lobe, and insular regions are the most common sites of tumors that produce seizures. In contrast, 42% of patients with glioblastoma multiforme, have seizures as the presenting symptom; ultimately, 62% of these patients will develop some form of seizures.

Regarding management, both seizure control as well as anti-tumor therapy should be considered. In choosing antiepileptic drugs it is generally preferable to avoid enzyme-inducing agents to minimize potential interactions with chemotherapeutic agents. There is no evidence supporting the use of prophylactic antiepileptic drugs to prevent seizures in patients with brain tumors with exception of the perioperative period. Valproic acid deserves special discussion: Valproic acid has been reported to improve survival in patients with high-grade brain tumors being treated with temozolomide (4). This is a fascinating consideration, given that the same drug is associated with increased teratogenicity in children of mothers who take this drug during pregnancy. Prospective studies on anticonvulsants with brain tumors are warranted, including their potential for favorable associations with chemotherapeutic agents and contribution to patient survival.

Antitumor therapy starts by obtaining a histological diagnosis—either by biopsy, surgery or, if possible, by gross total resection. Recent evidence supports early surgery for removal of low-grade gliomas over biopsy alone, irrespective of seizures, because of clear benefits on long-term survival (5). In addition, up to 50% of non-enhancing gliomas on imaging are actually anaplastic astrocytomas; therefore, it is difficult to rely on imaging alone for diagnosis and differentiation among tumor subtypes. On occasion, one may choose to use medical treatment only in patients with well controlled seizures and brain tumors that are benign in appearance or not easily accessible. Epilepsy surgery is particularly suited for patients with treatment-resistant seizures and benign or low-grade tumors. Resection should not only include tumor boundaries but possibly also extent beyond the lesion itself, possibly including hippocampal structures (if adjacent), given that the tumor margins are not always so distinct (6). The nature of the tumor will dictate subsequent treatment with radiation and chemotherapy; such treatment, where indicated, may also favorably impact seizure control. In fact, in one study, seizure reduction occurred in 60% of patients with tumor-related epilepsy who were receiving temozolomide versus 13% in the control group (7).

Figure 1 shows an algorithm for management of tumor-related epilepsy.

**Post-Traumatic Epilepsy**

There is clearly an increased risk of epilepsy associated with traumatic brain injury (8–30). The increased risk, however, is limited to those who are diagnosed with moderate or severe civilian traumatic brain injury, which comprises almost 5% of all cases of head trauma. In people who are under the age of 35, traumatic brain injury increases the risk for both generalized tonic–clonic seizures and complex partial seizures. Risk factors for the development of post-traumatic epilepsy include age 65 years or older, the presence of a brain contusion, subdural hematoma, linear depressed skull fracture, and loss of consciousness for more than 24 hours. It is also known that the risk for epilepsy after civilian traumatic brain injury is greatest in the first two years after traumatic brain injury in most studies; one study suggests that an increased risk for the development of seizures after severe traumatic brain injury can persist for up to 10 years.

Sadly, with all of the focus on traumatic brain injury, antiepileptogenesis remains a concept yet to translate to clinical management and treatment. Although several new biomarkers of epileptogenic risk are promising (e.g. imaging of hippocampal changes, fMRI, and interictal EEG spike features), there are clearly yet to be defined genetic biomarkers. Promising potential new tools include pathological high-frequency oscillations, alpha methyltryptophan, and positron emission tomography imaging (PET), as well as other PET ligand markers.

Prophylactic antiepileptic drugs can reduce early acute symptomatic seizures after severe traumatic brain injury, but
they do not prevent the development of late post-traumatic epilepsy. Antiepileptic drugs are really only useful in severe traumatic brain injury to prevent seizures within the first week after severe trauma (29–31).

Diagnostic tools, such as EEG and MRI, are very important in the diagnosis of posttraumatic epilepsy. Different techniques may be better at identifying different lesion types. These studies help provide data to identify those at risk for developing posttraumatic epilepsy. It may also be important to identify candidates for therapeutic intervention, when antiepileptogenic agents are found.

Antiepileptic drugs are the mainstay of therapy for post-traumatic epilepsy. No particular agent or combination of agents is considered to be singularly more beneficial than others, and studies have yet to confirm comparative differences for the use of various agents in posttraumatic epilepsy.

Surgical intervention for drug-resistant posttraumatic epilepsy is a viable option for some patients. However, there are caveats: The best candidates are those patients who have a single lesion in contrast to those who have apparent nonlesional or multifocal epilepsy. Those with a multifocal epileptiform EEG tend to have a worse prognosis and may not be the best candidates for surgical intervention. There is a need for multimodal assessment tools to better identify when surgery can be offered in these complex situations.

It is also essential to confirm the diagnosis of epilepsy in patients who have traumatic brain injury and present with spells. Traumatic brain injury and spells do not always imply epilepsy. Some individuals with a history of head trauma will have psychogenic nonepileptic seizures. Indeed those patients who have mild or minimal traumatic brain injury tend to have a stronger association with psychogenic nonepileptic spells and are less likely to have epilepsy. Posttraumatic stress disorder is often the cause associated with psychogenic nonepileptic spells. This is based on military population studies, but may be generalizable to civilian populations.

Figure 2 outlines an algorithm for the management of posttraumatic epilepsy. If patients have traumatic brain injury, they will fall into 1 of 3 categories: mild, moderate, or severe head trauma. If in the severe category, consideration should be given for prophylaxis with antiepileptic drugs in the first 7 days—not to prevent epilepsy but to prevent seizures within that week. This has been found helpful and is a guideline for management by the American Academy of Neurology (31). If spells continue, then one may need to confirm the diagnosis of epilepsy. In patients with mild and moderate traumatic brain injury, particularly if the history is atypical and seizures continue despite antiepileptic drug therapy, confirming the diagnosis of seizures and epilepsy with video EEG monitoring may be necessary. If epilepsy is found then further antiepileptic drug therapy is warranted. Failure of drug therapy should lead to assessment for seizure surgery, recognizing that this still offers the chance for curative treatment and improved quality of life. If a patient fails seizure surgery or is not a candidate, then other options would include additional antiepileptic drugs, neuromodulation with devices such as vagus nerve stimulation and newer stimulation techniques, the use of ketogenic or modified Atkins diet and, clearly, research trials.

In the end, it is essential to remember that epilepsy in both these lesional forms represents only one facet of a larger spectrum of symptoms, signs, and diseases. These patients demand a wholistic approach to their management and treatment. Remembering these factors and caring for the psychosocial, psychological, psychiatric conditions, and comorbidities that occur will help ensure improved quality of life for those individuals with either form of lesional epilepsy.

References


