MAYO CLINIC

Onco-Epilepsy: More Than Tumor and Seizures

William O. Tatum IV, DO, and Alfredo Quinones-Hinojosa, MD

From the Department of Neurology (W.O.T.) and Department of Neurosurgery (A.Q.H.), Mayo Clinic, Jacksonville, FL.

Seizures are a potentially devastating complication of brain tumors[1] and negatively affect quality of life and neurocognitive function,[2] with a burden of disease that includes psychosocial, economic, and management ramifications.[3] Both gliomas and seizures arise directly from the brain and alter multiple large-scale networks of neuronal function and connectivity, leading to bihemispheric disruption.[4] Changes in functional connectivity affecting both hemispheres of patients have been found using electroencephalography, magnetoencephalography, functional magnetic resonance imaging, and magnetic resonance tractography despite the presence of a tumor isolated to a single hemisphere.[3] Widespread global decreases in functional connectivity observed in patients with focal epilepsy probably reflect the deleterious electrophysiological effects of recurrent seizures as opposed to primarily metabolic alterations in remote areas.[4] Magnetoencephalographic recordings have exhibited similar alterations in functional connectivity in broadband frequency (0.5-60 Hz) and gamma frequency (30-80 Hz) analyses widely distributed in remote areas of the brain in patients with tumor.[3] Electrophysiological techniques correlating frequency domains and measures of Granger causality phase locking in gliomas and epilepsy could provide a link to the global network disruption caused by seizures.[4] Even gross total resection of brain tumors and a suspected epileptogenic zone may not result in successful outcomes because of preexisting functional connectivity in remaining brain regions.[3]

MOLECULAR MARKERS

Peritumoral homeostasis, altered neurotransmitters, and shared pathways are involved in glioma-associated seizures. Recent identification of tumor markers associated with an increased risk of seizures has improved our understanding of the pathophysiology of brain tumor and epilepsy.[5,6] Sequence variations of isocitrate dehydrogenases (IDHs) encoded by IDH1 and IDH2 occur in more than 70% of grade II and III gliomas.[5] In the mutated form, IDH1 reduces α-ketoglutarate to D-2-hydroxyglutarate and may serve as a biomarker in some patients with glioma and epilepsy.[6] The overproduction of D-2-hydroxyglutarate, which is structurally similar to glutamate, can promote seizures. In a recent retrospective study of glioma-associated epilepsy, the occurrence of high-frequency oscillations (HFOs) was not different between high-grade and low-grade gliomas; however, when HFOs were detected, the detection rate was higher in patients with IDH1 mutant than in those with IDH wild-type genotype,[5] suggesting HFOs as a potential electrophysiological biomarker. However, more work is needed to clarify the link between molecular markers and seizures, given the confounding effect of a structural brain lesion on seizure generation as well as the limited number of patients and methodology describing the association.

Shared mechanisms involving cystine-glutamine transporters regulate glutamate release and return through cellular exchange. Blockade of system $X^{c}6$ could lead to pharmaceutical development that could affect the excitotoxicity of both brain tumor and epilepsy (Figure). In addition, the overproduction of extracellular glutamate by the disturbed xCT (the catalytic subunit of the cystine glutamate transporter) system and regulatory excitatory amino acid membrane transport mechanisms, similar to γ-aminobutyric acid dysfunction, may provide additional areas for drug development.[6] Thus, a better understanding of the mechanisms and predictors of seizure triggers is essential in improving epilepsy-related outcomes in patients with diffuse gliomas.[5]

SHARED PATHWAYS

Because of shared pathways, current antiseizure drugs (ASDs) may affect treatment of patients

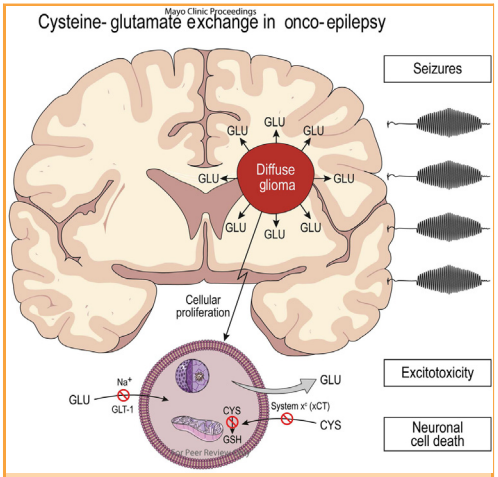

FIGURE. Cartoon depicting onco-epilepsy involving the relationship between a diffuse glioma, breakdown in the cysteine-glutamate exchange, resultant excitotoxicity with neuronal cell death, and epileptiform abnormalities/high-frequency oscillations with seizures. CYS = cysteine; GLT-1 = glutamate transporter-1; GLU = glutamate; GSH = glutathione.

with brain tumor, and various antitumor therapies are valuable for seizure management.[6] Antiseizure drugs may alter disease progression in patients with glioma and epilepsy.[7] Seizures in patients with glioma-associated epilepsy have been found to respond less favorably to ASDs compared with cohorts of adults with non–glioma-associated epilepsy.[8] Although the precise mechanism for an individual patient with a brain tumor is unknown, ASD resistance may encompass individual variation in metabolism, dysregulation of genetically mediated multidrug transport, decreased drug target sensitivity, increased neuronal apoptosis, cytoskeletal alterations, and reorganization of neuronal networks.[9] Various multidrug resistance proteins (eg, MRP1 [(ABCC1) is a family of multidrug resistance proteins]) including multiple drug resistance genes have been found to be overexpressed in cancer. In addition, they act as a transport protein that can cause efflux of antitumor drugs as well as some ASDs. Breast cancer resistance protein has been reported to be up-regulated in some studies involving the microvasculature of epileptogenic brain tumors as well as chronic drug-resistant epilepsy animal models.[9]

MANAGEMENT

Emerging evidence suggests that tumors stimulate seizures, and seizures stimulate tumor growth.[6] In addition, seizures associated with gliomas are resistant to ASDs 30% to 40% of the time.[7] When surgery is required for brain tumors, seizures often worsen existing neurological deficits, result in new deficits, and prolong hospitalization after surgery.[10] Generalizing brain tumor treatment to other etiologies that increase the risk of seizures does not appear to be substantiated. For example, acute seizure prophylaxis appears effective in trauma, but is not in brain tumor.[7,11] In retrospective trials, patients with glioblastoma treated with enzyme-inducing ASDs had a median survival considerably shorter than that of those who received valproate (VPA).[12,13] Valproate stimulates histone acetylation as a histone deacetylase inhibitor and leads to unfolding of the chromatin structure that leaves DNA more susceptible to the effects of chemotherapeutic drugs and radiation.[1] Epigenetic changes in brain cancer include histone deacetylation, genomic DNA hypomethylation, and demethylation of oncogene promoters and other cell cycle pathways (eg, methylation of tumor suppression: phosphatidylinositol-4,5-bisphosphate 3-kinase, tumor protein p53, retinoblastoma susceptibility gene, and nuclear factor-κB).[14] Combining VPA and temozolomide have induced apoptosis and autophagy of cancer cells. The use of VPA together with temozolomide resulted in 8 weeks longer survival of patients with glioblastoma multiforme after adjustment for age, extent of resection, and O^6-methylguanine DNA methyltransferase promoter methylation status.[13] Alterations in metabolomics-genomics are inherent to both gliomas and epilepsy.[14]

In a comprehensive literature review of 910 patients with low-grade glioneuronal tumors and drug-resistant epilepsy, early surgical gross total resection was found to be a critical factor in achieving a seizure-free outcome.[11] There is growing evidence that antitumor treatment contributes to better seizure control in low-grade glioma patients. In 1 report of 10 studies describing seizure outcome after radiotherapy and 14 after chemotherapy, all studies reported improvements in seizure outcome after antitumor treatment irrespective of changes visible in neuroimaging.[10]

Personalizing the brain site for surgical resection is critical for eliminating seizures in patients with epilepsy and gliomas, with gross total resection decisively more effective in both diseases when performed.[11] Preoperative functional neuroimaging, neuronavigation, intraoperative magnetic resonance imaging, and direct electrocortical stimulation are used to localize and map brain function and to monitor neurological performance of neuro-oncology and patients with epilepsy in the operating room.[6] Electrophysiological strategies implemented in the operating room have provided greater extent of resection to obtain long-term seizure control.[11] Developing a team approach between neurology and neurosurgery to maximal tumor removal and resect regions of the brain that appear "normal" yet are involved in an epileptogenic network is a good strategy to resolve discrepancies between preoperative evaluation and intraoperative identification of eloquent cortex.[11]

Conclusion

Terminology to describe seizures associated with brain cancer varies. Using a biological systems approach to "onco-epilepsy" brain tumor management should include the functional synaptic architecture involving epilepsy and cognition. Overlapping shared mechanisms and clinical management couple the 2 brain diseases and support a unique neurological nosology. Understanding the neurobiology will enable the use of better-targeted therapies and interventions for both diseases. New ASDs such as levetiracetam and non—enzyme-inducing ASDs such as VPA are current strategies bridging treatment. New intraoperative brain mapping strategies maximize the extent of surgical resection. Whether nanotechnology producing tumor reduction in animal models has the potential to reduce seizures in humans remains to be seen. Until more precise mechanisms define the bidirectionality of onco-epilepsy, physicians should be aware that antitumor therapy can have beneficial effects on epilepsy and some ASDs impair tumor growth. It is with a combined approach treating brain cancer and epilepsy that will lead to extending survival and improving quality of life.

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Correspondence: Address to William O. Tatum, DO, Department of Neurology, Mayo Clinic, Cannaday, 2 E, 4500 San Pablo Rd, Jacksonville, FL 32224 (tatum.william@mayo.edu).

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