COMMENTARY

Vagus Nerve Stimulation for Tumor-Related Epilepsy: Does It Make Sense?

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ABSTRACT

Seizure is a common presenting symptom for those with brain tumor due to its unique pathogenesis. Several choices of antiepileptic drug are available to use, but some patients can still go on to develop tumor-related refractory epilepsy. Vagus nerve stimulation is becoming a popular option for those with medical refractory epilepsy but no brain tumor due to its effectiveness. There are very few studies available that address the topic of using vagus nerve stimulation for tumor-related epilepsy. Here we discuss the evidence of using vagus nerve stimulation for refractory tumor-related epilepsy and its challenges and gaps moving forward.

INTRODUCTION

In the United States, the incidence of malignant brain tumors is estimated to be about 5.74 per 100,000 person-years. Central nervous system tumors account for 1.4% of new cancer diagnoses in the US. Seizures can be the presenting symptom in up to 30% of brain tumors, and those patients may require lifelong antiepileptic drug (AED) therapy.

It is not simply tumor burden and location that contribute to seizure. Basic science studies have identified an increased concentration of glutamate in the peri-tumor area for patients with glioma and refractory epilepsy. This can serve as an excitatory transmitter to lower the threshold for seizure. Alterations in chloride homeostasis can change the γ-aminobutyric acid (GABA)ergic signaling, such as from hyperpolarizing to depolarizing, to contribute to epileptogenesis. Impairment of potassium buffering due to loss of expression of the potassium channel Kir4.1 has also been suggested to play a supporting role to contribute to seizures. Furthermore, molecular makeup of the tumors also makes a difference. Patients with isocitrate dehydrogenase 1 (IDH1) mutant gliomas have been shown to have higher risk of seizures compared to IDH1 wildtype. This is likely due to mutant product d-2-hydroxylglutarate mimicking the activity of glutamate. Loss of heterozygosity of chromosome 19q and low Ki-67 expression are associated with decreased seizures while low expressions of O6-methylguanine-DNA methyltransferase (MGMT) and epidermal growth factor receptor (EGFR) have been reported to be associated with increased seizures.

Medical Management of Tumor-Related Epilepsy

Tumor resection does not necessarily lead to seizure freedom; up to 40% of those patients can continue to suffer epilepsy. For those with dysembryoplastic neuroepithelial tumors who underwent resection, the proportional estimates of seizure freedom (Engel Class I outcome) were 0.85 at 5 years. Finally, not every patient would want to undergo surgery for many reasons. Hence, medical therapy is still relevant. Currently, there are no large studies that show that the location, histological type, or molecular makeup for the tumors would make a difference in AED choice. We are also not aware of any consensus or practice guidelines from major seizure-related associations, such as International League Against Epilepsy or American Academy of Neurology, that address the choice of AED for tumor-related epilepsy.

One of the common challenges in choosing the right drug is avoiding interaction with chemotherapy. A newer generation drug, such as levetiracetam, has been recommended due to its favorable side effect profile and minimum interaction with other medications. Lacosamide has also been studied as an add-on therapy for tumor-related epilepsy patients and seems to be well tolerated. Valproic acid, a first-generation AED thought to increase survival rate for glioblastoma patients receiving chemoradiation, has not been shown to be the case on subsequent pooled data analysis. It is also important to use this drug with caution: chemotherapy and valproic acid share a similar side effect profile of thrombocytopenia and neutropenia.

Up to one-third of patients with tumor-related epilepsy may develop AED resistance. Not all tumors are the same. For example, half of ganglioglioma patients progress to drug-resistant epilepsy. Many of these patients can achieve seizure freedom after surgery, but up to 37% of them do not. Hence, additional treatment options may be considered for these patients.

Vagus Nerve Stimulation for Epilepsy

Vagus nerve stimulation (VNS) is becoming a popular add-on option for patients with medical refractory epilepsy. Approved by the Federal Drug Administration in 1997, it...
was originally shown to be effective for patients with focal onset epilepsy. However, it may also benefit people of all ages with generalized epilepsy.¹⁵

A meta-analysis showed that the seizure frequency was reduced by 36% at 3-12 months after the procedure and was reduced by 51% at 12 months after starting therapy.¹⁶ Even though less than 10% of patients become seizure free, the response rate does increase over time.¹⁶ Besides better seizure control, VNS also improves other quality-of-life metrics such as alertness, mood change, and school/ professional achievements.¹⁷ As a result of VNS studies, per the latest American Academy of Neurology guideline, VNS can be considered as an adjunctive therapy option.¹⁸

Evidence for VNS in Tumor-Related Epilepsy

While there is evidence of VNS for epilepsy patients, and it has been widely used in many epilepsy centers across the country, its effectiveness on specifically tumor-related epilepsy is unclear. Besides 2 studies from the same group of investigators, there is no other research or case reports we can identify that address VNS for tumor-related epilepsy.

Patel et al examined databases from 2 epilepsy centers and identified 16 patients who had brain tumor and intractable epilepsy that underwent VNS treatment. The result shows that seizure frequency decreased by 10.9% for those with progressing tumors and 65.6% for those with stable tumors, with a statistical difference between these 2.²⁰ The same author followed up with another larger study using an international database, the VNS Therapy Patient Outcome Registry, that was maintained by the company Cyberonics Inc. In this case-control analysis, the group of investigators again isolated patients with refractory tumor-related epilepsy. In the 107 cases they identified, seizure reduction was noted at 3 months to be 45% and 79% at 24 months after starting the therapy. Responder rate is about half at 3 months. Compared to the controls with epilepsy but no brain tumors, there was no statistical difference in seizure reduction. The difference in AED usage after 24 months is also not significant.²⁰ In this larger study, the author was not able to comment on the histology and progression of the tumors. Both studies are likely limited by sample bias as the registry was voluntary and patients were preselected to be good candidates for VNS.

Challenges of VNS and Gaps

VNS is safe to use for magnetic resonance imaging, but there are certain safety protocols that need to be followed, which may include turning VNS off temporarily. For brain tumor patients who often need periodic scanning, this requires coordination. Standard risks for VNS implantation still apply, such as infection, post-operative hematoma, and vocal cord palsy, but the studies on tumor-related epilepsy described earlier did not identify permanent complications.¹⁹,²⁰ The discontinuation rate should be considered because in the case series study of tumor-related epilepsy, 7 out of the 16 patients (44%) discontinued VNS at an average time of 2.8 years, mainly because of ineffectiveness.¹⁹ Long-term studies for epilepsy patients in general show a discontinuation rate of 11% to 18%,²³,²⁴ It is unclear why the discrepancy exists: whether it was because the higher rate of ineffectiveness for tumor-related epilepsy was simply more convenient for that population to remove the device during the subsequent tumor resection. The case series review also seems to suggest that patients with stable tumor have a better response, while patients with progressive tumor may be less likely to benefit from the device. Hence, VNS can be considered for tumor-related refractory epilepsy with a few caveats noted above. Nonetheless, lack of a high level of evidence makes it far from becoming a standard of care today.

CONCLUSION

Central nervous system tumors contribute a sizeable number of epilepsy patients with at least some that go on to become medically refractory. VNS is becoming a popular adjuvant option for those with drug-resistant epilepsy, but it still lacks high-quality studies on tumor-related epilepsy. More research is required before the device can be installed routinely for that category of patients.

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References


