Neurologia medico-chirurgica Advance Publication Date: June 5, 2024

Review Article doi: 10.2176/jns-nmc.2023-0299

Epilepsy in Patients with Gliomas

Takuro Ehara,[1] Fumiharu Ohka,[2] Kazuya Motomura,[2] and Ryuta Saito[2]

[1]*Department of Neuro-Oncology/Neurosurgery, International Medical Center, Saitama Medical University, Hidaka, Saitama, Japan*
[2]*Department of Neurosurgery, Nagoya University Graduate School of Medicine, Nagoya, Aichi, Japan*

Abstract

Brain tumor-related epilepsy (BTRE) is a complication that significantly impairs the quality of life and course of treatment of patients with brain tumors. Several recent studies have shed further light on the mechanisms and pathways by which genes and biological molecules in the tumor microenvironment can cause epilepsy. Moreover, epileptic seizures have been found to promote the growth of brain tumors, making the control of epilepsy a critical factor in treating brain tumors. In this study, we summarize the previous research and recent findings concerning BTRE. Expectedly, a deeper understanding of the underlying genetic and molecular mechanisms leads to safer and more effective treatments for suppressing epileptic symptoms and tumor growth.

Keywords: brain tumor, epilepsy, glioma, glutamate

Introduction

Brain tumor-related epilepsy (BTRE) is a complication that has significant effects on the quality of life, course of treatment, and prognosis of patients with brain tumors. In a recent large-scale cohort study, brain tumors were the cause of epilepsy in 8.6% of patients with an identified cause of epilepsy.[1)] Reportedly, over 50% of patients with glioma experience at least one seizure, and over 30% develop BTRE.[2)] Furthermore, understanding the pathogenesis of epilepsy is essential for the clinical management of brain tumors in affected patients. In this study, we review the recent reports and study findings that are related to this topic.

Differences from Acute Symptomatic Seizures

BTRE is a series of seizures caused by a brain tumor and is different from temporary seizures due to other diseases. For instance, acute symptomatic seizures take place in close temporal association with acute central nervous system conditions, such as metabolic, toxic, structural, infectious, and inflammatory disorders.[3)] Oushy et al. analyzed the characteristics of patients with new-onset perioperative seizures within 30 days of surgery for resection. They reported that the risk factors for perioperative seizures include intradural tumor location, intraoperative cortical stimulation, and extent of resection.[4)] Considering that acute symptomatic seizures are temporally associated with and occur because of certain intraoperative factors or conditions, they must be distinguished from BTRE, which is associated with multiple seizures. Nevertheless, acute symptomatic seizures may be a risk factor for BTRE[5)] and should be managed appropriately.

Incidence of BTRE

The incidence of BTRE varies with histological tumor type-it is reported to be approximately 75% among patients with low-grade astrocytoma, whereas the reported incidences among patients with glioblastomas, meningiomas, and metastases are 29%-49%, 29%-60%, and 20%-35%, respectively.[2)] These variations in incidence increase the possibility of the underlying epileptic mechanisms being related to the biological characteristics of the tumor rather than its mass effects on the brain.

Received December 22, 2023; Accepted March 2, 2024

Underlying Mechanisms in BTRE

Tumor microenvironment

Tumor microenvironment (TME) is the most important factor for characterizing BTRE. TME comprises tumor tissue and surrounding normal tissues, including astrocytes, microglia, and immune cells.[6] In the case of brain tumors, since TME is inextricably associated with neural networks, it is anticipated that the pathogenesis of epilepsy will be different from that of normal epilepsy, which is primarily explained by changes in the balance between the excitatory and inhibitory neurotransmitter levels in neural networks. Several interactions between cells are closely related to BTRE and tumor growth. The molecular characteristics and mechanisms of BTRE are discussed in the following sections based on the studies conducted until now.

1) Gene expression and BTRE

Aberrantly expressed enzymes and proteins in the TME have been shown to promote BTRE by altering the perineuronal environment. Chen et al. retrospectively assessed the possible relationships between mutant isocitrate dehydrogenase 1 (IDH^{mut}) and BTRE in large cohorts. They reported that although 18%-34% of patients with isocitrate dehydrogenase 1 (IDH1) wild-type glioblastoma had preoperative seizures, this rate increased to 59%-74% in IDH^{mut} patients ($p < 0.001$). They hypothesized that D-2-hydroxyglutarate (D2HG) produced by IDH^{mut} is similar to glutamate in terms of chemical structure, which in turn promotes neuronal activity.[7] Mortazavi et al. reported that D2HG may promote neuronal spiking by altering the peritumoral metabolic environment and activating the mammalian target of rapamycin (mTOR) signaling pathway.[8]

Feyissa et al. retrospectively examined the relationship between BTRE and tumor molecular markers in a cohort of 68 adult patients with glioma.[9] They reported that a higher percentage of $IDH1^{mut}$ patients had preoperative seizures ($p = 0.037$), and postoperative seizure control was more common in patients with O6-methylguanine-DNA methyltransferase (MGMT) gene promoter methylation. Nevertheless, alpha-thalassemia mental retardation X-linked (ATRX) retention, 1p/19q co-deletion, and p53 expression were not correlated with BTRE. Likewise, in an analysis of a large cohort of 442 patients with glioma in China, IDH mutations were associated with the development of epilepsy, whereas p53 expression, ATRX loss, MGMT gene promoter methylation, telomerase reverse transcriptase promoter mutations, and 1p/19q co-deletion status were not associated with the occurrence of BTRE.[10]

2) Molecular mechanisms of BTRE

Various molecular mechanisms and pathways have been reported to be involved in the pathophysiology of BTRE. We will discuss in the subsequent sections the mechanisms underlying this form of epilepsy, which are multifactorial, most of which exhibit an overlap with the mechanisms involved in glioma proliferation.

Glutamate signaling

Glutamate is an excitatory neurotransmitter, and the elevation of glutamate levels around neurons is closely associated with epilepsy. Recent studies have shown elevated peritumoral glutamate levels in patients with glioma. Marcus et al. employed microdialysis to measure glucose, lactate, pyruvate, and glutamate levels in perigliomal tissue and found that these tissues were metabolically active. The glutamate levels were almost 100 times higher than those in normal tissues.[11] The cystine-glutamate transporter (xCT) is believed to be responsible for this increase in glutamate levels in peritumoral tissue. xCT is an amino acid transporter known to take up extracellular cystine into the cell through exchange with glutamate.[12] As further discussed in the following paragraphs, xCT is important for tumor growth. xCT is overexpressed on tumor cells, elevating glutamate levels around neurons.[13]

Furthermore, studies have shown that neuronal hyperactivity is induced by glutamate released from tumors via xCT. Buckingham et al. utilized electroencephalography (EEG) analysis to prove that sulfasalazine, an xCT inhibitor, suppressed seizure waves in the brains of severe combined immunodeficiency disease mice models transplanted with patient-derived glioma cells.[14] Excitatory amino acid transporters 1 and 2 (EAAT1 and EAAT2), which are responsible for glutamate re-uptake, are poorly expressed on glioma cell membranes and further contribute to elevated extracellular glutamate levels.[15] Moreover, branched-chain amino acid transaminase 1, the source of glutamate production, is expressed at especially high levels in glioblastomas, and this can lead to increased glutamate levels in tumor cells and ultimately cause an increase in extracellular glutamate levels.[16]

xCT is also closely related to tumor growth potential. Cystine transported into tumor cells by xCT is converted into the antioxidant glutathione, inhibiting the accumulation of reactive oxygen species in cancer cells and increasing their resistance to oxidative stress, thereby promoting tumorigenesis.[17] The released glutamate also acts on N-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptors expressed on the tumor surface, increases Ca^{2+} levels in tumor cells, and induces tumor cell proliferation, migration, and invasion via the phosphatidylinositol-3 kinase (PI3K)-protein kinase B (Akt) and mitogen-activated protein kinase (MAPK) pathways.[18,19] Ishiuchi et al. revealed that glioblastoma cells overexpress Ca^{2+}-permeable AMPA-type glutamate receptors on their membrane and that using adenovirus-mediated cDNA transfer to make these receptors Ca^{2+}-impermeable inhibited cell motility and induced apoptosis.[20] Therefore, epilepsy and the proliferative capacity of glioma cells are inextricably connected.

GABAergic signaling and chloride regulation

γ-Aminobutyric acid (GABA) inhibits neuronal excitability by binding to $GABA_A$ receptors and causing an influx of Cl^- into neurons. This influx of Cl^- hyperpolarizes the nerve and suppresses excitation. In gliomas, the density of GABAergic synapses on peritumoral pyramidal cells is low, and inhibition by GABA is inadequate.[21]

For GABA to function appropriately, the Cl^- concentration in neurons must be constantly low, and the K-Cl cotransporter isoform 2 (KCC2) and Na^+-K^+-Cl^- cotransporter isoform 1 (NKCC1) are responsible for this role. KCC2 acts more strongly on this balance than NKCC1 in neurons. In other words, intracellular Cl^- is maintained at a low level because the amount of Cl^- exhaled out of the cell by KCC2 is relatively higher than that of Cl^- taken up into the cell by NKCC1.[19] In neurons around glioma cells, the regulatory roles mediated by KCC2 and NKCC2 are disrupted, and intracellular Cl^- levels are maintained at abnormally high levels. In this situation, due to the extracellular efflux of Cl^-, GABA signaling may cause epileptic discharges.

mTOR pathway

mTOR forms two complexes that are known to promote cell proliferation and contribute to tumor formation in dividing cells.[22] Tuberous sclerosis (TSC) is caused by loss-of-function mutations in the mTOR regulators TSC1 or TSC2, leading to various symptoms, including epilepsy.[23] Several studies have explored the mechanisms underlying epilepsy due to mTOR hyperactivation. For instance, upregulation of mTOR-dependent expression of GluN2C-containing N-methyl-D-aspartate receptors (NMDARs) may cause sustained and repetitive excitation.[24]

TSC2-deficient human neurons fire more frequently and synchronously than normal human neurons. Recent studies have shown that these neurons have increased mTOR complex 1 (mTORC1)-dependent expression of L-type calcium channels and increased calcium influx from the extracellular space during depolarization.[25] These findings indicate that increased extracellular calcium influx may be involved in BTRE in brain tumor cases with abnormal mTOR signaling.

Long- and short-range modes

BTRE has two different modes: the long- and short-range modes.[6] In long-range mode, glutamate, Ca^{2+}, and other neurotransmitters released by tumor cells cause neuronal hyperexcitation. By contrast, in short-range mode, astrocytes and microglia directly activated by tumor cells via gap junctions are epileptogenic. Gap junctions are formed by the linkage of hexameric sequences of membrane proteins called connexins and serve to communicate between tumor cells. For instance, astrocytic tumor cells invade, proliferate, and connect over long distances between tumor cells through gap junctions associated with dendritic communication pathways known as tumor microtubes.[26] Intercellular communication through gap junctions is an important pathway for cell proliferation and differentiation[27] and may play important roles in BTRE.

Nedergaard et al. observed direct signaling from astrocytes to neurons via increased calcium concentrations in mixed cultures of astrocytes and neurons in the rat brain.[28] Octanol, a gap junction blocker, inhibited the neuronal response, suggesting that signaling between astrocytes and neurons is mediated by gap junctions.

Neuronal Excitation and Tumor Growth

As shown by recent studies, neuronal excitation itself influences glioma cell growth. Humsa et al. reported activated neurons' in vivo mitogenic effects on normal neural and oligodendroglial progenitors, which are believed to have critical roles in the cellular origin of high-grade gliomas.[29] They identified the neuroligin-3 protein as a mitogen and suggested that it may activate the PI3K-mTOR pathway to lead to tumor growth.[30]

Some studies have also indicated that synaptic currents propagate to tumor cells. Venkatesh et al. stimulated Schaffer collateral and commissural afferent axons that emanate from the cornu ammonis 3 (CA3) region of the mouse hippocampus, measured the responses of glioma cells implanted in the CA1, and visually confirmed that an excitatory post-synaptic potential was induced in glioma cells.[31] They also found that in comparison to the controls, glioma cells depolarized by optogenetics strongly promoted glioma xenograft growth. Limiting this depolarization limited the growth rate of tumor cells and prolonged mouse survival.

Recently, neurogliomal synapses (NGSs) have been found to form around tumor microtubes in sections derived from patient gliomas and tumors in different mouse models.[32] NGSs are functional synapses that generate post-synaptic currents via AMPA subtype glutamate receptors and thus contribute to tumor growth via glutamatergic activity. Such synaptic structures between neurons and tumors typically develop in refractory human gliomas and mouse models but not in low-grade primary brain tumors. These findings exhibit a specific contribution of NGSs to the malignant potential of astrocytic gliomas.

A brief summary of the relationship between epilepsy and tumor growth in the tumor microenvironment described so far is shown in Fig. 1.

Treatment of BTRE

Treatment of brain tumors leads to epilepsy control

As mentioned thus far, BTRE is closely related to TME, and treating brain tumors is essential for epilepsy control. These treatments mainly include surgical removal, radiation therapy, and chemotherapy. Table 1 shows previously reported BTRE control rates by treatment modality.

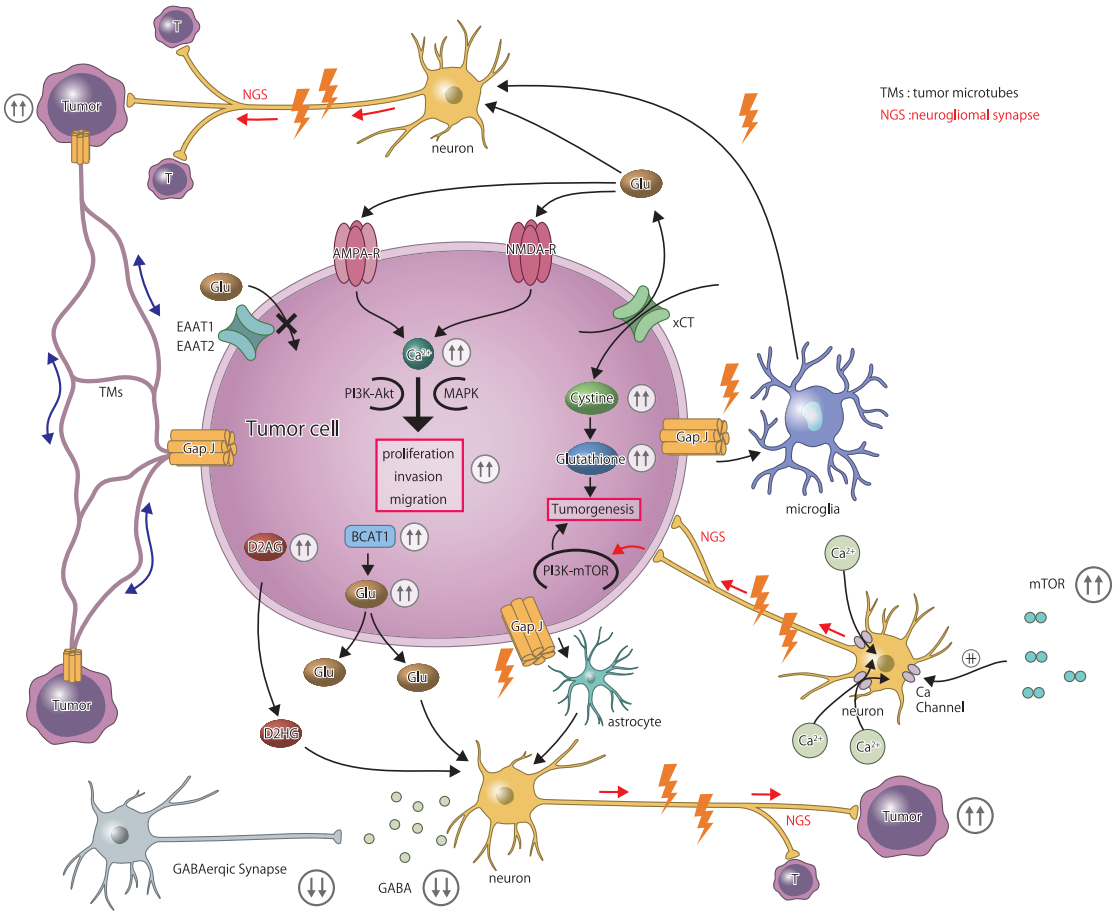

Fig. 1 Relationships between epilepsy and tumor growth in the tumor microenvironment.
Glutamate binding to AMPA and NMDA receptors increases Ca levels in tumor cells, activating the PI3K-Akt and MAPK pathways, leading to tumor growth. Overexpression of xCT on the tumor cell membrane increases the glutamate concentration in the surroundings, leading to epileptogenicity. Conversely, EAAT1 and EAAT2 are expressed at lower levels on tumor cell membranes, and the intracellular uptake of glutamate is suppressed. xCT increases the concentration of glutathione, an antioxidant, in tumor cells, promoting tumor growth. BCAT1, which produces glutamate from branched-chain amino acids, is also expressed at high levels, especially in glioblastomas. The high expression of BCAT1 in glioblastomas can result in increased glutamate levels within tumor cells, ultimately causing an increase in extracellular glutamate levels. In glioma cells with IDH mutations, D2HG, structurally similar to glutamate, is produced and excites neurons extracellularly, rendering them epileptogenic. In gliomas, GABAergic synaptic density on nearby pyramidal cells is reduced, and GABA-mediated inhibition is impaired. Meanwhile, in gliomas, mTOR overactivity can result from changes in upstream regulation, such as upregulation of PI3K–Akt signaling, and mutations in PTEN. Hyperactivation of the mTOR pathway affects neuronal excitability, causing excessive neuronal firing. Tumor cells stimulate astrocytes and microglia via gap junctions and activate surrounding neurons. The activated neurons, in turn, activate the PI3K–mTOR pathway in the surrounding tumor cells via NGSs, thereby promoting tumor growth. Tumor cells communicate with each other through TMs, which are structures mediated by gap junctions.
Glu: glutamate, D2HG: D-2-hydroxyglutarate, xCT: cystine–glutamate transporter, NMDA-R: N-methyl-D-aspartate receptor, AMPA: α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid, EAAT: excitatory amino acid transporter, BCAT1: branched-chain amino acid transaminase 1, PI3K: phosphatidylinositol-3 kinase, Akt: protein kinase B, MAPK: mitogen-activated protein kinase, GABA: γ-aminobutyric acid, mTOR: mammalian target of rapamycin, GapJ: gap junction, TMs: tumor microtubes, NGS: neuroglioma synapse

Tumor removal is an effective treatment for BTRE, leading to seizure resolution in 67% of BTRE patients with low-grade gliomas, including those with drug-resistant seizures, at 12 months postoperatively. Poor postoperative seizure control risks included a long seizure history and incomplete tumor removal.[33] In another study, the rate of resolution of epileptic seizures in patients with malignant brain astrocytomas, including anaplastic astrocytomas and glioblastomas, was 77% at 12 months postoperatively.[34]

Radiation is also effective for treating BTRE. One retrospective study on the effect of radiation therapy on BTRE suppression in a group of patients with grades 2 and 3

Table 1 Previously reported BTRE control rates by treatment modality [33-35, 38]

Treatment modality	Tumor diagnosis	Seizure-free rate at 12 months
Surgical removal	Low-grade glioma	67%
	Malignant astrocytomas including glioblastoma	77%
Radiation therapy	Grade 2	76%
	Grade 3	32%
Chemotherapy (temozolomide)	Low-grade glioma	63.2% showed ≥50% reduction in seizures

BTRE: brain tumor-related epilepsy

Table 2 Mechanisms of action and characteristics of various antiepileptic drugs against BTRE [42-59]

Antiepileptic drugs	Mechanism	Interactions with other drugs	Antiepileptic effects for BTRE in monotherapy	Antitumor effect
Levetiracetam	Binds to SV2A	Low	◎	None in clinical doses
Valproic acid	Na^+ channel blocker, blocking T-type Ca channels		○	None in clinical doses
Lamotrigine	Na^+ channel blocker	Low	Not reported	
Lacosamide	Na^+ channel blocker	Low	○	
Topiramate	Na^+ channel blocker, AMPA antagonism	Low	○	
Phenytoin	Na^+ channel blocker		◎	
Pregabalin	Binds to Ca^{2+} channel subunit α2δ and inhibits Ca^{2+} influx		◎	
Perampanel	AMPA antagonism		Not reported	Unknown. Further research is required.

BTRE: brain tumor-related epilepsy

gliomas found that 76% had reduced seizures and 32% had resolved seizures at 12 months post-treatment.[35] Considering that earlier treatment may have a stronger inhibitory effect on BTRE than delayed treatment, the timing of radiotherapy is also important.[36] Nevertheless, data on the effects of radiotherapy on seizures are scarce. Therefore, further investigations are required in the future.

Although its antiepileptic effects on patients with glioblastoma are poor,[37] various reports on the antiepileptic efficacy of temozolomide (TMZ) in patients with low-grade gliomas exist. Koekkoek et al. found that 49.0%, 63.2%, and 61.8% of patients with low-grade glioma showed a ≥50% reduction in seizures at 6, 12, and 18 months after starting TMZ treatment, respectively.[38] Additionally, among patients with low-grade glioma who underwent TMZ treatment, the percentage of patients with partial and complete seizure control was 29%-89.7% and 19.4%-72%, respectively.[39] Although the mechanisms underlying the antiepileptic effects of TMZ remain unknown, they may involve its P-glycoprotein (P-gp) inhibitory effect. P-gp is a typical adenosine-5'-triphosphate (ATP)-binding cassette transporter that employs ATP hydrolysis energy to transport substrate drugs outside the cell. P-gp is expressed in cancer cells and several normal tissues, such as the blood-brain barrier (BBB), intestine, liver, and kidneys. Zhang et al. examined the mechanisms underlying the synergistic antitumor effects of TMZ and doxorubicin. They reported that TMZ inhibited the ATPase activity of P-gp and significantly increased the doxorubicin accumulation in cells.[40] Since many anticonvulsants are substrates of P-gp, it is possible that TMZ delays drug excretion across the BBB and potentiates anticonvulsant effects through a similar mechanism.

Antiepileptic drugs

Presently, there are no guidelines on using antiepileptic drugs to treat BTRE, and tumor histology, grade, and molecular markers do not influence the choice of antiepileptic drugs.[41] Table 2 shows the mechanisms of action and characteristics of frequently used antiepileptic drugs. Until the 2010s, levetiracetam (LEV) and valproic acid (VPA) were the main drugs for BTRE treatment in clinical practice.[42] Novel antiepileptic drugs such as LEV, lamotrigine, lacosamide (LCM), and topiramate, which have fewer interactions with anti-neoplastic drugs, are recommended for use in treatment.[43] For example, compared to other antiepileptic drugs, LEV is associated with fewer medication adjustments, lower rates of concomitant medication re-

quirement and adverse events, and longer overall survival.[44] Moreover, in a retrospective comparative study, LEV was superior to VPA in reducing convulsions, and the rates of side effects were comparable.[45] Also reportedly, using LEV can improve cognitive function in patients with high-grade glioma, especially verbal memory.[46]

Regarding other drugs, a recent study carried out in Italy on the efficacy of LCM alone in suppressing BTRE revealed that 64.4% of patients had resolution of seizures at 3 months and 55% at 6 months.[47] Furthermore, there were no significant differences in the cumulative incidence of treatment failure and adverse events that are associated with BTRE and LCM.[48] A recent review of 66 studies revealed that LEV, phenytoin, and pregabalin are the most effective BTRE drugs in monotherapy. However, the level of evidence for numerous of the studies was low, and more prospective comparative studies are required.[49]

As BTRE is often drug-resistant and if seizures are difficult to control using a single agent, it may be useful to add on other drugs. In approximately one-third of cases, BTRE cannot be controlled using a single agent[45], requiring the addition of another type of drug. There have been several published studies on add-on therapy. For instance, a recent large-scale retrospective study found that two-drug combination therapy using LEV and VPA had better rates of epilepsy control and similar side effects when compared to LEV or VPA plus another antiepileptic drug.[50]

Perampanel (PER) selectively and noncompetitively inhibits AMPA receptors and is one of the few drugs that exert anticonvulsant effects by acting on the post-synaptic membrane. According to Chonan et al., adding low-dose (2-4 mg) PER was effective for patients with uncontrolled seizures using LEV.[51] Maschio et al. also studied the add-on effect of PER on BTRE not controlled by single agents such as LEV, VPA, and LCM. They found that the average number of seizures per month decreased from 10.8 to 1.7, which indicates that this is an effective treatment option for BTRE.[52] Nonetheless, large-scale prospective studies on the add-on effects of PER are insufficient, and further research is required.

Some antiepileptic drugs have been shown to have inhibitory effects on tumor growth.[53] For instance, VPA, a histone deacetylase inhibitor, has been reported to induce apoptosis in various carcinomas by promoting histone acetylation and disrupting chromatin structure.[54] It has also been demonstrated to induce DNA damage in combination with TMZ in glioma cells.[55] Moreover, LEV enhances the therapeutic sensitivity of glioma cells by inhibiting the transcription of MGMT, a DNA repair protein. Pallud et al. analyzed 460 patients with IDH wild-type glioblastoma. They found that the presence or absence of LEV during standard chemotherapy was an independent factor associated with longer median overall survival.[56] Nevertheless, reports summarizing several large clinical trials have ruled out the antitumor effects of LEV and VPA, at least at clinically used doses.[57] The antitumor effects of PER have also attracted attention recently, with reports of inhibition of cell proliferation by the induction of apoptosis[58] and reduction of intracellular metabolism.[59] However, whether PER at the dose used in clinics exerts antitumor effects is unknown, and further research is mandatory.

BTRE requiring attention

Status epilepticus (SE) is an emergent condition that can cause considerable neuronal damage, alter neuronal networks, and have long-term consequences. SE is generally defined as 30 min of continuous seizure activity or two or more consecutive seizures without complete recovery.[60] Reportedly, approximately 30% of patients with initial SE have mild-to-severe new neurological deficits, including aphasia, paralysis, and impaired consciousness, and the 3-month prognosis in terms of death or severe disability is worse for SE associated with tumor growth than for SE without tumor growth.[61]

Early detection is especially important, as nonconvulsive SE (NCSE) is associated with significant mortality. NCSE may not have external symptoms, and diagnosis may be delayed. A retrospective study found that among 1101 patients with brain tumors, 2% had NCSE, which resolved with treatment in 92% and improved clinically in 75% of the cases.[62] In this study, only a subset of patients received EEG, and NCSE associated with brain tumors is likely underdiagnosed. Even though NCSE poses a serious threat to life, it is curable, and if it is suspected, continuous EEG monitoring should be aggressively pursued. Recently, some reports have revealed that arterial spin labeling perfusion-weighted MRI is a useful diagnostic tool for NCSE.[63,64]

Conclusion

BTRE is caused by changes in various networks in the TME and is also closely linked to tumor growth. Further research into the underlying genetic and molecular mechanisms is expected to lead to better strategies for suppressing epilepsy and tumor growth.

Acknowledgments

We want to thank all the staff of the Brain Tumor Group at Nagoya University for their guidance in preparing this paper, and we would like to thank them again here.

We want to thank Editage (www.editage.jp) for English language editing.

Abbreviations

ABC, ATP-binding cassette; Akt: protein kinase B; AMPA, α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid ; ASL, arterial spin labeling; ATP, adenosine-5'-triphosphate; ATRX, alpha-thalassemia mental retardation X-linked; BBB, blood-brain barrier; BCAT1: branched-chain amino acid

transaminase 1; BTRE, brain tumor-related epilepsy; D2HG, D-2-hydroxyglutarate; EAAT, excitatory amino acid transporter; EEG, electroencephalography; GABA, γ-aminobutyric acid; IDH1, isocitrate dehydrogenase 1; KCC2, K-Cl transporter 2; LCM, lacosamide; LEV, levetiracetam; MAPK, mitogen-activated protein kinase; MGMT, O6-methylguanine-DNA methyltransferase; mTOR, mammalian target of rapamycin; NCSE, nonconvulsive status epilepticus; NGS, neurogliomal synapse; NKCC1, Na^+-K^+-Cl^- transporter; NMDA, N-methyl-D-aspartate; NMDAR, N-methyl-D-aspartate receptor; P-gp, P-glycoprotein; PER, perampanel; PI3K: phosphatidylinositol-3 kinase; SCID, severe combined immunodeficiency disease; SE, status epilepticus; TERT, telomerase reverse transcriptase; TME, tumor microenvironment; TMZ, temozolomide; TSC, tuberous sclerosis complex; VPA, valproic acid; xCT, cystine-glutamate transporter

Conflicts of Interest Disclosure

The authors declare no conflicts of interest.

References

1) Chipaux M, Szurhaj W, Vercueil L, et al.: Epilepsy diagnostic and treatment needs identified with a collaborative database involving tertiary centers in France. *Epilepsia* 57: 757-769, 2016
2) van Breemen MSM, Wilms EB, Vecht CJ: Epilepsy in patients with brain tumours: epidemiology, mechanisms, and management. *Lancet Neurol* 6: 421-430, 2007
3) Commission on Epidemiology and Prognosis, International League Against Epilepsy: Guidelines for epidemiologic studies on epilepsy. *Epilepsia* 34: 592-596, 1993
4) Oushy S, Sillauu SH, Ney DE, et al.: New-onset seizure during and after brain tumor excision: a risk assessment analysis. *J Neurosurg* 128: 1713-1718, 2018
5) Bech KT, Seyedi JF, Schulz M, Poulsen FR, Pedersen CB: The risk of developing seizures before and after primary brain surgery of low- and high-grade gliomas. *Clin Neurol Neurosurg* 169: 185-191, 2018
6) Mao XY, Tokay T, Zhou HH, Jin WL: Long-range and short-range tumor-stroma networks synergistically contribute to tumor-associated epilepsy. *Oncotarget* 7: 33451-33460, 2016
7) Chen H, Judkins J, Thomas C, et al.: Mutant IDH1 and seizures in patients with glioma. *Neurology* 88: 1805-1813, 2017
8) Mortazavi A, Fayed I, Bachani M, et al.: IDH-mutated gliomas promote epileptogenesis through d-2-hydroxyglutarate-dependent mTOR hyperactivation. *Neuro Oncol* 24: 1423-1435, 2022
9) Feyissa AM, Worrell GA, Tatum WO, et al.: Potential influence of IDH1 mutation and MGMT gene promoter methylation on glioma-related preoperative seizures and postoperative seizure control. *Seizure* 69: 283-289, 2019
10) Shen S, Bai Y, Zhang B, Liu T, Yu X, Feng S: Correlation of preoperative seizures with a wide range of tumor molecular markers in gliomas: an analysis of 442 glioma patients from China. *Epilepsy Res* 166: 106430, 2020
11) Marcus HJ, Carpenter KLH, Price SJ, Hutchinson PJ: In vivo assessment of high-grade glioma biochemistry using microdialysis: a study of energy-related molecules, growth factors and cytokines. *J Neurooncol* 97: 11-23, 2010
12) Bannai S, Kitamura E: Transport interaction of L-cystine and L-glutamate in human diploid fibroblasts in culture. *J Biol Chem* 255: 2372-2376, 1980
13) Yuen TI, Morokoff AP, Bjorksten A, et al.: Glutamate is associated with a higher risk of seizures in patients with gliomas. *Neurology* 79: 883-889, 2012
14) Buckingham SC, Campbell SL, Haas BR, et al.: Glutamate release by primary brain tumors induces epileptic activity. *Nat Med* 17: 1269-1274, 2011
15) Ye ZC, Rothstein JD, Sontheimer H: Compromised glutamate transport in human glioma cells: reduction-mislocalization of sodium-dependent glutamate transporters and enhanced activity of cystine-glutamate exchange. *J Neurosci* 19: 10767-10777, 1999
16) Tönjes M, Barbus S, Park YJ, et al.: BCAT1 promotes cell proliferation through amino acid catabolism in gliomas carrying wild-type IDH1. *Nat Med* 19: 901-908, 2013
17) Ishimoto T, Nagano O, Yae T, et al.: CD44 variant regulates redox status in cancer cells by stabilizing the xCT subunit of system xc (–) and thereby promotes tumor growth. *Cancer Cell* 19: 387-400, 2011
18) Lyons SA, Chung WJ, Weaver AK, Ogunrinu T, Sontheimer H: Autocrine glutamate signaling promotes glioma cell invasion. *Cancer Res* 67: 9463-9471, 2007
19) Huberfeld G, Vecht CJ: Seizures and gliomas-towards a single therapeutic approach. *Nat Rev Neurol* 12: 204-216, 2016
20) Ishiuchi S, Tsuzuki K, Yoshida Y, et al.: Blockage of Ca(2+)-permeable AMPA receptors suppresses migration and induces apoptosis in human glioblastoma cells. *Nat Med* 8: 971-978, 2002
21) Marco P, Sola RG, Cajal SRY, DeFelipe J: Loss of inhibitory synapses on the soma and axon initial segment of pyramidal cells in human epileptic peritumoural neocortex: implications for epilepsy. *Brain Res Bull* 44: 47-66, 1997
22) Zou Z, Tao T, Li H, Zhu X: mTOR signaling pathway and mTOR inhibitors in cancer: progress and challenges. *Cell Biosci* 10: 31, 2020
23) Prather P, de Vries PJ: Behavioral and cognitive aspects of tuberous sclerosis complex. *J Child Neurol* 19: 666-674, 2004
24) Lozovaya N, Gataullina S, Tsintsadze T, et al.: Selective suppression of excessive GluN2C expression rescues early epilepsy in a tuberous sclerosis murine model. *Nat Commun* 5: 4563, 2014
25) Hisatsune C, Shimada T, Miyamoto A, Lee A, Yamagata K: Tuberous sclerosis complex (TSC) inactivation increases neuronal network activity by enhancing Ca^{2+} influx via L-type Ca^{2+} channels. *J Neurosci* 41: 8134-8149, 2021
26) Osswald M, Jung E, Sahm F, et al.: Brain tumour cells interconnect to a functional and resistant network. *Nature* 528: 93-98, 2015
27) Moinfar Z, Dambach H, Faustmann PM: Influence of drugs on gap junctions in glioma cell lines and primary astrocytes in vitro. *Front Physiol* 5: 186, 2014
28) Bennett MV, Barrio LC, Bargiello TA, Spray DC, Hertzberg E, Sáez JC: Gap junctions: new tools, new answers, new questions. *Neuron* 6: 305-320, 1991
29) Nedergaard M: Direct signaling from astrocytes to neurons in cultures of mammalian brain cells. *Science* 263: 1768-1771, 1994
30) Venkatesh HS, Johung TB, Caretti V, et al.: Neuronal activity promotes glioma growth through neuroligin-3 secretion. *Cell* 161: 803-816, 2015
31) Venkatesh HS, Morishita W, Geraghty AC, et al.: Electrical and synaptic integration of glioma into neural circuits. *Nature* 573: 539-545, 2019

32) Venkataramani V, Tanev DI, Strahle C, et al.: Glutamatergic synaptic input to glioma cells drives brain tumour progression. *Nature* 573: 532-538, 2019
33) Chang EF, Potts MB, Keles GE, et al.: Seizure characteristics and control following resection in 332 patients with low-grade gliomas. *J Neurosurg* 108: 227-235, 2008
34) Chaichana KL, Parker SL, Olivi A, Quiñones-Hinojosa A: Long-term seizure outcomes in adult patients undergoing primary resection of malignant brain astrocytomas. Clinical article. *J Neurosurg* 111: 282-292, 2009
35) Ruda R, Magliola U, Bertero L, et al.: Seizure control following radiotherapy in patients with diffuse gliomas: a retrospective study. *Neuro Oncol* 15: 1739-1749, 2013
36) van den Bent MJ, Afra D, de Witte O, et al.: Long-term efficacy of early versus delayed radiotherapy for low-grade astrocytoma and oligodendroglioma in adults: the EORTC 22845 randomised trial. *Lancet* 366: 985-990, 2005
37) Climans SA, Brandes AA, Cairncross JG, et al.: Temozolomide and seizure outcomes in a randomized clinical trial of elderly glioblastoma patients. *J Neurooncol* 149: 65-71, 2020
38) Koekkoek JAF, Dirven L, Heimans JJ, et al.: Seizure reduction is a prognostic marker in low-grade glioma patients treated with temozolomide. *J Neurooncol* 126: 347-354, 2016
39) Yue J, Yin C, Chen L, Xu R, Zhao D: Is there a role for temozolomide in glioma related seizures? A systematic review. *Neurol India* 70: 864-871, 2022
40) Zhang R, Saito R, Shibahara I, et al.: Temozolomide reverses doxorubicin resistance by inhibiting P-glycoprotein in malignant glioma cells. *J Neurooncol* 126: 235-242, 2016
41) Maschio M, Aguglia U, Avanzini G, et al.: Management of epilepsy in brain tumors. *Neurol Sci* 40: 2217-2234, 2019
42) Kerrigan S, Grant R: Antiepileptic drugs for treating seizures in adults with brain tumours. *Cochrane Database Syst Rev* 2011: CD 008586, 2011
43) Klinger NV, Shah AK, Mittal S: Management of brain tumor-related epilepsy. *Neurol India* 65: S60-S70, 2017
44) Cardona AF, Rojas L, Wills B, et al.: Efficacy and safety of levetiracetam vs. other antiepileptic drugs in Hispanic patients with glioblastoma. *J Neurooncol* 136: 363-371, 2018
45) van der Meer PB, Dirven L, Fiocco M, et al.: First-line antiepileptic drug treatment in glioma patients with epilepsy: levetiracetam vs valproic acid. *Epilepsia* 62: 1119-1129, 2021
46) de Groot M, Douw L, Sizoo EM, et al.: Levetiracetam improves verbal memory in high-grade glioma patients. *Neuro Oncol* 15: 216-223, 2013
47) Mo F, Meletti S, Belcastro V, et al.: Lacosamide in monotherapy in BTRE (brain tumor-related epilepsy): results from an Italian multicenter retrospective study. *J Neurooncol* 157: 551-559, 2022
48) van Opijnen MP, van der Meer PB, Dirven L, et al.: The effectiveness of antiepileptic drug treatment in glioma patients: lamotrigine versus lacosamide. *J Neurooncol* 154: 73-81, 2021
49) de Bruin ME, van der Meer PB, Dirven L, Taphoorn MJB, Koekkoek JAF: Efficacy of antiepileptic drugs in glioma patients with epilepsy: a systematic review. *Neurooncol Pract* 8: 501-517, 2021
50) van der Meer PB, Dirven L, Fiocco M, et al.: Effectiveness of antiseizure medication duotherapies in patients with glioma: a multicenter observational cohort study. *Neurology* 99: e999-e1008, 2022
51) Chonan M, Saito R, Kanamori M, et al.: Experience of low dose perampanel to add-on in glioma patients with levetiracetam-uncontrollable epilepsy. *Neurol Med Chir (Tokyo)* 60: 37-44, 2020
52) Maschio M, Zarabla A, Maialetti A, et al.: Perampanel in brain tumor-related epilepsy: observational pilot study. *Brain Behav* 10: e01612, 2020
53) Avila EK, Tobochnik S, Inati SK, et al.: Brain tumor-related epilepsy management: A Society for Neuro-oncology (SNO) consensus review on current management. *Neuro Oncol* 26: 7-24, 2024
54) Cipro Š, Hřebačková J, Hraběta J, Poljaková J, Eckschlager T: Valproic acid overcomes hypoxia-induced resistance to apoptosis. *Oncol Rep* 27: 1219-1226, 2012
55) Van Nifterik KA, Van den Berg J, Slotman BJ, Lafleur MVM, Sminia P, Stalpers LJA: Valproic acid sensitizes human glioma cells for temozolomide and γ-radiation. *J Neurooncol* 107: 61-67, 2012
56) Pallud J, Huberfeld G, Dezamis E, et al.: Effect of levetiracetam use duration on overall survival of isocitrate dehydrogenase wild-type glioblastoma in adults: an observational study. *Neurology* 98: e125-e140, 2022
57) Happoid C, Gorlia T, Chinot O, et al.: Does valproic acid or levetiracetam improve survival in glioblastoma? A pooled analysis of prospective clinical trials in newly diagnosed glioblastoma. *J Clin Oncol* 34: 731-739, 2016
58) Salmaggi A, Corno C, Maschio M, et al.: Synergistic effect of perampanel and temozolomide in human glioma cell lines. *J Pers Med* 11: 390, 2021
59) Lange F, Weßlau K, Porath K, et al.: AMPA receptor antagonist perampanel affects glioblastoma cell growth and glutamate release in vitro. *PLoS One* 14: e0211644, 2019
60) Prasad M, Krishnan PR, Sequeira R, Al-Roomi K: Anticonvulsant therapy for status epilepticus. *Cochrane Database Syst Rev* 2014: CD003723, 2014
61) Knudsen-Baas KM, Power KN, Engelsen BA, Hegrestad SE, Gilhus NE, Storstein AM: Status epilepticus secondary to glioma. *Seizure* 40: 76-80, 2016
62) Marcuse LV, Lancman G, Demopoulos A, Fields M: Nonconvulsive status epilepticus in patients with brain tumors. *Seizure* 23: 542-547, 2014
63) Shimogawa T, Morioka T, Sayama T, et al.: The initial use of arterial spin labeling perfusion and diffusion-weighted magnetic resonance images in the diagnosis of nonconvulsive partial status epileptics. *Epilepsy Res* 129: 162-173, 2017
64) Shimoda Y, Kanamori M, Saito R, Osawa S, Mugikura S, Tominaga T: Aphasic status epilepticus after glioma resection: two case reports. *Acta Neurochir (Wien)* 163: 3109-3113, 2021

Corresponding author: Ryuta Saito, MD, PhD
Department of Neurosurgery, Nagoya University Graduate School of Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya, Aichi 466-8550, Japan.
e-mail: ryuta@med.nagoya-u.ac.jp