LIBYAN INTERNATIONAL JOURNAL OF ONCOLOGY

Libyan International Journal of Oncology. 2026;5(1):8-16
e-ISSN: *2957-6717*

Review article

Brain Tumor-Related Epilepsy: A Comprehensive Review of Pathophysiology, Molecular Biomarkers, Surgical Outcome, and What is the New Frontier in Clinical Management

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Abstract
Brain Tumor-Related Epilepsy (BTRE) is a complex clinical challenge at the intersection of oncology and neurology, significantly impacting patients' quality of life. Seizure prevalence is estimated between 30% and 50% in adults with brain tumors, reaching up to 80% in specific tumor types. This comprehensive literature review aims to synthesize and analyze the current knowledge on BTRE, focusing on its epidemiology and clinical correlations, molecular and pathophysiological mechanisms, and therapeutic strategies. The analysis revealed that Low-Grade Gliomas (LGGs) and Long-Term Epilepsy-Associated Tumors (LEATs), such as Ganglioglioma (GG) and Dysembryoplastic Neuroepithelial Tumor (DNT), are the most epileptogenic, particularly when localized in the temporal or frontal lobes. The review also underscored the pivotal role of modern molecular classification (WHO 2021), where genetic mutations like BRAF V600E and IDH play a direct role in epileptogenesis. Pathophysiologically, an "Epileptogenic Niche" forms in the peritumoral microenvironment, characterized by neurotransmitter imbalance (glutamate excess and GABA deficiency), neuroinflammation, and Blood-Brain Barrier (BBB) disruption. Shared molecular pathways, including PI3K/AKT/mTOR and RAS-RAF-MAPK, contribute to both tumor growth and neuronal hyperexcitability. In clinical management, drug-drug interactions between Antiseizure Medications (ASMs) and chemotherapy pose a major challenge. Enzyme-Inducing ASMs (EIAEDs) are discouraged in favor of Non-Enzyme-Inducing ASMs (NEIAEDs) like Levetiracetam. Surgical resection of the tumor remains the most effective treatment for seizure control, especially for LEATs, often requiring extended resection to achieve long-term seizure freedom. This review emphasizes the necessity of a multidisciplinary and personalized therapeutic approach to improve outcomes for patients with BTRE.
Keywords. Epileptogenesis, Neuro-oncology, Tumor Microenvironment.

***Received**: 11/01/26*
***Accepted**: 04/03/26*
***Published**: 15/06/26*

Introduction

Epilepsy Associated with Brain Tumors (BTRE) is a challenging medical condition at the boundary of oncology and neurology and has appeared to considerably affect the life quality and treatment course of patients [1]. Epilepsy has ceased to be considered only an associated symptom of brain tumors and has started being understood more and more as part of the complex biological interaction between tumor and brain environment. Recent studies propose that seizures could actively contribute to tumor growth and that controlling them might be part of the therapeutic strategy in this case too [2].

The prevalence of epileptic seizure manifestation is estimated between 30% and 50% for brain tumors among adults, with some tumor types reaching a prevalence of 80% [3]. However, there is a specific group of tumors referred to as Long-Term Epilepsy-Associated Tumors (LEATs) that is the leading cause of pharmacoresistant epileptic seizure, especially among children and young individuals [4]. The specific tumors mentioned that belong to this category are those with histological benignity (World Health Organization Grade 1 tumors) that consist of Gangliogliomas (GG) and Dysembryoplastic Neuroepithelial Tumors (DNT); these are mainly site-specific lesions found in the temporal and cortical regions of the brain [5].

Such is the objective of this integral literature review, which aspires to examine and combine the existing state of knowledge about BTRE, turning the analysis around three different axes: first, by examining the epidemiology and clinical data of the most epileptogenic tumors, second by exploring the complicated molecular and genetic pathways of epileptogenesis in the peritumoral microenvironment of the brain, and finally by examining the different clinical options available in the actual treatment of BTRE, as well as the challenges of drug interactions in the use of anti-seizure medications in chemotherapy.

Epidemiology and Clinical Presentations of Epilepsy Secondary to Brain Tumor

The association between tumor type, grade, and incidence of epilepsy has been well defined in the medical literature. Overall, the incidence of epilepsy has been found to be high in the case of LGGs in comparison to HGGs [6].

Variation in Incidence Rates by Histological Type and Grade

Epidemiologic studies have established the existence of differences in the incidence of tumor-related epilepsy according to histopathologic and molecular tumors' classification. Indeed, it has been noted that:

- **Low Grade Gliomas (LGGs):** have an incidence rate of epilepsy reaching 80-85%, especially in tumors containing oligodendroglial elements [7].
- **Anaplastic Gliomas:** have an incidence rate of epilepsy reduced to about 69%.
- **Glioblastoma (GBM):** or Grade IV astrocytoma, the most aggressive primary brain tumor, has relatively lower incidence rate of epilepsy, 49%, as an initial presentation, although up to 80% will have had at least one seizure during the clinical course [8].

This hypothesis proposes that the biologic aggressiveness of the tumor is not solely a determining factor for epileptogenesis but that what matters most is rather the nature of the interaction that exists between tumor cells and the microenvironment.

Long-Term Epilepsy-Associated Tumors (LEATs) and the Classification Shift (WHO 2021)

LEATs are usually nothing but benign neuroepithelial tumors of WHO Grade 1, and are mostly associated with resistant epilepsy in young patients. These tumors have distinct clinical and biological properties. The recent WHO classification of CNS tumors in 2021 has brought about a complete paradigm shift in understanding these tumors. The diagnosis of these tumors is now based on molecular characteristics of the tumor, along with a lesion in the LEAT group of tumors. The newly discovered entities in the LEAT group include tumors [13].

Gangliogliomas (GG)

GGs represent the majority of LEATs, with about 70% of tumors found in the temporal lobe [9]. This type of glioma has a biphasic histology, consisting of a combination of astrocytes and neurons. At the molecular level, the BRAF V600E mutation has been identified in a substantial portion of cases of GG tumors, which plays a pivotal role in the development of tumors and epileptic conditions [10]. It has been observed that the BRAF V600E mutation contributes to the excitability of neurons, which has been linked to cytokine secretion modulation in the microenvironment of the tumors [43].

Dysembryoplastic Neuroepithelial Tumors (DNT)

DNTs are the second most frequent LEAT and are distinguished for being predominantly or entirely restricted to the cerebral cortex and for showing a multinodular pattern. The defining characteristic of DNT is the presence of "oligodendrocyte-like" cells forming a "mucoid matrix," which is admixed with "floating neurons" [11]. DNTs are usually found in association with FCD Type IIIB and thus reflect the close association between "neurodevelopmental anomalies and epileptogenesis." Most cases of DNT are associated with mutations in the FGFR1 gene and activate the "MAPK pathway," which contributes to its "epileptogenic potential" [12].

Pilocytic Astrocytomas (PA)

Though PAs are the most frequent type of brain tumor found in infants, they can be included under LEATs if a child suffers from epilepsy [44]. They are benign (Grade 1) tissue, with Rosenthal fibers, as can be identified by histology. It is essential to understand that PA, within the temporal or cortical region, has a high potential to produce epilepsy, making the location a very crucial point.

Modern Molecular Classification (WHO 2021) and New Entities

The 2021 classification system of the WHO also supports the role of molecular characteristics in the diagnostic and classification process of tumors, including those that occur in epilepsy. For instance, IDH Astrocytomas, even grade IV, are highly susceptible to epileptogenesis rather than IDH-WT tumors [13]. Some of the new entities that are now LEATs include Polymorphous Low-Grade Neuroepithelial Tumor of the Young (PLNTY) and Multilocular and Vacuolating Neuronal Tumor (MVNT). All this is reflective of an evolving approach from histology to an integrated approach that considers histology and molecular findings for comprehensively understanding BTRE.

Anatomical Location and Epileptogenesis

The risk of epilepsy is not solely dependent on the tumor's histological type but is also significantly influenced by its anatomical location. Tumors situated in the cortical or subcortical regions of the temporal and frontal lobes exhibit the highest rates of epileptogenesis [45].

- **Temporal Lobe:** This is the most common site for epileptogenic tumors, especially LEATs. This is attributed to the lower seizure threshold in this lobe, which plays a central role in epileptic networks.
- **Frontal Lobe:** Tumors in this lobe are also associated with high rates of epilepsy, often presenting as motor seizures.

- **Cerebellum and Brainstem:** Tumors in these areas are associated with very low seizure rates, supporting the hypothesis that direct interaction with the cerebral cortex is a crucial factor in epileptogenesis.

Understanding these anatomical, histological, and molecular interactions is vital for identifying high-risk patients and designing preventive therapeutic strategies.

Pathophysiological and Molecular Mechanisms of Tumor-Related Epileptogenesis (BTRE Pathophysiology)

The knowledge of the processes, which alter the peritumoral brain environment to an epileptogenic focus, represents one of the major steps forward in identifying new therapeutic approaches. The process of epileptogenesis in BTRE is now known to involve not only the mechanical compression and destructive changes, but also an active biological process, which entails interactions of tumor cells, neuronal cells, glial cells, and molecular constituents of Tumor Microenvironment (TME) [14].

Modifications of the Tumor Microenvironment (TME) and the "Epileptogenic Niche"

The TME represents the main site for the phenomenon of epileptogenesis. The interaction between tumor cells, glial cells, and neurons establishes the so-called "Epileptogenic Niche," which represents an area of elevated and sustained neuronal excitability [46]. These changes include the following:

Neurotransmitter Imbalance

This dissociation between excitation and inhibition represents the pioneering definition of epilepsy. In the case of BTRE, there's a diminishment of inhibitory transmission, especially GABA-related, and an increase of excitatory transmission, like Glutamate-related.

- **Glutamate:** Excessive glutamate secretion by cancer cells, especially gliomas, induces the excito-toxicity (hyperexcitement) and death of adjacent neurons, a causative element of seizures [16]. This happens through the activation of glutamate transporters that secrete glutamate outside the neuronal cell, where it activates the NMDA and AMPA receptors of adjacent neurons.
- **GABA:** GABA receptors have been identified by researchers in cancer cells. This allows them to hijack the GABA from the adjacent neurons, creating a deficiency of GABA as an inhibitory neurotransmitter. Moreover, ion imbalance within the neurons, especially the deficiency of chloride transporters like **KCC2**, generates an excitatory signal instead [17].

3.1.2. Neuroinflammation

Neuroinflammation is an important pathmechanism in epileptogenesis. Tumor cells and microglia/astrocytes produce pro-inflammatory substances like cytokines and chemokines [18]. These substances are involved in processes such as:

- **Modulation of Ion Channels:** They alter the function of sodium, potassium, and calcium channels, thereby reducing the threshold for epilepsy.
- **Disruption of Blood-Brain Barrier (BBB):** BBB disruption is a widespread phenomenon observed in tumor cells in the brain and an essential component in the pathogenesis of epilepsy [19]. When this barrier is compromised due to tumor presence or surgery, serum proteins, including albumin, leak out into the brain tissue. This leaked albumin binds to astrocytes in the brain and causes them to activate to reactive astrogliosis**,** leading to the production of pro-inflammatory substances and an inability to properly remove glutamate from the space, thereby contributing to hyperexcitability of nerve cells due to high glutamate in the environment [49].

Structural and Electrical Changes

The structural changes associated with the peritumoral brain, for example, neuronal loss and circuit changes, result in the generation of abnormal and hypersynchronized neuronal circuits [50]. Furthermore, changes in the extracellular concentration of potassium ions, caused by astrocyte abnormalities, also contribute to the high electro-excitability.

Molecular and Genetic Mechanisms

These epilepsy-associated tumors, particularly LEATs, carry specific genetic mutations which drive not only tumor growth itself but also contribute directly to epileptogenesis via cellular signaling.

The PI3K/AKT/mTOR Pathway

The **PI3K/AKT/mTOR** pathway represents a common link to both tumor growth and epileptogenesis. Mutations in this pathway, as found in DNTs and some gliomas, are associated with neuronal hyperactivity

and the development of FCD. Overactivation of such a pathway leads to increased protein synthesis and neuronal hypertrophy, contributing to the generation of an abnormal and hyperexcitable neural network.

The RAS-RAF-MAPK Pathway

The **BRAF V600E** mutation in GG represents one of the best examples of participation of the RAS-RAF-**MAPK** pathway in BTRE [22]. Activation of this pathway impels tumor growth and has all effects on the microenvironment that promote neuronal excitability. Inhibition of this pathway has been shown to reduce neuronal excitability in animal models, thus also offering dual therapeutic potential [51].

Metabolic Changes (Metabolomics)

Recent evidence suggests that metabolic alterations induced by the tumor itself are implicated in epilepsy. For instance, impaired glucose metabolism in tumor cells may result in the accumulation of specific metabolites serving as pro-epileptogenic factors [23]. Altered levels of D-2-hydroxyglutarate (D-2-HG)**,** a metabolite produced by the IDH mutation, may also contribute to epileptogenesis in IDH-mutant gliomas [52].

Table 1. Pathomechanisms of tumor related epileptogenesis

Pathomechanism	Key Elements	Epileptogenesis Effects	Associated Tumors
Neurotransmitter Imbalance	Glutamate, GABA, Chloride Transporters	Neuronal hyperexcitation and reduced inhibition	All BTRE tumors, especially LGGs
Neuroinflammation	Cytokines, Albumin, Reactive Astrocytes	Lowered seizure threshold, breakdown of BBB, increased excitability	High- and Low-Grade Gliomas
PI3K/AKT/mTOR Pathway	Genetic mutations, such as FGFR1	Neuronal hypertrophy, FCD formation, hyperexcitability	DNT, some LGGs
RAS-RAF-MAPK Pathway	BRAF V600E mutation	Tumor growth; microenvironment modulation to increase excitability	Gangliogliomas (GG)
Metabolic Changes	D-2-hydroxyglutarate, Glucose Metabolism	Accumulation of pro-epileptogenic metabolites	IDH-Mutant Gliomas

Clinical Management of Brain Tumor-Related Epilepsy (BTRE Management)

The clinical management of BTRE requires a complex and multidisciplinary therapeutic approach, balancing seizure control, tumor treatment, and the preservation of the patient's quality of life (QoL) [24]. Drug-drug interactions between antiseizure medications (ASMs) and anti-cancer therapies (such as chemotherapy) pose a major challenge in this field.

Pharmacological Antiseizure Treatment (ASMs)

Pharmacological treatment is the first line of defense for seizure control in BTRE. However, the choice of the appropriate drug is significantly influenced by the tumor treatment regimen.

Drug-Drug Interactions

Drug-drug interactions between ASMs and chemotherapy are the most critical consideration. ASMs are classified into two main groups based on their effect on liver enzymes (Cytochrome P450, CYP450):

1. **Enzyme-Inducing ASMs (EIAEDs):** Such as phenytoin**,** carbamazepine**,** and phenobarbital.
   - **Effect:** These drugs increase the metabolism of many chemotherapy agents (e.g., Irinotecan, Temozolomide), reducing their plasma concentration and diminishing their anti-tumor efficacy [25].
   - **Recommendation:** The use of EIAEDs is strongly discouraged in brain tumor patients who are receiving or are likely to receive chemotherapy.
2. **Non-Enzyme-Inducing ASMs (NEIAEDs):** Such as Levetiracetam, Lamotrigine, and Gabapentin.
   - **Effect:** These drugs do not significantly affect CYP450 enzymes, thereby minimizing the risk of drug interactions with chemotherapy [26].
   - **Recommendation:** Levetiracetam is considered the preferred and first-line choice for BTRE due to its efficacy, minimal drug interactions, and relatively good tolerability, although some patients may experience psychiatric side effects [27].

Seizure Prophylaxis
The role of prophylactic ASM treatment for patients who have not yet experienced seizures after surgery or radiotherapy remains controversial. Current guidelines suggest that routine prophylactic treatment is not generally recommended, except for the immediate post-operative period (usually for one week), where the risk of seizures is high [28].

Surgical Treatment as a Core Strategy for Seizure Control
Surgical resection of the tumor is the most effective treatment for seizure control in BTRE, especially in the case of Long-Term Epilepsy-Associated Tumors (LEATs). In fact, surgery in the context of BTRE is often viewed as Epilepsy Surgery as much as it is tumor surgery.

Surgery in LEATs: Extended Resection
LEATs, such as GG and DNT, show excellent outcomes after surgery, with long-term Seizure Freedom rates reaching 80% or more [29]. This success is attributed to:

- **Well-Defined Nature:** These tumors are often well-demarcated, facilitating complete resection.
- **Extended Resection:** Evidence suggests that extended resection, which includes the tumor plus the surrounding **Peritumoral Cortex** believed to be the source of epilepsy, leads to the best outcomes in terms of seizure control [30]. In some cases, this may require the resection of cortical areas that appear histologically normal but show epileptic activity on intraoperative Electroencephalography (EEG), confirming that the epileptogenic focus may extend beyond the visible tumor boundaries [53].

Surgery in High-Grade Gliomas (HGGs)
While the primary goal of surgery in HGGs (like Glioblastoma) is tumor debulking and survival extension, maximal safe resection is also associated with better seizure control [54]. The use of intraoperative mapping and electrocorticography is crucial to balance maximal tumor removal with the preservation of eloquent brain function and the epileptogenic zone [55].

Quality of Life and Psychosocial Aspects
The impact of BTRE is not limited to neurological and oncological aspects but extends significantly to the patient's Quality of Life (QoL) and psychosocial well-being. Dealing with the dual diagnosis of a brain tumor and chronic epilepsy imposes a substantial burden on the patient and their family [34].

Psychosocial Burden
BTRE patients are faced with a series of challenges, both psychologically and socially:

- **Social Stigma:** Epilepsy is faced by a challenge of social stigma. The condition results in a sense of loneliness and being excluded from society on the part of the patient. Social stigma may also hamper the patient in rejoining his/her normal professional and social life [35].
- **Comorbid Psychiatric Disorders:** Anxiety and depression are highly common psychiatric conditions among epilepsy sufferers in general, and severity is accentuated by the BTRE oncological diagnosis. Comorbid psychiatric disorders can also impact treatment negatively [36].
- **Medication Side Effects:** Certain ASMs, especially Levetiracetam, may also be predisposed to contributing to the aggravation of psychiatric symptoms such as irritability and mood swings, thereby requiring close monitoring and psychological support if needed [37].

Impact on Cognitive Function
The cognitive function of BTRE patients is influenced by several intermingling aspects, which include the tumor, the occurrence of epilepsy, and drug therapy.

- **Tumor and Location Effect:** Having the tumor in the brain parts that generate language and memory might impair cognitive functions.
- **Seizure Effect:** Neurological damage can be caused by recurring seizures and may also affect the memory and concentration of the person.
- **ASM Effect:** Certain ASMs, particularly older EIAEDs, can cause central side effects like impaired mental processes and somnolence. The selection of NEIAEDs with more favorable central effects is critical for maintaining QoL [38].

Importance of Holistic Care
To address these psychosocial and cognitive factors, it is important that a more holistic approach be adopted, one that views the patient not as a case but as a person. The healthcare team should include:

- **Psychological and Social Support:** Providing psychological counseling and social support for the patient and their family to help them cope with the illness.
- **Rehabilitation:** Neuro-cognitive rehabilitation courses that help in regaining lost functions.

- **Education:** Education of the patient regarding the nature of the disease, its treatment, and ways to overcome the stigma of the disease [39].

Challenges and Future Directions

Despite important advances in the understanding and management of BTRE, there are many unresolved issues, which provide several directions in future research.

Current Challenges

- **Refractory Epilepsy:** Refractory epilepsy is a notable feature of BTRE, as a high proportion of these patients experience drug-resistant epilepsy, making their current ASMs ineffective.
- **Outcome Prediction:** At this stage, there is no accurate biomarker that can be used to predict the development of epilepsy or the responsiveness of the patient to the treatment. A predictive tool in the form of molecules or imaging can be useful for treatment personalization to be attained [40].
- **Dual Therapeutic Effect:** The need to develop a therapeutic compound effective concurrently on tumor growth and epileptogenesis is a critical aim to achieve, because the use of multiple compounds may cause associated side effects.

Future Research Directions

Future studies in BTRE include:

- **Multi-Omics Approaches:** Leveraging the latest technologies, such as genomics, proteomics, and metabolomics, to discover a distinct molecular profile of BTRE that may provide additional targets for therapy [41].
- **Functional Neuroimaging:** Using techniques such as functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) scans to better identify the hyperexcitable areas around the tumor, thus helping in surgical planning [42].
- **Targeted Therapy:** Developing targeted molecular inhibitors that target pathways in a maximally specific manner and also have fewer effects on cognition. For instance, mTOR and MAPK.

Conclusion

BTRE is a complex, bidirectional pathology in which the tumor and the epileptic network mutually influence one another. The shift in classification (WHO 2021) toward molecular features has deepened understanding of the epileptogenic potential of various tumors, particularly LEATs, which are frequently driven by genetic alterations such as BRAF V600E and FGFR1. These mutations activate signaling pathways including PI3K/AKT/mTOR and RAS-RAF-MAPK, thereby contributing to both tumor progression and epileptogenesis [56]. Management strategies are evolving, with a clear preference for non-enzyme-inducing antiseizure medications (NEIAEDs), such as levetiracetam

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