Brain-tumor related epilepsy: review of the literature

Review Article

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Received: 27 March 2012; Revised: 17 April 2012
Accepted: 19 April 2012; electronically published: 20 April 2012

Summary

Epilepsy is not uncommon in patients with brain tumours, and it is likely to become intractable. In some respects, this phenomenon is partially understood; however, the nature of the condition is not clear. The focus for researchers and clinicians is the prognosis of tumours and seizure control, which is affected by multiple factors, including the histopathological type, the tumour location and the management strategy. Surgery is mainly recommended for brain tumours with different extents of resection. Furthermore, anti-epileptic drugs comprise the primary management approach, as new medications are found to have improved efficacy, as well as fewer side-effects and drug interactions. However, prophylactic intervention is not always the best approach. If prophylaxis is insufficient, then other adjuvant treatments, such as a ketogenic diet and vagus nerve stimulation, may be useful.

I. Introduction

Brain tumours have been known to be common causes of epilepsy, especially intractable medical epilepsy, for over a century. Brain tumours have been found in certain patients following several decades of seizures (Kargiotis et al., 2011). Brain tumours are subdivided into primary tumours and metastatic tumours that may be either slow-growing or rapid-growing. Current studies show that tumours associated with epilepsy are more likely to be low-grade based on the World Health Organization (WHO) low-grade classification, and they occur more frequently in the cortex. These tumours grow slowly and are associated with slight mass effects and diffuse proliferations of microvessels. On the contrary, high-grade tumours grow rapidly and have distinct mass effects and shorter disease histories. These patients are usually middle-aged or elderly and exhibit other neurological deficits (Villanueva et al., 2008). Our review focuses on discussions of epilepsy associated with brain tumours of different histopathological types, and we briefly discuss the underlying provoking mechanisms. Furthermore, we analyse interventions for brain tumour-related epilepsy (BTRE) to improve the clinical outcome and patient care.

II. Incidence and epidemiology

One study showed that approximately 4% of the cases of epilepsy are induced by brain tumours, and a considerable proportion of cases are considered intractable. Over 30% of patients with brain tumours also suffer from epilepsy (Hauser et al., 1993), although the incidence of seizure depends heavily on the type of tumours. One study (Shamji et al., 2009) reported that the seizure frequency could be quite variable. Based on current studies, gangliogliomas (WHO grade I) and dysembryoplastic neuroepithelial tumours (DNT) (WHO grade I) were the most common types of tumours, and in paediatric patients, WHO grade I glioneuronal tumours account for over 50% of all brain tumours causing intractable epilepsy. There have been no reports of seizures in patients with central nervous system solitary fibrous tumours (cSFRs); however, more evidence is required. Hypothalamic hamartomas (HHs) are also considered to be rare and congenital, and they are found in the tuber cinereum and third ventricle in young patients. Nonetheless, gelastic seizures, complex partial seizures, generalised seizures and drop attacks, which are typical symptoms of HHs, can be relieved by
surgery (Maixner, 2006). In reality, HHs are not neoplastic, and they were removed from the classification of brain tumours by the WHO in 2000 (Louis et al., 2007). For intractable epileptic patients who received surgery, 17% represented brain tumours in which low-grade astrocytomas are frequent, and 30-50% of these tumours were associated with epileptic seizures as an initial symptom that compelled the patient to visit the doctor. BTRE, a type of symptomatic epilepsy, requires special considerations for treatment. Patients with tumours located in the temporal (60%), parietal (16%) and frontal (12%) lobes are more likely to exhibit seizures than those with tumours in the occipital lobe (9%), irrespective of the histopathological type of tumour (Villanueva et al., 2008).

III. Seizure types and tumour locations

An association between seizure type and tumour location has been described (Schaller, 2006). Patients with temporal neoplasms mostly present complex partial seizures in which the clinical presentations show no significant differences between neoplasms and other causes, such as temporal central sclerosis (Seeck, 2003). For tumours located adjacent to the sensori motor area, simple sensory seizures, simple motor seizures or both are typically present. For frontal central lesions, supplementary motor seizures are the most common. Both simple and complex partial seizures could occur in patients with either frontal or occipital tumours, and these occurrences indicate lesion areas.

IV. Epileptogenesis of brain tumours

Several mechanisms have been proposed for BTRE, although the nature of epileptogenesis is not clear. Rapid-growing tumours are typically associated with symptoms induced by intracranial hypertension, but they are less likely to involve seizures, whereas with slow-growing tumours, seizures are usually present, and they may predate other manifestations and the diagnosis by decades (van Breemen et al., 2007). Epileptogenic activities arise in the tumour lesions or at sites distant from the tumours, indicating that the epileptogenic mechanisms for patients with brain tumours are not common.

A. Tumour pathological injuries

Malformations of cortical development (MCD), which include focal cortical dysplasia, lissencephaly, heterotopias and polymicrogyria, are frequently epileptogenic. Slow-growth tumours have repeatedly been shown to be associated with cortical dysplasia in both animal and human studies (Bozzi et al., 2012; Kargiotis et al., 2011). MCDs occur in the neocortex, white matter and/or hippocampus and result from defects in neuron proliferation and impairments of neuronal migration and differentiation. Different histopathological grades of neuronal migration disorders were found in the peritumoural cerebral cortex of patients with brain tumours (Lee et al., 2006). Also, γ-aminobutyric acid (GABA)ergic neurons, which are crucial inhibitory interneurons, could not migrate to the cortex, and thus the balance of excitatory/inhibitory balance is impaired, resulting in pathophysiological neural network hyperexcitability.

B. Biochemical roles

The microenvironments of brain tumours are considerably altered by elevated glutamate concentrations and abnormalities in the ionotropic glutamate receptors, as demonstrated in patients with gliomas. In a magnetic resonance spectroscopy (MRS) study of 13 patients with brain tumours by (Shamji et al., 2009), it was shown that the levels of glutamate and glutamine, which are the major excitatory amino acid neurotransmitters, were up-regulated in 10 patients. The elevation of glutamate and glutamine levels contributed to hyperexcitability and presented a pathological mechanism for seizure generation. In another study of patients with dysembryoplastic neuroepithelial tumours (DNTs) and medically intractable epilepsy, magnetic resonance imaging combined with electroencephalography (EEG), electrocorticography and depth-electrode EEG was applied to localise the epileptogenic lesions. It was found that the DNTs contained cells that were immunopositive for N-methyl-D-aspartate receptor 1 (NR1) and NR2A/B in tumours. Meanwhile, immunopositive signals for the glutamate receptors 2 (GluR2) and GluR3 were detected in the peritumoural tissues (Lee et al., 2006). The imbalance of excitatory glutamatergic and inhibitory GABAergic neurotransmission may be the cause of seizures. Meanwhile, the expression of kainite receptors was increased in the peritumoural lesions, where it may downregulate inhibitory stimuli, leading to the formation of an epileptic focus. Thus, overstimulation of the signalling pathways results in alterations in intracellular communication, increased expression of abnormal receptors and perpetuation of the cycle of the disease.

Several researchers have proposed that anomalous levels of Cl(-) in the peritumoural microenvironment is a key feature of epileptogenesis in patients with glioma (Conti et al., 2011). These researchers found that the GABA-evoked currents were associated with a more highly depolarised reversal potential in Xenopus oocytes that had been injected with membranes from the peritumoural cortex of epileptogenic patients compared to membranes from healthy cortical tissues. The differences in the GABA-evoked currents could be eliminated by injection of the Na-K-2Cl cotransporter-1 (NKCC1), which acts as a transporter for intracellular...
and extracellular Cl(-). Furthermore, the up-regulated expression of NKCC1 was detected by western blot.

C. Genetic roles

Genetic variants in BTRE patients have been shown in some studies. A study was performed in 103 patients with low-grade gliomas (LGGs) to investigate the role of genetics in BTRE (Huang et al., 2011). The results showed that patients without loss of heterozygosity (LOH) at 19q were more likely to exhibit seizures, especially secondary generalised seizures. An investigation of the leucine-rich glioma inactivated 1 (LGII) gene demonstrated that LGII was highly expressed in different T98G cell clones, and this gene regulated the axon guidance pathway by reorganising the actin cytoskeleton (Kunapuli et al., 2010). These results indicate that the LGII gene plays a role in suppression of glioma metastasis and the development of epilepsy. The IL-1β-511, IL-1β-3953 and IL-1β-889 genes were reported to be involved in immune-mediated neuronal damage to peritumoural tissue in the cortex, and these genes might be involved in the development of BTRE (Bermntsson et al., 2009). However, the genetic roles in the BTRE are not known, and more studies are necessary.

V. Seizures and histopathologic types of tumours

A. LGGs

The WHO has provided a classification of tumour grade according to the histological features of tumours (i.e., necrosis, mitotic figures, cellularity) (Bondy et al., 2008), and LGGs are considered to be grade I and II tumours (Louis et al., 2007). Oligodendrogliomas and grade II astrocytomas are typical LGGs with a moderate increase of cellularity and occasional nuclear atypia. Each of these tumours has its own unique characteristics. For grade II astrocytomas, necrosis is not present, and there are only three subtypes: fibrillary, gemistocytic and protoplasmic astrocytomas. Oligodendrogliomas occur more frequently in the white matter and are present in approximately 5-15% of gliomas (Bauman et al., 2009). Previous studies have shown that LGGs are common primary central nervous systemic tumours with a frequency of 15% (Fisher et al., 2007). LGGs occur more in adults in the range of 30–50 years old, and seizures, which are among the most common symptoms, are present in 60-85% of cases. The most epileptogenic LGGs appear to be superficial and have a slow growth rate.

When patients are diagnosed with LGGs, surgery is considered as the first-line intervention. Surgical seizure control is related to the extent of surgery, the neoplasm location and the involved tissue (Sanai et al., 2011). The seizure-free rate after surgery for LGG is approximately 62.5%, and most patients presented chronic medical seizures. Several important factors are involved in the seizure control. The first factor is the tumour mass, which has been found to be important in many studies. A high degree of seizure control may be obtained, despite incomplete tumour resection. Additionally, a shorter history of seizures and gross resection of brain tissue appeared as associated with a favourable prognosis. It has been shown that only 43% of patients were free of seizures following subtotal mass resection, but 79% were seizure-free after gross-total lesionectomy, and 87% were seizure free after tailored resection with hippocampectomy plus corticectomy (Englot et al., 2011). Another study showed that 90.9% of patients were seizure-free in 3 years after an operation with mass plus additional spike-positive resection, but only 76.9% of patients were seizure-free after lesionectomy alone (Seeck, 2003). Although the surgical outcome partly depends on the patient’s age, the patient’s performance and the duration of epilepsy, surgical treatment strategies are critical for BTRE (Luiken et al., 2003).

Antiepileptic drugs (AEDs) are also used for efficient seizure control. However, choosing an appropriate regimen is still a challenge for clinicians. AEDs can be categorised into two groups according to their market year as either traditional AEDs, including carbamazepine (CBZ), clonazepam (CZP), ethosuximide (ESM), phenobarbital (PB), phenytoin (PHT), primidone (PMT) and valproate (VPA), which were licenced as antiepileptic interventions before 1992, or new AEDs, including gabapentin (GBP), lamotrigine (LTG), levetiracetam (LEV), oxcarbazepine(OXC), topiramate (TPM), pregabalin, rufinamide, vigabatrin and zonisamide (ZNS) (Verrotti et al., 2011). Based on previous studies, monotherapies using new AEDs, such as OXC and TPM, may be preferable for BTRE patients, due to their high efficacy, fewer side effects and fewer drug-drug interactions (DDIs) involving the cytochrome P450 enzyme system, which is involved in the metabolism of a wide spectrum of anti-tumour drugs (Maschio et al., 2011a; Maschio et al., 2009; Maschio et al., 2008). The use of LEV is controversial as monotherapy or add-on therapy (Maschio et al., 2011b; van Bremmen et al., 2007). Concerning tolerability, a slow titration of AEDs is necessary to reduce the incidence of dermatologic reactions or other adverse effects, which, although rare, can be life-threatening (Mockenhaupt et al., 2005). Meanwhile, OXC is not recommended as the first choice of treatment in patients who are receiving holocranial radiotherapy, due to the risk of skin reactions, which cannot be underestimated (Maschio et al., 2009). For uncontrolled seizures, concomitant use can provide good management, i.e., a combination of VPA and LEV.

The addition of chemotherapy to the treatment regimes for LGGs requires further exploration (Brada et al., 2003). A combination of procarbazine, lomustine and vincristine (PCV) was shown to be effective with a response rate of 60–70% for oligodendroglial patients, and it was 95-100% for patients with oligodendrogliomas and a combined loss of the short arm of chromosome 1 and the long arm of chromosome 19. Nevertheless, the patients presented side effects,
including cognitive impairment, myelosuppression, liver dysfunction and dermatological reactions, which may vary from mild and reversible to severe and lethal. BTRE patients have a higher risk of side effects than the overall population when their epilepsy is managed with AEDs (Giuliani et al., 2000; Moores et al., 1995; Partap and Fisher, 2009). Consequently, temozolomide (TMZ) may be better choice, due to its good tolerability. However, more evidence is needed regarding long-term administration.

To date, there is no defined conclusion regarding radiotherapy for patients with LGGs (Brada et al., 2003). Meanwhile, the side effects of radiotherapy should not be ignored. Several studies have shown that a high dose of radiation provides no significant improvement in the prognosis; in contrast, it increases the risk of side effects. BTRE patients were more prone to develop severe side effects when they were treated with a combination of radiotherapy and AEDs (including the traditional and the new medications). It was reported that all of the patients who experienced skin rashes had also accepted radiotherapy with AEDs (Maschio et al., 2011a). Life-threatening dermatological reactions, such as Stevens-Johnson syndrome, were observed in patients with cranial radiotherapy who were simultaneously receiving PHT, CBZ or PB (Beghi and Perucca, 1995; Delattre et al., 1988). Thus, the use of radiotherapy should be reserved for recurrent LGG.

Molecular therapies that inhibit the Akt-mTOR pathway may play a role in the treatment of LGGs (Sanai et al., 2011). However, the role of this pathway remains uncertain, and current trials are on-going.

**B. Gangliogliomas**

Gangliogliomas are typically regarded as benign and slow-growing tumours with grade I (Brainer-Lima et al., 2006; Yang et al., 2011). Approximately 5% of gangliogliomas are classified as grade III by the WHO, and these tumours are more aggressive (Brainer-Lima et al., 2006; Louis et al., 2007). Additionally, malignant gangliogliomas have been reported with characteristics of WHO grade IV tumours, including necrosis, a high mitotic rate and microvascular proliferation. This type of rare central nervous tumour, accounting for approximately 0.6-1.3% of the overall incidence of brain tumours, is more frequently found in young patients and typically occurs in the temporal lobe (Fisher et al., 2007). Patients with gangliogliomas present chronic seizures with a frequency of 80-90%, and they are more likely to exhibit complex partial seizures that are commonly intractable and drug-resistant.

Gross total resection (Yang et al., 2011) is applied to all gangliogliomas for a better outcome when surgery is considered to be feasible. The results have shown that seizure control is obtained in 78% of cases in less than 3 years compared with 47% beyond 3 years. Adjuvant radiotherapy and/or chemotherapy are not recommended for gangliogliomas of grade I and II. It was reported that the low-grade gangliogliomas may become malignant after radiotherapy (Ildan et al., 2001). Thus, the appropriate treatment for these tumours remains to be defined. In total, patients with gangliogliomas have a good prognosis, depending on the tumour location, the presence of seizures and the histopathological manifestations. The survival rates for high-grade neoplasms are not optimistic.

**C. Dysembyroplastic neuroepithelial tumours (DNTs)**

DNTs are rare tumours that were first identified 24 years ago (Daumas-Dupont et al., 1988). These tumors were classified as low-grade glioneuronal tumours (grade I), although malignant progression was rarely observed (Louis et al., 2007). Histopathologically, oligodendroglia-like cells, which are designated as DNT tumour cells, do not exhibit mitotic activity or necrosis. A seizure frequency of up to 100% is observed in patients with DNTs (Lee et al., 2009), and seizures may be a unique characteristic. Complex partial seizures were the most common type of seizures associated with these tumours. A total of 80% of DNTs were shown to be located in the temporal lobe (Fisher et al., 2007) followed by 16% in frontal lobe. DNTs occur most often in children and young adults. The onset of seizures was less than 20 years ago. Surgery is commonly performed for DNTs (Daumas-Dupont et al., 1988; Rushing et al., 2003), and DNTs are considered to have a good prognosis. During a follow-up study, freedom from seizures was obtained by 66% of patients, and a reduction of seizures was reported for 90% of patients.

**D. Meningiomas**

Meningiomas are extra-axial brain tumours that originate from arachnoid cap cells. They account for 13-26% of the overall intracranial tumours (Christensen et al., 2003; Marosi et al., 2008). Meningiomas occur rarely in children and adolescents with a peak incidence at 60-70 years of age. The prevalence differs between genders with a female: male ratio of between 3:2 and 2:1. Meningiomas are subdivided into 3 types (Louis et al., 2007; Radner et al., 2002): benign (grade I, 90%), atypical (grade II, 5-7%) and malignant (grade III, 2%) according to the histopathological manifestations. Meningiomas are most often found in the parasagittal area. These tumours frequently show expansive growth, and 20-50% of patients present with seizure as the initial manifestation.

Surgery is an important intervention for patients with meningiomas. Evidence has shown that there is a lower risk of recurrence after complete resection of the neoplasms. Approximately 80% of patients are cured by surgery, and 62.7% of patients obtain seizure control (Marosi et al., 2008). Patients with meningiomas have a favourable prognosis. The survival rate is 69% at 5
years, irrespective of the histopathological types. The rates of tumour recurrence are 3% for benign tumours, 38% for atypical tumours and 78% for anaplastic meningiomas at 5 years post-operation. The use of radiotherapy (Klein et al., 2002) has been controversial, but there is consensus regarding its application for atypical and recurrent meningiomas. A total dose of 45-60 Gy has been demonstrated to be effective. To date, chemotherapy (Newton et al., 2004) has not proposed due to side effects, but interferon as an antiangiogenic therapy and mifepristone as a hormonal therapy are promising.

E. Pleomorphic xanthoastrocytomas (PXAs)
PXAs is a rare primary brain tumour, representing less than 1% of astrocytomas, that affects children and adolescents (Fisher et al., 2007; Nishikawa, 2000; Wallace et al., 2011), particularly young patients less than 10 years old. PXAs are more superficial and involve the cerebral cortex and meninges. PXA was defined as a grade II tumour in 1993 by WHO. Cellular pleomorphism of spindle cells is one of the most important pathological manifestations (Sugita et al., 2000; Sundaram et al., 2000). Immunohistochemically, glial fibrillary acidic protein (GFAP) is positively expressed in the tumour cells. The tumour location is variable with a predilection for the temporal and parietal lobe supra-sella and the inferior tectum. Seizure is the typical presentation of PXAs, and 80% of patients manifested seizures at the time of diagnosis. A portion of patients have no signs of mass effects. PXAs are found in 10.5% of cases with intractable epilepsy caused by temporal lobe tumours. Simple partial seizures, complex partial seizures, complex partial seizures and generalised seizures have been reported.

Surgery is performed in patients with PXAs, whereas the use of chemoradiotherapy remains to be investigated (Fouladi et al., 2001; Nishikawa, 2000). For patients with recurrent diseases, chemoradiotherapy may be regarded as an adjuvant intervention. PXAs are frequently benign, although PXAs that transform into glioblastoma multiforme have been reported. Excellent long-term results for seizure control have been demonstrated. PXAs have a favourable prognosis, and the recurrence-free survival is approximately 81% at 5 years and 70% at 10 years.

F. Glioblastoma multiforme (GBM)
GBM, also known as glioblastoma, is a common malignant brain tumour that is classified as grade IV by the WHO. Glioblastoma is characterised by nuclear atypia, necrosis, hypercellularity and microvascular proliferation (the sine qua non of grade IV) (Louis et al., 2007). GBMs account for 10-15% of the overall primary brain tumours and occur more frequently in middle-aged and elderly people, particularly the age group ranging from 45-70 years of age (Ferguson, 2011; Fisher et al., 2007). These tumours are more often located in the frontal lobe and can infiltrate several lobes. GBMs have 2 subtypes: primary tumours or secondary tumours that evolve from low-grade astrocytomas. For patients with GBM, 29-49% of cases presented epileptic seizures.

The treatments for GBM include surgery (Ferguson, 2011; Furnari et al., 2007; Reardon and Wen, 2006), radiochemotherapy and other adjuvant interventions. The surgical extent influences the control of the tumour and the seizures. A more thorough resection of the tumour tissues is reported to provide a significant advantage. Meanwhile, it should be considered whether the surgery will intensify any the neurological deficits. The response of GBMs to radiotherapy varies from 40%-80%. When combined with temozolomide as a chemotherapy, the patient’s survival is improved. A novel targeted therapy (i.e., epidermal growth factor receptor tyrosine kinase inhibitors) provides an effective treatment, but the mechanism remains uncertain. GBMs are malignant and prone to recurrence. Meanwhile, patients commonly experience other neurological deficits. In conclusion, GBMs have a poor prognosis with a survival rate of 5% at less than 3 months if not be treated and 10% at 2 years, even following therapy.

G. Brain metastases (BM)
A total of 10-30% patients with systemic tumours have BM, which account for 10-15% of brain tumours (Fisher et al., 2007). BMs are most often metastases of lung cancer, breast cancer, melanoma and renal cell carcinoma, while hepatocellular carcinoma, bladder carcinoma and prostate cancer are much less frequent (Kyrissis et al., 2012). Seizures, including partial complex seizures, may be clinically observed in 20-50% of cases. Evidence suggests that surgery should be considered for patients with BM (Aragon-Ching and Zujewski, 2007).

Previous studies have shown that a combination of surgery and radiotherapy improved the survival and seizure control for solitary BM. It was reported that prophylactic whole-brain radiotherapy (WBRT) reduced the risk of BM after 1 year but did not improve survival. Stereotactic radiotherapy (SRS) has been extensively studied and shown to improve the patient’s quality of life due to its efficacy, minimal invasion and high selectivity, although WBRT is more common. Gamma knife SRS (GKSRS) was considered to be feasible in a study of 51 patients with small cell lung cancer and BM for whom the WBRT had not succeeded (Harris et al., 2012). Meanwhile, GKSRS was well tolerated, with few patients developing acute side effects, and the majority of patients were able to return to work shortly after GKSRS (Chao et al., 2012). Hypofractionated SRS was demonstrated to be safe and effective for the local control of BMs with a diameter of 3.1-5.5 cm, and the toxicity was acceptable (Fang et al., 2012). However, SRS alone did not yield significant benefits in tumour volume reduction or survival for BMs larger than 26 cm (3) with approximate maximum diameters of 3.5 cm (Han et al., 2012). WBRT plus SRS provided significant improvement of local tumour control rates compared
with WBRT alone for patients with fewer than 3 brain metastases, and SRS alone was recommended to be more feasible for patients with more than 4 brain metastases (Ellis et al., 2012). A large retrospective cohort trial was conducted in 502 patients with brain metastases, and the trial suggested that WBRT plus SRS significantly improved the survival irrespective the number of BMs, the manifestation of systemic disease and the score of the Karnofsky performance status (Sanghavi et al., 2001). Furthermore, a chemotherapy regimen is not commonly proposed, except in cases involving small cell lung cancer (Kyritsis et al., 2012; Sioka and Kyritsis, 2009). The prognosis of BM is considered unfavourable. The survival time depends upon the tumour type, therapies and patient’s physical status. Nonetheless, the median survival time varied from 21 to 129 weeks (Sperduto et al., 2010; Sperduto et al., 2011).

H. Primary central nervous system lymphomas (PCNSLs)

PCNSLs account for 0.3-1.5% in primary brain tumours and have high-grade histopathological presentations (Fisher et al., 2007). Previous studies have reported that approximately 10% of patients with PCNSL suffered from seizures. Surgery with both total and partial resection was performed in these patients followed by chemotherapy and/or radiotherapy. High-dose methotrexate (HD-MTX) with a mean dose of 3.0 g/m² and radiotherapy with a dose of 45 Gy was observed to prolong the survival somewhat (Poortmans et al., 2003; Yi et al., 2006). Even so, the prognosis is not favourable, with 3-26% survival at 5 years being observed.

VI. Prophylactic intervention

Prophylactic intervention is always controversial for patients with who have newly detected brain tumours but who have never had a seizure. On one hand, approximately 30% of patients with tumours do present epilepsy. On the other hand, the efficacy of prophylaxis is uncertain. Furthermore, the adverse effects and drug-drug interactions (DDIs) should not be ignored (Villanueva et al., 2008).

Both randomised controlled and cohort studies have been undertaken to examine the prophylactic value. The results demonstrated that prophylactic treatments were ineffective (Glantz et al., 2000). Thus, prophylactic treatments are not recommended by the Quality Standards Subcommittee of the American Academy of Neurology. Moreover, the discontinuance of AEDs in the first week after surgery is recommended for the brain tumour patients who have never had a seizure. The focus in these studies was on the traditional AEDs (PHI, PB and VPA), whereas studies focusing on the new generation of AEDs are lacking (van Breemen et al., 2007).

VII. Other nonspecific interventions

The ketogenic diet is a high-fat and low-carbohydrate diet that has exhibited efficacy in patients with BTRE (Scheck et al., 2011). This diet’s mechanism remains unknown. One possible theory is that the ketogenic diet results in high rates of fatty acid oxidation and increases the production of acetyl-CoA, which is useful for normal brain tissue (Gasior et al., 2006), but the majority of energy for tumours comes from glucose (Seyfried et al., 2003). Thus, the tumour growth is inhibited. Gene and gene cascades may also play a role in the control of BTRE through the ketogenic diet (Scheck et al., 2011). Certain adverse side effects have been noted, such as growth retardation, bone fractures and renal calculi (Kosoff et al., 2009), which may prevent the long-term use of the ketogenic diet in children.

Vagus nerve stimulation (VNS) was approved by the United States Food and Drug Administration in 1997 as an adjunctive therapy (1995; Labar and Dean, 2002; Obeid et al., 2009; Sugano et al., 2007), due to its efficacy and safety for patients with medically intractable epilepsy who are not recommended for surgery. Nonetheless, there have been few specific studies on the use of VNS in BTRE. Thus, it will be of interest to study the role of VNS in BTRE.

VIII. Conclusion:

Collectively, approximately 15% of the cases of intractable epilepsy are caused by slow-growing brain tumours (i.e., mostly low-grade neoplasms). Gangliogliomas, low-grade astrocytomas and oligodendrogliomas are the most typical tumours. Other tumours, such as DNTs, do not occur in high frequency, but intractable epilepsy may present with a risk up to 100%. The study of the development of BTRE was motivated by the growing need for medical practitioners and clinical researchers to evaluate the available treatments. Indeed, the lack of studies on BTRE is an important obstacle for clinicians. We hope to adopt a common scheme for the treatment of BTRE. Surgery is an important intervention for both neoplasm and seizure control. AEDs, particularly the newer drugs, including OXC and TPM, are used as the countermeasure when administered as monotherapies, due to their high efficacy and fewer side effects and DDIs. Nonetheless, OXC is not recommended for use in combination with radiotherapy, due to the occurrence of severe side effects. Application of LEV as monotherapy or as an add-on therapy is controversial. Prophylactic intervention is usually not feasible. The ketogenic diet
and VNS may be recommended; however, additional studies are required.

References


