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Seizures in Patients with Brain Tumors

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Objective : To determine the presentation, incidence, and risk factors of seizures in patients treated for brain tumors.
Methods : One hundred patients who consecutively underwent a craniotomy for the treatment of supratentorial brain tumors were assessed. The pathologies of the patients enrolled in the study included glioma (n=56), meningioma (n=31), metastatic brain tumor (n=7), primary central nervous system lymphoma (n=4), and central neurocytoma (n=2). Anti-epileptic drugs (AEDs) were administered to all patients for up to six months after the surgery. Pre-defined variables for outcome analysis included tumor grade and location, extent of tumor resection, number of seizures, age at tumor diagnosis, adjuvant therapy, medication and radiological abnormalities.
Results : Thirty patients (30%) presented at least a single episode of seizure at the time of admission. Five of these patients (16.7%) developed the seizure during the follow-up period. Newly developed seizure was noticed in six out of seventy patients (8.6%) without prior seizure. Histopathology was malignant gliomas in 10 and supratentorial meningioma in one. Early seizure developed only in two patients.
Conclusion : Compared with patients without seizure, patients with seizure at the time of admission showed younger age (p=0.003), a higher portion of low-grade glioma (p=0.001), tumor location in the frontal and temporal lobes (p=0.003) and cortical involvement (p=0.017). Our study suggestes that tumor progression is considered a significant risk factor for seizure development in glioma patients.

KEY WORDS : Brain tumor · Anti-epileptic drugs · Seizure · Risk factors.

Introduction

Seizures commonly occur in patients with brain tumors and they are related to the location of the tumor and probably to their pathology as well[4,7,12]. Seizure has been reported in more than 80% of low-grade gliomas[20], in 30 to 60% of high-grade gliomas[13], in as many as 40% of meningiomas[10] and in approximately 20% of primary central nervous system lymphomas[5].

Most tumor-associated seizures are initially focal; however, secondary generalization may occur rapidly, and therefore the focal phase may pass unnoticed.

The pathogenesis of tumor-related seizures may involve a deficiency of gamm-aminobutyric acid-mediated inhibition[6]. A surgical insult to the brain causes free radical formation and delayed neuronal damage, which is linked to epileptogenic focus formation. Conventional anti-epileptic drugs (AEDs) seem promising for the prevention of early seizure after craniotomy although the effect on postoperative late seizure remains controversial[1,2,11,16,18]. Some patients with brain tumors continue to experience seizures despite treatment and the administration of AEDs. We assessed the presentation, incidence, and associated factors of seizures in the follow-up of patients treated for brain tumors.

Materials and Methods

This study was carried out retrospectively. The study subjects were patients who underwent supratentorial craniotomy for primary and metastatic brain tumors between January 2003 and December 2004. The patients were monitored for at least twelve months after the craniotomy. Parenteral AEDs were administered to all patients prior to the operation, even when seizure was not a presenting symptom. Oral AED monotherapy was administered for up to six months after the surgery and after the oral meal was allowed.

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Seizures were defined on the basis of clinical manifestations, especially involuntary movements, alterations in consciousness or abnormal motor, sensory or psychosensory phenomena. The electroencephalographic findings were occasionally used as adjunct criteria in making the seizure diagnosis. Seizure occurrence was monitored by directly hearing from the patients at their regular visits. The patients and their caregivers were trained to recognize the subtle manifestations of seizures and were carefully questioned at every appointment.

The drug switch to other AED was performed when medical problems, such as a skin rash, increased the hepatic enzyme levels or drug fever, occurred. Another AED was added to the therapy for patients with monotherapy failure.

For the statistical comparison, we performed a Chi-square test and logistic regression analysis using the SPSS 10 software package for Windows (SPSS, Inc., Chicago, IL, USA). A p-value of less than 0.10 was considered statistically significant.

Results

Histopathology included glioma (n=56), meningioma (n=31), metastatic brain tumor (n=7), primary central nervous system lymphoma (n=4), and central neurocytoma (n=2) (Table 1). There were 58 female and 42 male patients whose age at the time of diagnosis was between 18 and 76 years (mean age 51.9). The mean follow-up period after surgery was 16.6 months.

In clinical review of enrolled patients, thirty patients (30%) presented at least a single episode of seizure at the time of admission. Five of these patients (16.7%) developed the seizure after surgery. Newly developed seizure was in six out of seventy patients (8.6%) without an initial occurrence of seizure as a presenting symptom (Fig. 1).

The risk factors associated with the occurrence of seizure as a presenting symptom were analyzed. Younger age, the pathology (especially, low grade glioma) and the tumor location in the frontal or temporal lobes were determined to be significant risk factors for seizure at the time of admission (Table 2).

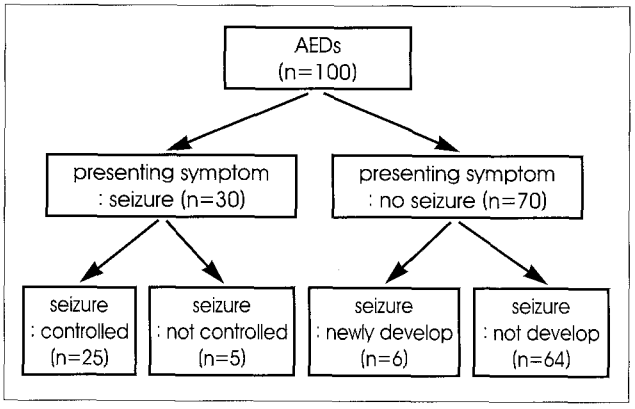

Fig. 1. Clinical outcomes of patients.

Table 1. *Pathology of enrolled patients*

Pathology	No of patients
Glioblastoma	22
Anaplastic astrocytoma	8
Anaplastic oligodendroglioma	7
Gliomatosis cerebri	2
Astrocytoma	9
Oligodendroglioma	4
Ganglioglioma	4
Meningioma*	31
Primary central nervous system lymphoma	4
Central neurocytoma	2
Metastatic brain tumor	7
Total	N=100

*exclude skull base lesion

Table 2. Comparison between with and without seizure as a presenting symptom

Characteristics		Seizure		
		+ (n=30)	− (n=70)	*p*-value
Age (*mean*)		45	54	.003
Pathology				.001
	≥ grade III glioma	10	29	
	≤ grade II glioma	14	3	
	meningioma	6	25	
	other	−	13	
Location				.003
	frontal	14	15	
	temporal	7	5	
	frontotemporal	2	2	
	other	7	48	
Cortical involvement		26	41	.017

The characteristics of the patients who developed the seizure during the follow-up period were summarized in Table 3. Ten patients were diagnosed with gliomas. Radiotherapy was performed in all patients and chemotherapy performed in nine. Early seizure (within 1 week after the surgery) developed in two patients including one meningioma. We compared glioma patients who developed the seizure during follow-up period with the glioma patients who did not experience seizures at all. Univariate analysis suggested that the tumor location (frontal and temoral lobe) and the disease progression could be used as predictors of the seizure episode in the treatment of glioma patients (Table 4).

Discussion

There is little debate about the use of AEDs as a treatment option once a seizure has occurred and the risk of future seizures is predictable. The use of AEDs in patients who have a brain tumor but no prior history of seizures remains

Table 3. Characteristics of patients developing the seizure during anti-epileptic drug (AED) therapy

No.	Age	Sex	Seizure*	AED	Pathology	Adjuvant Tx.	Surgery~1st. surgery	Tumor progress
1	20	F	–	PHT	glioblastoma	RT, chemo.	24 months	+
2	44	F	–	VPR	glioblastoma	RT, chemo.	7 months	+
3	49	F	–	PHT	astrocytoma	RT	6 months	–
4	52	M	–	PHT	AA	RT, chemo.	15 months	+
5	58	M	–	PHT	glioblastoma	RT, chemo.	6 months	+
6	62	M	–	PHT	glioblastoma	RT, chemo.	2 months	+
7	19	F	GTC	PHT	AA	RT, chemo.	5 months	+
8	36	F	GTC	TPM	meningioma	–	1 week	–
9	37	M	GTC	PHT	AO	RT, chemo.	4 months	+
10	38	M	GTC	TPM	AO	RT, chemo.	4 months	–
11	69	M	focal	PHT	glioblastoma	RT, chemo.	1 week	–

*as a presenting symptom, GTC : generalized tonic-clonic, PHT : phenytoin, TPM : topiramate, VPR : valproic acid, AA : anaplastic astrocytoma, AO : anaplastic oligodendroglioma, RT : radiotherapy, chemo. : chemotherapy

Table 4. Univariate analysis of factors associated with seizure developing in glioma patients

Variable	*p*-value
Age (<40 vs ≥40)	0.317
Seizure at admission	0.802
Location (frontal, temporal vs other)*	0.091
Cortical involvement	0.339
Surgery (total, subtotal vs partial, biopsy)	0.961
Pathology (high vs low grade)	0.197
Chemotherapy	0.517
Radiotherapy	0.540
Disease progression*	0.086

*p<0.10

questionable. In 2000, the American Academy of Neurology published a practice parameter recommendation that prophylactic anticonvulsants should not be routinely used in patients with newly diagnosed brain tumors, and that such drugs should be tapered within one week after surgery for such tumors[3]. However, one survey demonstrated that the routine use of AED prophylaxis in patients with brain tumors remains the prevailing practice of members of the American Association of Neurological Surgeons (AANS) despite the lack of convincing evidence in support of such an approach. More than 70% of respondents reported the routine use of AED prophylaxis for the treatment of patients with intra-axial gliomas or brain metastases[14].

The formal guideline for the use of AEDs has not been established and the legal issue should be considered in Korea. We have experienced AED prophylaxis for all brain tumor patients who underwent a surgical procedure despite substantial evidence that it is ineffective[15,17]. However, this approach could reflect a clinical practice. Low-grade glioma, cortical involvement, especially in the frontal and temporal lobes, and younger age were determined to be the primary risk factors for the development of seizure as a presenting symptom in our study. Eleven out of the one hundred patients enrolled in this study developed at least a single episode of seizure during the follow-up. We cannot rule out the possibility of the overuse of AEDs in our patients. However, our study suggested that tumor progression was a significant risk factor for seizure development in glioma patients. The progression can give rise to the new epileptogenic focus. Three patients experienced the initial seizure more than six months after the surgery. Their experiences can be explained by the new epileptogenic focus formation, and the failure of prophylactic AEDs should be ruled out. Therefore, the different strategy of AED therapy should be given to patients with gliomas rather than with other tumors such as meningioma or metastases.

Although chemotherapy and radiotherapy did not show the statistical significance associated with seizures in our study, the interactions between chemotherapeutic drugs and AEDs have been known to cause insufficient tumor and seizure control or lead to toxicities. Most drug interactions between AEDs and chemotherapeutic agents result from sharing the cytochrome P-450 isoenzyme metabolic pathways[19]. The avoidance of enzyme-inducing AEDs is recommended in patients with brain tumors, particularly in association with chemotherapy. Corticosteroid, commonly used to treat cerebral edema in patients with brain tumors, also induces enzyme-mediated metabolism[8,9]. In clinical practice, the plasma concentration of AEDs should be frequently monitored if used in combination with corticosteroid or chemotherapeutic agents.

The clinical decision to initiate and terminate AED therapy is based on the judgment that the risk of seizure occurrence outweighs the risks associated with AEDs and their toxic effects. Serious rash, including Stevens-Johnson syndrome, can occur with AEDs administration. AEDs may mimic tumor progression through their neurologic side effects and may cause or aggravate depression, which may affect the quality of life. There is a need for studies that address the practical guidelines for AED therapy in patients with brain tumors. Furthermore, studies that randomize patients with various types of brain tumors are needed.

Conclusion

Seizures are commonly associated with brain tumors. Younger age, low-grade glioma, frontal and temporal

tumor location, and cortical involvement are risk factors for developing seizure as a presenting symptom. However, the disease progression is associated with seizure development during AED therapy in glioma patients.

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Commentary

This article describe the risk factors of seizure development of patients with brain tumor. The authors conclude that younger age (<40 years old), low-grade glioma, frontal and temporal location, and cortical involvement are the risk factors of seizure-related tumor. They suggest development of seizure had the possibility of tumor progression in glioma patients. Also, this article provide high risk group of seizure and need of antiepilptic medication in patients with tumor-related seizure.

They did not mentioned the patients with recurrence and no change of seizures even after surgery, probably due to short follow-up period. The authors, however, may inevitably face to patients with uncontrolled seizure in long term follow up. I like to recommend to look into the risk factors in long term follow up, evaluation methods and treatment plan for these kinds of patients.

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