Clinical Article

Significance of Chronic Epilepsy in Glial Tumors

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Objective : The aim of this study is to compare the frequency of postoperative epilepsies of patients with chronic as opposed to recent onset epilepsy due to glial tumors in the frontal or temporal lobe with the hypothesis that patients with chronic epilepsy do worse.

Methods : We compared the clinical and diagnostic characteristics of the patients(n=73) who had seizures preoperatively to those of the patients(n=153) who did not. Among those who have had seizures preoperatively, we compared those(n=32, chronic seizure group) who had seizures a year or more prior to surgery to those(n=41, acute seizure group) who had seizures within a year prior to surgery.

Results : Among the various factors, the frequency of benign pathology and favorable neurological state were higher in seizure group than in non-seizure group($p<0.05$). Complex partial seizure and low-grade tumors were frequent in chronic seizure group, whereas simple partial seizure and high-grade tumors were frequent in acute seizure group. Seizure-free rate was significantly higher in acute seizure group than in chronic one ($p<0.05$). Also, the difference of seizure control rate between surgical strategies were statistically significant($p<0.05$).

Conclusion : This study indicates that preoperative seizure durations and frequencies have a close relationship with the frequency of postoperative epilepsy of glial tumors. A longer lapse may allow the formation of epileptogenic foci, leading to chronic epilepsy, and eventually having a negative effect on the prognosis of the patients. Factors including histopathological characteristics of the tumor, its location, seizure duration/frequency, and semiology should be taken account of deciding on surgical strategies.

KEY WORDS : Brain neoplasms · Glioma · Epilepsy.

Introduction

Seizures are a common presenting feature in patients with intracranial tumors, especially low grade gliomas[1,8,17,18,19,20]. The incidence of epilepsy associated with brain tumors is approximately 35% when all locations and histologic types are considered[3,8,12]. Although seizure is one of the most frequent symptoms of brain tumors, its exact pathogenesis is currently unknown.

The critical factors responsible for the development of epilepsy appear to be associated with the indolent growth pattern and location of the lesion[5,17,20]. Seizures are more common with the relatively slow growing tumors, e.g. low grade astrocytomas, oligodendrogliomas, mixed oligodendroastrocytomas, and gangliogliomas[9]. Many of the rapidly growing gliomas predominantly involve the white matter and appear to be less epileptogenic[19,20]. The chronic nature of a mass lesion will often account for the adverse effects of the tumor on the adjacent cortical neurons[17], which occur morphologically and biochemically in the form of neurotransmitter alterations[10].

The present study was conducted under the assumption that if the seizure foci form around the brain tumor as reported above, more chronic epileptic patients would have stronger aberrant neuronal network, thus more frequent postoperative epilepsies. We compared the frequency of postoperative epilepsies with chronic as opposed to recent onset preoperative epilepsies due to glial tumors in the frontal or temporal lobe with the hypothesis that patients with chronic epilepsy do worse.

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Materials and Methods

Two hundred twenty-six patients(age range 32 to 71 years; 121 males and 105 females) with the glial tumor were studied retrospectively as the subjects, who had under-

gone brain surgery from January 1995 to December 2001. Exclusion criteria in this study are as follow; 1) operative or postoperative mortality, 2) tumor locations except frontal and temporal lobe, 3) tumor histopathology except ganglioglioma, astrocytic gliomas, 4) positive family history of epilepsy, 5) recurrent glial tumors. Demographic data, including age at presurgical evaluation, age at seizure onset, duration and frequency of seizure disorder, neurologic deficits at presentation, and etiologic factors, were acquired from the medical records. Laboratory tests at admission, fasting blood glucose and serum electrolyte levels(calcium, magnesium, and sodium), were reviewed. Based on the ictal semiology and EEG findings, patient's seizures were classified as simple partial(simple motor or sensory), simple partial with secondary generalization, complex partial, complex partial with secondary generalization, or primary generalized seizure. Chronic seizure was defined as seizure occurring a year or more prior to surgery.

The following surgical procedures were performed : subtotal tumor resection(n=62), focal tumor resection without seizure foci mapping(n=109), radical tumor resection without seizure foci mapping(n=43), and radical tumor removal with seizure foci mapping(n=12). The term 'Radical tumor removal' was defined that brain adjacent to the lesion was also included in the resection strategy in addition to removing the tumor.

The pathological diagnosis was classified as ganglioglioma (grade I~II), pilocytic astrocytoma(grade I), diffuse astrocytoma(grade II), anaplastic astrocytoma(grade III) and glioblastoma(grade IV) according to World Health Organization classification of the neuroepithelial tumors[11]. Of the 226 patients, 33 were diagnosed as grade I, 51 as grade II, 46 as grade III, and 96 as grade IV.

The postoperative observation periods ranged from 5 to 63 months (mean, 29 months). With respect to the postoperative seizure state, patients were assigned to two different outcome classes, seizurefree or not.

Statistical analysis was performed by Student's t-test and cross tabulation test using the Statistical Package for Social Science Statview Package(SPSS Inc., Chicago, IL, USA) with a p value < 0.05 considered statistically significant.

Results

Clinicopathological characteristics of the patients with glial tumors

Clinicopathological profiles of the patients with glial tumors related to seizures are listed in Table 1. There were a total of 226 patients, with 73 patients(32.3%) in seizure group, and 153 patients(67.7%) in non-seizure group. At time of operation, patient's average age was 36.7 and 39.8 for seizure group and non-seizure group, respectively, showing no significant difference. Male to female ratio for seizure group was 48:25 and for non-seizure group was 73:80, showing no significant difference. The number of patients with neurological deficits on admission was 112 for non-seizure group(73.2%), which were considerably more than 18 for seizure group(24.7%). Tumors for seizure group were more frequently observed in the temporal lobe, whereas tumors for non-seizure group were commonly involved in more than two adjacent cerebral cortexes. Histopathological examination showed that anaplastic astrocytoma and glioblastoma were more frequent in non-seizure group than in seizure group, but the relatively frequent tumor pathology in seizure group was ganglioglioma and diffuse astrocytoma($p < 0.05$).

Clinicopathological profiles of the patients with glial tumor-associated epilepsy

Seventy-three patients in seizure group were further divided in chronic seizure group(seizure duration($\geq$ 1 year, n=32) and acute seizure group(seizure duration < 1 year, n=41). Clinicopathological profiles of the patients with glial tumor-associated epilepsy are listed in Table 2. In both groups there were more males with sex ratios of 19:13 and 29:12 for chronic and acute seizure groups respectively. Average age at the point of operation was 33.2 and 36.3 in respective group. There was

Table 1. Clinicopathological profiles of the patients with glial tumors related to seizures

	Seizure (n=73)	Non-seizure (n=153)	p-value*
Age(mean, year)	36.7	39.8	0.452
Sex (male : female)	48:25	73:80	0.182
Neurological deficits on admission	18 (24.7%)	112 (73.2%)	0.014
Location of tumor			
Frontal lobe	18 (24.7%)	50 (32.7%)	
Temporal lobe	36 (49.3%)	34 (22.2%)	
Adjacent two more cortexes**	19 (26.0%)	69 (45.1%)	
Histopathology			0.024
Ganglioglioma (I~II)	5 (6.8%)	0 (0.0%)	
Pilocytic astrocytoma (I)	6 (8.2%)	22 (14.4%)	
Diffuse astrocytoma (II)	36 (49.3%)	15 (9.8%)	
Anaplastic astrocytoma (III)	11 (15.1%)	35 (22.9%)	
Glioblastoma (IV)	15 (20.6 %)	81 (52.9%)	

* Student's t-test was used for a statistical comparison of continuous variables. Discrete variables were compared by cross tabulation tests, ** Adjacent two more cortexes included of fronto-temporal, fronto-parietal, temporo-parietal, and fronto-temporoparietal areas

no significant difference of age and sex between two groups. The number of cases with abnormal laboratory findings at admission was 6(18.8%) and 16(39.0%) in each group respectively, with no significant difference between two groups. The number of cases with neurological deficits on admission was 8(25.0%) and 10 (24.4%), with no significant difference between two groups. Ten of 19 patients in chronic seizure group and 3 of 8 patients in acute seizure group had interictal epileptiform discharges on electroencephalography, with no significant difference. Temporal lobe was the most frequent site for glial tumors in both groups. Mean seizure duration was 18.4 and 3.6 months and mean seizure frequency was 4.5 and 1.5 times/year in respective group, with significant difference($p<0.05$). As for seizure patterns, both groups had the highest number of primary generalized seizure. Complex partial seizure and complex partial seizure with secondary generalization were relatively frequent seizure pattern in chronic seizure group, whereas simple partial and simple partial with secondary generalization were relatively common in acute seizure group. In histopathological examination of brain tumor, diffuse astrocytoma was more frequent in chronic seizure group than in acute seizure group, and glioblastoma was more frequently observed in acute seizure group than in chronic seizure group. However, this difference between tumor grade and seizure duration was not significant.

Seizure outcome related to seizure duration and surgical strategies

Table 3 shows the outcome of 73 patients with respect to seizure control. Seizure-free rate after surgery was 62.5% in chronic seizure group, whereas 82.9% in acute seizure group. This difference of seizure control rate between two groups was statistically significant($p<0.05$). With the surgical strategies, the most favorable results were observed in patients who underwent radical tumor resection with seizure foci mapping(seizure-free rate; 91.7%). The ratio of seizure-free patients who underwent incomplete tumor resection was lower(50%). Whereas 13 of 16 patients(81.3%) who underwent radical tumor resection without intraoperative monitoring became free of seizures, only 23 of 31 patients(74.3%) who underwent focal tumor resection without seizure foci mapping was seizure-free. These differences were stati-stically significant($p<0.05$).

Discussion

Eeizure is one of the most frequent symptoms of brain tumor and many patients with benign supratentorial glioma are first admitted to hospital with the seizure manifestation[23]. Cases of malignant tumor manifesting as seizure is relatively rare, however seizure is frequent during the clinical course, with about 60% of malignant glioma patients experiencing seizure[13]. Of a lot of factors, the most important factor has been known as the location of the tumor[5,17,20]. With respect to the tumor location, 22-68% of patients with supratentorial tumor experience seizure[6,21]. The frequency of seizure is high in the superficial area or cortex of tumor location, whereas low in deep subcortical region[12,24]. In this study design, therefore, we focused on only temporal or frontal cortex in tumor location.

Seizure also has a correlation with the chronicity of tumor[5,6,20]. Slowgrowing tumors such as benign astrocytoma, gangli-

Table 2. Clinicopathological profiles of the patients with glial tumor-associated epilepsy

	Chronic seizures (n=32)	Acute seizures (n=41)	p-value*
Age (mean, year)	33.2	36.3	0.432
Sex (male : female)	19:13	29:12	0.287
Laboratory abnormalities	6 (18.8%)	16 (39.0%)	0.065
Neurological deficits on admission	8 (25.0%)	10 (24.4%)	0.823
Interictal epileptiform discharges on electroencephalography (%)	55.5% (10/19)	37.5% (3/8)	0.083
Location of tumor			
Frontal lobe	8 (25.0%)	10 (24.4%)	
Temporal lobe	14 (43.7%)	22 (53.6%)	
Adjacent two more cortexes**	10 (31.3%)	9 (22.0%)	
Seizure duration (mean, months)	18.4	3.6	0.001
Seizure frequency (mean, times/year)	4.5	1.5	0.014
Semiology			
Simple partial	3 (9.4%)	7 (17.1%)	
Simple partial with SG[a]	1 (3.1%)	3 (7.3%)	
Complex partial	3 (9.4%)	2 (4.9%)	
Complex partial with SG[a]	5 (15.6%)	0 (0.0%)	
Primary generalized seizure	20 (62.5%)	29 (70.7%)	
Histopathology			0.062
Ganglioglioma (I~II)	4 (12.5%)	1 (2.4%)	
Pilocytic astrocytoma (I)	3 (9.4%)	3 (7.3%)	
Diffuse astrocytoma (II)	20 (62.5%)	16 (39.0%)	
Anaplastic astrocytoma (III)	3 (9.4%)	8 (19.5%)	
Glioblastoma (IV)	2 (6.2%)	13 (31.8%)	

* Student's t-test was used for a statistical comparison of continuous variables. Discrete variables were compared by cross tabulation tests, ** Adjacent two more cortexes included of fronto-temporal, fronto-parietal, temporo-parietal, and fronto-temporoparietal areas, [a] : secondary generalization

oglioma, dysembryoplastic neuroepithelial tumor have the high frequency of seizure[24]. Relatively fast-growing tumors have reduced frequency of seizure[12]. In the present study, patients with the low grade gliomas such as ganglioglioma and diffuse astrocytoma experienced the higher frequency of seizure disorder than those with malignant glial tumors such as anaplastic astrocytoma and glioblastoma. The chronic nature of a mass lesion will often account for the adverse effects of a tumor on the adjacent cortical neurons[17], which form abnormal local excitatory and inhibitory neuronal circuits morphologically or occur in neurotransmitter alterations biochemically[10]. It has also been demonstrated that the hyperexcitable cortex surrounding the tumor nidus in low grade gliomas has a significantly decreased population of γ-aminobutyric acid and somatostatin containing neurons when compared to adjacent non-tumor, non-epileptogenic cortex from the same patient[7]. These reports support the hypothesis that the mechanisms of seizure in malignant and benign tumors are different. This study was focused on the chronicity of seizure and was designed to compare the seizure control rate of patients with chronic as opposed to recent onset seizure due to glial tumors with the hypothesis that patients with chronic seizures do worse. It has pragmatic value both to the clinical practitioner as well as to the academic researcher for studying epileptogenesis in brain tumors. This study set a period of one year as a criterion to distinguish acute and chronic seizure groups, though this standard is rather arbitrary. The period of a year was determined as being long enough for an individual epileptogenic zone to be formed around the brain tumor, considering that seizure frequency is the highest within the first year of post-traumatic epilepsy[15]. In reality, differences in clinical prognosis of the patients classified with this standard could be observed in the results of this study.

Table 3. Seizure outcome related to seizure duration and surgical strategies

	Seizure-free (n=54)	Seizure recur (n=19)	p-value*
Seizure duration			0.028
Chronic (≥ 1 year) (n=32)	20	12	
Acute (< 1 year) (n=41)	34	7	
Surgical strategies			0.012
Subtotal tumor resection (n=14)	7	7	
Focal tumor resection without SFM[a] (n=31)	23	8	
Radical tumor resection without SFM[a] (n=16)	13	3	
Radical tumor resection with SFM[a] (n=12)	11	1	

a : seizure foci mapping

Understanding the spatial and causal relationships between structural lesions and epilepsy is essential to rational therapeutic strategies. Although there may be evidence to support the concept of separate seizure foci surrounding a tumor[14,17], controversy exists as to whether it is essential to include these peripheral epileptogenic zones in the surgical resection. Favorable results have been reported after lesionectomy, with a percentage of seizure-free patients ranging from 65 to 80%[2,4,8,16,20]. They suggest that the cortex surrounding the tumor loses the ability to independently initiate and propagate seizures once the tumor itself has been removed[14,19]. Others noted the importance of defining and extirpating the epileptogenic zone[2,4,16,20,22]. Accordingly, the resection of the epileptogenic zone in patients with tumor-associated epilepsy provided a high level of postoperative seizure control. Affirmatively, in our patients, seizure control was better if the zone of seizure origin and the zone of maximal interictal spiking were completely excised.

However, the available literature on the question of whether excision of the epileptogenic brain area results in a better seizure control than lesionectomy alone is heterogeneous with regard to tumor location, tumor type, and the degree of malignancy of the tumors; the data and conclusions are conflicting[2,8,20,22]. This question is important, particularly because of the high costs of intraoperative monitoring and the need to refer patients to sophisticated epilepsy centers[2]. Thus, our study has a high significance in indicating guidelines for decision of surgical strategies. Seizure-free rate after surgery was 82.9% in acute seizure group composed of tumors with a high-grade relatively, with a high percentage of seizure control rate. Therefore, we suggest that lesionectomy alone is sufficient in patients with tumor-associated with acute seizure, especially in malignant tumors. Radical resection without intraoperative monitoring was also recommended if tumor is located on non-functional areas. On the other hand, only 62.5% of patients in chronic seizure group were seizure-free, with a lower percentage than in acute seizure group. We recommend that additional resection of the epileptogenic zone is required to achieve optimal seizure control in chronic seizure group, especially in low-grade gliomas.

Conclusion

This study indicates that the longer seizures persist, the poorer prognosis is. In cases of low-grade gliomas, a longer lapse allows formation of epileptogenic foci, leading to chronic epilepsy, and eventually having negative effect on the prognosis of the patients. Thus, the management of patients with chronic seizure associated with low-grade gliomas has included identification and resection, when possible, of the

seizure foci in addition to performing a complete tumor removal. The standard of chronic seizure was established a period of one year in this study, but is rather arbitrary. Further clinical studies will provide useful information.

Complete resection of tumors provides the most important condition for seizure relief. Others including histopathological characteristics, location of the tumor, and semiology should be taken account of deciding on surgical strategies.

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