

# Epilepsy—associated risk factors in patients with brain tumors in a Mexican Hospital

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## Abstract

**Objective:** To determine the risk factors associated to the development of epilepsy in patients with intraparenchymal brain tumors.

**Materials and methods:** Retrospective cohort study. Adult patients with intraparenchymal brain tumor diagnosed in a 5– year time period were included. Data was collected using a collection sheet including the record number, gender, age, type of tumor, location of the tumor, and the presence of seizures. In patients who developed epilepsy, the time of appearance after the brain tumor diagnosis, the development of status epilepticus, and the antiepileptic treatment were reported. Patients with previously diagnosed epilepsy were excluded. A multivariate analysis was done using a multiple logistic regression model for the epilepsy development risk factors. A multiple logistic regression test was done taking as a result variable the presence of epilepsy.

**Results:** 123 patients were included. The average time of tumor evolution was 10.8 months. Primary brain tumors were mostly observed (61.8%). 59 patients (47.9%) developed epilepsy after the diagnosis of brain neoplasm and 10 patients (16.9%) developed status epilepticus. The most frequently used antiepileptic drug was Phenytoin (59.3%). Mostly, the observed tumor location was supratentorial (87%). Those patients who developed epilepsy had a longer time of tumor evolution (13.3 months vs. 8.6 months,  $p = 0.012$ ) and had a supratentorial location (96.6% vs. 78.1%,  $p = 0.0023$ ) compared to those who did not develop epilepsy.

**Conclusion:** Development of epilepsy is more frequently found in those patients with tumors located supratentorially and also highly related to longer evolution neoplasms.

**Keywords:** brain tumors; epilepsy; risk factors; Mexico

**Abbreviations:** WHO: world health organization, ILAE: international league against epilepsy, BTE: brain tumor related epilepsy, ES: status epilepticus, DNETS: dysembryoplastic neuroepithelial tumors, CNS: central nervous system, CT: computed tomography, MRI: magnetic resonance imaging

## Introduction

Epilepsy is a major health problem among the adult population. According to the data provided by the World Health Organization (WHO), around 50 million people worldwide suffer with epilepsy making it one of the most common neurological disorders. It represents 0.6% of the global burden of disease with significant economic repercussions because of the health care that it requires.<sup>1</sup>

Epilepsy is normally defined as a brain disorder characterized by a permanent predisposition to generate epileptic seizures and neurobiological, cognitive, physiological, and social consequences of the condition.<sup>2</sup> It was defined conceptually in 2005 as a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures. This definition is usually practically applied as having two unprovoked seizures >24h apart. The International League Against Epilepsy (ILAE) accepted recommendations of a taskforce altering the practical definition for special circumstances that do not meet the two unprovoked seizure criteria.<sup>3</sup> Traditionally, the diagnosis of epilepsy requires the appearance of at least two unprovoked seizures, but with a predisposing condition like brain tumors, a unique crisis

can justify the diagnosis due to the high risk of recurrence.

Brain tumors can originate from brain tissue or from tumors outside Central Nervous System (metastases), and are relatively frequent.<sup>4</sup> Around 14 per 100,000 inhabitants per year are diagnosed with primary brain neoplasm in the United States.<sup>5</sup>

One of the complications of brain tumors is the development of epilepsy also known as “Brain Tumor related Epilepsy” (BTE). Approximately 10– 15% of adult– onset epilepsy is caused by brain tumors.<sup>4</sup> According to Englot Dj et al.<sup>5</sup> up to 70% of patients with brain tumors will present epilepsy during their disease being the first clinical manifestation of the neoplasm in 50% of the cases. The impact of epilepsy on the total burden of the disease is high. In addition, both epilepsy and the use of anti– epileptic drugs predispose to deterioration of cognitive function which add more problems to these patients.<sup>7</sup>

Status Epilepticus (ES) is a more severe form of epilepsy. It is a neurological emergency that can occur in 15%–22% of patients with BTE. Non–convulsive SE may be more common in patients with a brain tumor and should be considered as a differential diagnosis for those patients that present changes in their mental status which is not explained by another cause.<sup>8</sup>

Any brain tumor can cause epilepsy. The associated risk depends largely on the histological type of the neoplasm,<sup>9</sup> being more

commonly found in neuroglial tumors and low-grade gliomas such as dysembryoplastic neuroepithelial tumors (dnet) and gangliogliomas.<sup>10</sup> It is less frequently found in metastatic tumors which represent an incidence of 20%–35%<sup>11</sup> and in primary central nervous system lymphoma.

Brain tumor-related epilepsy tends to be symptomatic being the focal seizures the most frequent kind.<sup>12</sup> The type of crisis is variable in brain tumors a simple partial type can be described in 23%–58% of the cases; complex partial in 7%–31% and generalized in 10%–68%.<sup>14</sup>

The pathogenesis is entirely unknown. Studies have postulated changes in neurotransmitters and their receptors, and tissue changes around the lesion (such as reactive astrocytosis, inflammation, and microglial proliferation).<sup>15</sup> The tumor cells themselves can be epileptogenic due to the secretion of glutamate (excitatory neurotransmitter). Also, an inadequate homeostasis in the peritumoral tissue that causes an alteration between the excitation–inhibition balance which increases susceptibility to epilepsy has been described.<sup>16</sup>

The treatment of epilepsy for these patients is complicated because seizures may be refractory to treatment, may persist despite surgical treatment, and antiepileptic drugs may interact with chemotherapy and may not have adequate penetration into the blood–brain barrier due to the abnormal environment of the tumor. Currently, there are no guidelines that recommend any type of antiepileptic drug over another for brain tumors. Therefore, their options depend on the tolerance and pharmacokinetic interactions with chemotherapeutics. The prophylactic use of antiepileptic drugs is not recommended in patients who have not yet presented seizures.<sup>15</sup>

There are few prospective studies for the treatment of epilepsy in patients with brain tumors despite high frequency of treatment-resistant presentations. On the other hand, much is known about the surgical treatment for refractory epilepsy including those cases associated with brain tumors of histological low-grade.<sup>15</sup>

We did not find any publication about brain tumors related to epilepsy in our country. Thus, it is in our best interest to describe the characteristics of this population.

The objectives of this study are to determine the risk factors associated to the development of epilepsy in patients with intraparenchymal brain tumors, to recognize the association between benign and malignant brain tumors with epilepsy, and to recognize the most frequent location of intraparenchymal brain tumors associated with epilepsy

## Materials and methods

An intentional search for patients with intraparenchymal brain tumor diagnosis in a 5-year time period was done. The data was collected using a data collection sheet which included the record number, gender, age, type of tumor, location of the tumor, and the presence of seizures. The histological variant of the tumor was documented based on the pathology report and the time of tumor evolution was based on the clinical record. In case of not having a pathology report, the histological variant was determined based on the image study characteristics and according to the location of the primary tumor. The tumor location report included the presence or absence of cortical involvement according to the results of the imaging study, and the relation of the tumor to the tentorium (supra or infratentorial). In patients who developed epilepsy the time of appearance after the brain tumor diagnosis, the development of status epilepticus, and the antiepileptic treatment was reported.

The study design was a retrospective cohort which included adult patients with intraparenchymal brain tumor diagnosis during a 5-year period at the Hospital Central “Dr. Ignacio Morones Prieto” in San Luis Potosi, Mexico. The included patients were older than 18 years and had a brain tumor diagnosis. We excluded those patients who were previously diagnosed with epilepsy, those that presented epilepsy of other etiologies than brain tumor, and patients with incomplete data.

## Statistical analysis

The database was built using Microsoft Excel (2018,16.16.7) and the statistical analysis done using the Statistics $\square$  (version 13) program. The data was reported as means including standard deviation or as a percentage according to the sample distribution. Qualitative variables were shown as numbers or percentages. The demographic variables were compared using the T-student test or Chi-Square Test. A multivariate analysis was done using a multiple logistic regression model for the development of epilepsy risk factors. The multiple logistic regression test was done taking as a result variable the presence of epilepsy and as independent variables the age, sex, location, time of evolution, and the type of tumor. P values less than 0.05 were considered statistically significant.

## Ethical considerations

This study was approved by the Ethics Committee of the Hospital Central “Dr. Ignacio Morones Prieto”. This research work was considered a risk-free. Therefore, it did not require an informed consent. Discretion was maintained by handling the information as anonym.

## Results

In total, 123 patients were included. Most of them were women (62). The mean age was 53.4 years and the mean time of tumor evolution was 10.8 months (0.25–66). The majority of the patients had a primary CNS tumor (61.8%). Based on the histological type we found that 31.5% were high-grade tumors, 22.8% low-grade and 41.5% were not confirmed histopathologically.

About 59 patients (47.9%) developed epileptic seizures after the brain tumor diagnosis. In this group, 21 patients (35.6%) had seizures as first symptom of the brain tumor and 10 patients (16.9%) developed status epilepticus. The most frequently prescribed medication for these patients was Phenytoin (59.3%) followed by Levetiracetam (35.6%) (Table 1).

The most frequent tumor location was located supratentorial (87%). Cortical involvement of the lesions was present in 30.1%, absent in 20.3%, and it was not possible to determine the location for the remaining 49.6% (Figure 1).

### Figure 1: Brain tumor location

The most frequently found low-grade tumor was oligodendroglioma (12.2%), followed by astrocytoma (11.4%). The most common high-grade tumor was multiform glioblastoma (22.8%). Metastasis occurred in 46 patients (37.4%) (Figure 2).

### Figure 2: Histological variant of brain tumors

When comparing the patients who developed epilepsy and those who did not, we observed that the age in both groups was similar (54.5 and 52.4 years,  $p=0.49$ ). Epilepsy was more frequent in males (32 vs 29,  $p=0.23$ ). It could not be established if there was involvement of the cerebral cortex in most of the cases (47.5% vs 51.6%,  $p=0.66$ ).

The most frequent tumors in both groups were primary CNS tumors (62.7% vs 62.5%,  $p=0.86$ ); the majority of the histological grade classifications were inconclusive (37.3% vs 43.8%,  $p=0.58$ ); the frequency of high-grade tumors was very similar in both groups (32.2% vs 32.8%) and in patients who developed epilepsy, low-grade tumors were more frequently found (27.1% vs 18.8%,  $p=0.58$ ).

Patients who presented symptomatic epilepsy had a longer time of tumor evolution compared to those who did not (13.3 months vs 8.6 months,  $p=0.012$ ). The most common tumor location was supratentorial in both groups (96.6% vs 78.1%,  $p=0.0023$ ) (Table 2).

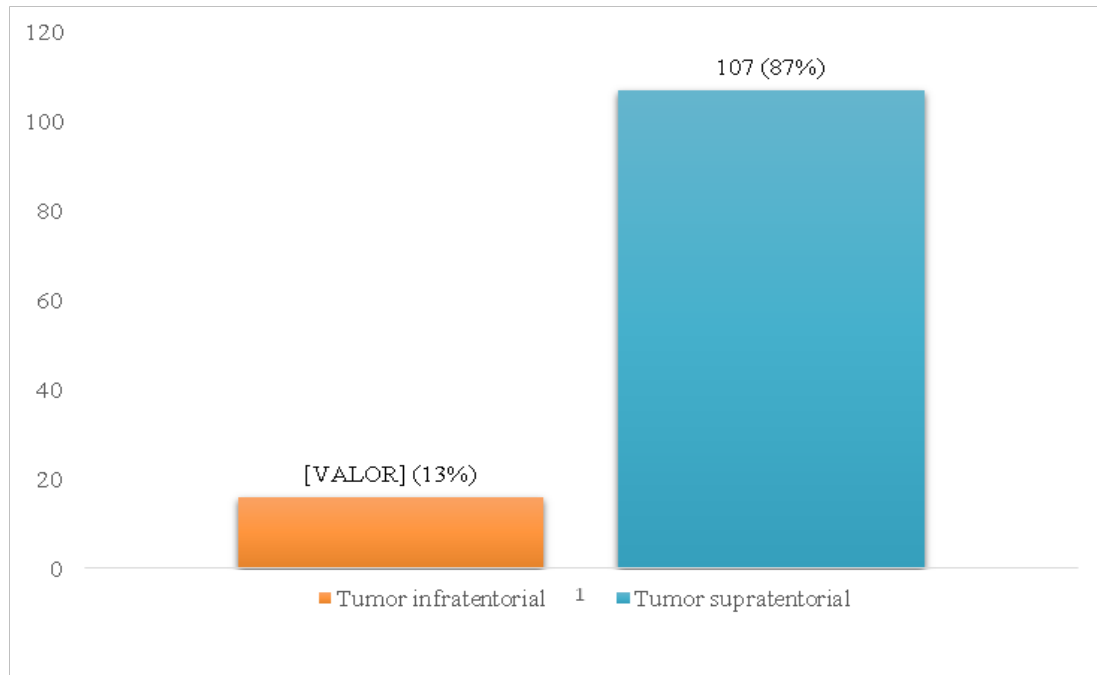


Figure 1: As was expected the most of the tumors were localized in supratentorial situation. Temporal and frontal cortical areas are more convulsive.

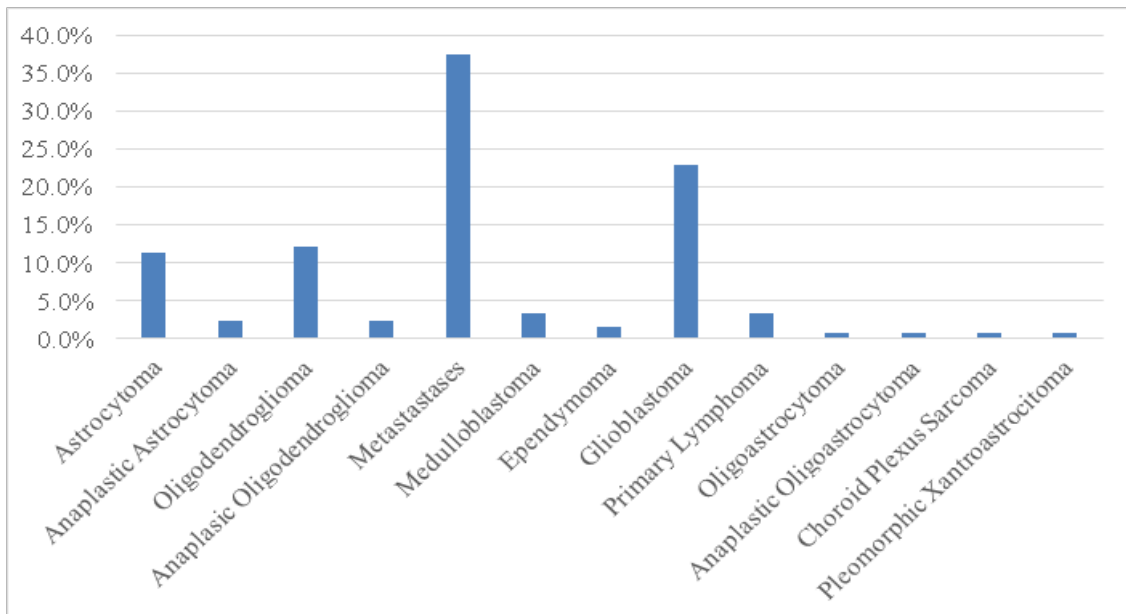


Figure 2: Types of tumors by histopathology.

**Table 1:** Demographic characteristics, tumors, seizures, and pharmacological treatment.

<b>Age</b>		
Female	62	50.40%
Male	61	49.60%
Mean age (years)	53.42	
Average time of tumor evolution (months)	10.8	(0.25–66)
<b>Origin</b>		
CNS primary tumor	77	62.6%
Metastases	46	37.4%
<b>Histological grade of tumor</b>		
Low-grade	28	22.8%
High-grade	40	32.5%
Mesodermic	5	4.1%
Non-confirmed histopathology	50	40.7%
Seizures	59	47.90%
Initial manifestation with seizures	21	35.6%
Status epilepticus	10	16.9%
<b>Treatment</b>		
Phenytoin	35	59.3%
Magnesium valproate	2	3.4%
Levetiracetam	21	35.6%
Carbamazepime	2	3.4%
Others	2	3.4%

**Table 2:** General characteristics of the cases.

Variable	<b>Tumors+epilepsy (n=59)</b>		<b>Tumors without epilepsy (n=64)</b>		<b>p value</b>
Age	54.5		52.4		0.49
Sex					
Female	27	45.8%	35	54.7%	0.23
Male	32	54.2%	29	45.3%	
Time of tumor evolution (months)	13.3		8.6		0.011
Cortical involvement					
Cortical lesion	20	33.9%	17	26.6%	
Non-cortical lesion	11	18.6%	14	21.9%	0.66
Undetermined	28	47.5%	33	51.6%	
Tumor location					
Supratentorial	57	96.6%	50	78.1%	0.0023
Infratentorial	2	3.4%	14	21.9%	

Table Continued

Variable	Tumors+epilepsy (n=59)		Tumors without epilepsy (n=64)		p value
Type of tumor					
CNS primary	37	62.7%	40	62.5%	0.86
Metastases	22	37.3%	24	37.5%	
Histological grade					
Low-grade	16	27.1%	12	18.8%	0.58
High-grade	19	32.2%	21	32.8%	
Mesodermic	2	3.4%	3	4.7%	
Inconclusive	22	37.3%	28	43.8%	

## Discussion

Our study aimed to determine if there are any risk factors that predispose patients with brain tumors to develop epilepsy. Our results show that patients with a supratentorial location of the tumor and with longer time of tumor evolution have an increased risk for epilepsy.

We observed an average age of 53.4 years. According to Englot et al.<sup>6</sup> it is considered that there is a direct proportional relationship between age and the presence of a brain tumor, occurring on average between the age of 50 and 65 years.

Primary CNS tumors (77 patients) were mostly found. Nevertheless, it is considered that brain metastases (46 patients in this study) occur more frequently than primary CNS tumors. This could be explained by the use of different image studies for tumor diagnosis and evaluation. Some patients had a brain CT scan and others a brain MRI. Also, the lack of a histopathological study and evaluating tumor lesions based on imaging studies alone could underestimate the frequency of metastatic lesions.

Most of the population had a histopathological report with high-grade tumor (32.5%) compared with low-grade tumor reports (22.8%). Primary gliomas or high-grade tumors comprise 80% of malignant tumors<sup>17</sup> with glioblastoma reported as the most common of these (60–70%). In this study, glioblastoma was the most common primary tumor (22.8%) which is of low incidence compared to what has been previously reported in the literature. This could be explained by the inability to obtain a histological sample in all cases; by the brain imaging characteristics of the lesion, and also because it is currently recommended to make a molecular diagnosis due to similarities in the histopathological characteristics among high-grade tumors (such as anaplastic tumors and glioblastoma multiforme).

The development of epilepsy in patients with brain tumors is variable. It is reported that around 50% to 70% of these patients will have seizures as the initial manifestation of the brain tumor.<sup>6</sup> However, in our study population only 49.7% presented epilepsy and only in 35.6% the seizures were the initial symptom. The development of epilepsy in brain tumors depends on several causes. According to Pruitt et al.<sup>9</sup> any brain tumor can develop epilepsy depending on its histological structure. About 100% of the low-grade or slow-growing tumors lead to epilepsy while others like metastatic tumors and primary CNS lymphoma develop in 20% to 35% of the cases.

Tumors of supratentorial location provoke seizures more frequently. In sporadic cases the infratentorial tumors also provoke seizures due

to their complications e.g. Hydrocephalus. The superficial cortical areas are frequently associated with seizures especially at temporal and frontal lobes level.<sup>18</sup> In this study 30.1% of the lesions had cortical involvement.

The most frequently used drugs for seizure control in descriptive studies have been carbamazepine, Phenytoin and valproic acid.<sup>19</sup> One of the considerations before choosing the antiepileptic drug is the oncological treatment that the patient is receiving due to possible interactions with chemotherapy. In patients with persistent seizures levetiracetam helps and does not interact with chemotherapy. It was the second most used antiepileptic drug in the study although seizure control was not considered as a study variable.

Another factor that influences the development of epilepsy in brain tumors is the time of tumor evolution. An association between a longer time of tumor evolution and the development of epilepsy was found in this study: 13.3 months in patients who developed epilepsy compared with 8.6 months in patients who did not develop it. This could be caused by peritumoral changes at the cellular, ionic, and neuronal receptor level in the brain. In addition, low-grade tumors were found more frequently in the population that developed seizures (27.1% vs 18.8%).

The following study limitations were found: First, the tumor diagnosis was not made by histopathological study in all the patients. Although the imaging studies support the diagnosis, they are not considered the gold standard for diagnosis since there is no characteristic pattern of each tumor, especially of high-grade tumors. Also, it is currently recommended to make molecular tests, such as the mutation of isocitrate dehydrogenase and 1p/19q codeletion to provide a more accurate diagnosis, establish a better prognosis, and to evaluate treatment response.

Another limitation was the lack of follow-up to assess adequate seizure control. Brain tumors affect the quality of life of the patient and the development of epilepsy. As a consequence of the tumor the patient has more morbidity. Thus the importance of an adequate seizure control.

## Conclusion

There is an association between epilepsy, a longer time of tumor evolution and supratentorial location. There is no difference in relation to gender, primary CNS, metastatic tumor or histological grade.

The most widely antiepileptic drug used is Phenytoin although



there is no consensus for the medication choice. The combination of valproic acid with levetiracetam has shown good results for seizure control. More studies are required to establish an optimal treatment for these patients.

The present study may be used as a reference for prospective studies that confirm the observed results as well as to help to identify other factors that lead to epilepsy.

## Perspectives

- MRI should be done in all patients with brain tumors.
- The diagnosis of epilepsy should be made in a timely manner and these patients must have a close follow-up to have a better disease control.
- The treatment of symptomatic epilepsy caused by brain tumors should be decided according to each patients' characteristics including adverse effects, prognosis, histological type of tumor, and chemotherapy treatment.
- The prognosis for patients with brain tumors has been modified during the recent years. A complete approach is required including histopathological studies, molecular markers, and an adequate treatment.

## Compliance with Ethical Standards

**Ethical approval:** "All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards".

## Conflict of interest

There are no conflicts of interesting this research, certainly is involving human participants but it was a retrospective study involving only the analysis of the files, without the inclusion of the names of the participants, it was approved by the Ethical and Research Committee of the institution where the study was realized and the patients treated.

Informed consent was not needed according to the characteristics of the study.

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