

GANGLIOGLIOMA

Comparison with other low-grade brain tumors

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ABSTRACT - Method: Forty-two patients with low-grade brain tumor and refractory epilepsy were studied. The mean age was 22.3 years. They were divided into two groups: Group A, patients with ganglioglioma (n=19) and group B, patients with other low-grade tumors (n=23) (14 astrocytoma, 6 oligodendroglioma, 2 dysembryoplastic neuroepithelial tumor, and 1 xanthoastrocytoma). **Results:** Age at seizure's onset was 7 years or less in 73% of the patients in group A and in 30.4% of the patients in group B ($p=0.045$). Complex partial occurred frequently in group A and B (94.7% versus 82%, respectively). Seizure's frequency was higher in group B ($p=0.002$). Computerized tomography (CT) was normal in 36.8% of group A patients and abnormal in all group B patients. Magnetic resonance imaging (MRI) was abnormal in all patients. Surgical removal was complete in 89.5% of the patients in group A and in 78.2% of the patients in group B. **Conclusion:** The association of refractory epilepsy and complex partial seizures, at a relatively low frequency, in young patients potentially normal CT and a MRI hypointense temporal lobe lesion in T1-weighted slices were habitual image findings in ganglioglioma, rather than other low-grade tumor.

KEY WORDS: ganglioglioma, refractory epilepsy, low-grade brain tumors.

Ganglioglioma: estudo comparativo com outros tumores cerebrais primarios de baixo grau

RESUMO - Método: Foram estudados 42 pacientes com tumor cerebral primário de baixo grau e epilepsia refratária. A idade média foi 22,3 anos. Eles foram divididos em dois grupos: no grupo A os pacientes com ganglioglioma (n=19) e no grupo B os pacientes com outros tumores primários de crescimento lento (n=23) (14 astrocitomas, 6 oligodendrogliomas, 2 tumores desembrionoplástico neuroepiteliais e um xantastrocitoma). **Resultados:** A idade de início das crises convulsivas foi 7 anos ou menos em 73% dos pacientes no grupo A e 30,4% dos pacientes no grupo B ($p=0,045$). A crise convulsiva do tipo parcial complexa foi a mais identificada nos grupos A e B (94,7% versus 82%, respectivamente). A frequência de crise foi mais alta no grupo B ($p=0,002$). A tomografia computadorizada foi normal em 36,8% dos pacientes no grupo A e anormal em todos no grupo B. A ressonância magnética foi anormal em todos os pacientes. A remoção cirúrgica foi completa em 89,5% dos pacientes no grupo A e 78,2% no grupo B. **Conclusão:** A associação de epilepsia refratária e crise parcial complexa, principalmente quando a frequência não é muito alta, em pacientes jovens, mesmo com tomografia computadorizada normal e alteração hipointensa na sequência de T1 da ressonância magnética é sugestiva de ganglioglioma mais que outros tipos de tumor cerebral primário de baixo grau.

PALAVRAS-CHAVE: ganglioglioma, epilepsia refratária, tumor cerebral de baixo grau.

Ganglioglioma (GG) is one of the commonest causes of tumor-related refractory epilepsy in young patients¹, and together with other low-grade brain neoplasms, comprises 10-30% of the pathological substrate in patients with chronic intractable partial epilepsy². GG is frequently found in patients younger

than 30 years (80%) with refractory epilepsy. It represents 0.5 to 1.7% of all neuroepithelial tumors³ and constitutes 1.7% to 7.6% of all tumors of the central nervous system in the pediatric population^{4,5}. The association of GG with dysembryoplastic neuroepithelial tumors and cortical dysplasia reinforces the pos-

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sibility that such lesions are of embryonal type⁶. GGs are included in the category of primary cerebral tumors in which mature ganglion cells and dysplastic neurons may be present⁷.

GG contains neoplastic glial cells, mainly astrocytes in varying states of differentiation⁸⁻¹⁰. These glial cells directly affect the biological behavior of the tumor; they are usually benign and are related to histological features typical of low-grade pilocytic astrocytoma⁸. The presence of an increased number of NMDA (N-methyl-D-aspartate) receptors and the abnormal production of neurotransmitters found in the cortex around GG, unlike what is seen in other low-grade tumors, might explain the increased tendency towards seizure's generation before an after tumor resection in some patients¹¹. GG occurs mainly in the temporal lobe, it is well defined and intracortical, firm consistency and shows calcifications and cystic components in about 50% of the patients. When surgical removal is incomplete, radiotherapy is warranted if anaplastic histological findings or tumor progression are documented. These occur in less than 20% of the patients^{9,12}.

Most previous studies on brain tumor and epilepsy have analysed patients with different low-grade tumors as a single group, without specifically delineating the findings in those with ganglioglioma. In this study, we performed a retrospective analysis of patients with intractable epilepsy and histologically verified ganglioglioma and other low-grade brain tumors that underwent tumor resection. We compared clinical, neurophysiologic and neuroimaging findings in these two groups in order to better define the patients with GG.

METHOD

The presence of medically intractable epilepsy (at least 1 complex partial seizure per month over the last 2 years), low-grade primary cerebral tumor and at least 2 years of postoperative follow-up were the clinical inclusion criteria in this series of consecutive patients (n=42). Patient's postoperative outcome in relation to seizures was rated according to Engel's classification¹³. All patients whose tumors have shown any sign of malignancy were submitted to complementary treatment with radiotherapy and chemotherapy.

In all patients, at least two pre and postoperative interictal EEG recordings were obtained during sleep and wakefulness, using the 10-20 system, with at least 1 hour of duration. Both computerized tomography (CT) and magnetic resonance image (MRI) (1.5T) were acquired using high resolution scanners and thin slices.

Operative techniques included stereotactic tumor localization^{14,15}, electrocorticographic (ECoG) monitoring and brain mapping to identify eloquent nonresectable rolandic and

language cortex. Two operations were performed with the patient under local anesthesia and neuroleptoanalgesia.

Intraoperative ECoG was performed in all patients. It consisted of placement of carbon-tipped electrodes for surface recordings over the lateral cortex and multicontact subdural strips and grids to sample subtemporal cortex.

Cortical mapping of the motor cortex under general anesthesia was obtained with bipolar square pulses with 2 to 10 mA, at 100Hz and with 0,1 msec of duration.

Thirty men and 12 women with ages between 6 and 57 years (mean 22.3 years) were studied.

Patients were divided in two groups, according to histological findings: in Group A (n=19), patients had GG and in group B (n=23), other low-grade tumors were present (astrocytoma, oligodendroglioma, dysembryoplastic neuroepithelial tumor and xanthoastrocytoma).

The following variables were studied in groups A and B: age at surgery, age at onset of epilepsy, time before diagnosis, types of seizure, number of seizures per month, results of neurological examination, electroencephalogram, CT and MRI findings, surgical technique, and outcome results in relation to seizures.

Statistical analysis was carried out using techniques of descriptive statistics, through tables, including absolute or percentile distributions and statistical measures. Chi-square or Fisher exact tests were used whenever necessary. The significance level was $p < 0.05$.

RESULTS

The pathological findings can be seen in Table 1.

A summary of clinical data can be seen in Table 2 and 3. Group A consisted of 14 men and 5 women and group B comprised 16 men and 7 women. The cerebral tumors were located within the temporal lobe in 14 (73.6%) of the patients in group A and in 15 (65.2%) in group B. There were 3 frontal lobe, 2 parietal lobe and 1 occipital lobe tumors in group A. In group B, 4 frontal, 2 parietal and 2 occipital lobe tumors were found.

Epilepsy began at a mean age of 7.8 years (range 2.4-48 years) in group A and 12,0 years (range 4.1-34 years) in group B. The number of patients eight years

Table 1. Etiology in patients with primary brain tumors and refractory epilepsy.

Histology	Frequency	%
Ganglioglioma	19	45.2
Astrocytoma	14	33.3
Oligodendroglioma	6	14.3
Xanthoastrocytoma	1	2.4
Dysembryoplastic neuroepithelial tumor	2	4.8
Total	42	100

Table 2. Summary of clinical findings.

	Total or mean/median (range or percentage)	
	Group A	Group B
Male/female	14/5	16/7
Age at seizure onset	7.8/7.1 (2.4-48)	12/9.8 (4.1-62)
Age at surgery	20.2/18.8 (12-57)	23.1/20.2 (6-62)
Duration of epilepsy	11.1/9.4 (5-30)	10.4/8.8 (2-21)
Number of seizures per month	30.1/8.7 (1.2-42)	78.5/12.7 (1.8-300)
Aura	14 (73.7%)	12 (52.1%)
Secondarily generalized seizures	3 (15.8%)	5 (21.7%)
Abnormal neurological examination	6 (31.5%)	6 (26.1%)

Table 3. Distribution of the patients according to seizures, neurophysiology, neuroimaging and the groups of cerebral tumor.

	Group				p value
	A		B		
	N	%	N	%	
Age at seizure onset (yrs)					
7 or less	12	63.1	7	30.4	$\chi^2=4.2$
From 8 to 30	7	36.9	16	69.6	p=0.0045
Age at operation (yrs)					
6 to 20	11	57.9	10	43.5	$\chi^2=0.477$
21 to 62	8	42.1	13	56.5	p=0.490
Duration of epilepsy (yrs)					
2 to 9	9	47.4	13	56.5	$\chi^2=0.093$
10 to 30	10	52.6	10	43.5	p=0.760
Mean preoperative seizure frequency (per mo)					
1 to 16	16	84.2	5	21.7	$\chi^2=9.445$
17 to 30	3	15.8	18	78.3	p=0.002
Interictal scalp EEG epileptiform discharges	13	68.4	19	82.6	P=0.370
Postoperative EEG epileptiform discharges	11	57.9	15	65.2	P=0.480
CT with lesion demonstrated	12	63.2	23	100	p=0.010
MRI gadolinium enhancement	11	57.9	17	74.0	p=0.240
MRI mass effect	8	42.1	15	65.2	p=0.170
MRI and CT calcifications	12	63.1	8	34.8	p=0.084
Temporal lobe location	14	73.7	15	65.2	p=1.000
Complete resection	17	89.5	18	78.2	p=0.455
Seizure outcome	18	94.7	20	87.0	p=1.000

p value based on Fischer's Exact Test.

or over at the beginning of their seizures was significantly higher (p=0,045) in group B (n=16) than in group A (n=7).

At the time of surgery, patients in group A had experienced an average of 11.2 seizures per month and those in group B 18.1 seizures per month. An average number of seizures higher than 17 per

month was significantly more common in group B (n=18) than in the group A patients (n=3). Complex partial seizures, alone or in combination with other seizure's type were observed in 20 patients (87%) in group B and 18 patients (94.7%) in group A, without statistical difference. All patients with temporal lobe tumors had complex partial seizures, as did 78%

of the patients in group A and 64% in group B. An aura, described by 14 patients in group A (73.7%) and 12 patients in group B (52.1%), was present in all those with temporal lobe epilepsy. Secondly generalized seizures were present in 5 patients in group B and 3 patients in group A, all with temporal lobe epilepsy, and predominantly in the first second years of their history of epilepsy.

Neurological status was normal in 13 (68.4%) patients of group A and in 17 (73.9%) of group B ($p > 0.05$). The neurological examination abnormalities found in these patients were related to the localization of the tumor, with no statistical difference between the groups (visual field defects in 8, dysarthria in 2, and hemiparesis in 5).

Interictal epileptiform discharges occurred in 13 (68.4%) of the patients in group A, while in group B these abnormalities were detected in 19 patients (82.6%). The EEG findings were most often focal in both groups A and B (62% and 54%, respectively); they were multifocal in 24% and 35%, and generalized in 5% and 8%, respectively, in groups A and B.

Postoperative EEG recordings were available in all patients. Epileptiform discharges were present in 11 (57.9%) patients in group A and 15 (65.2%) in group B (no statistical difference).

Computed tomography was abnormal in all patients in group B and normal in 7 (36.8%) patients of group A ($p < 0.05$).

MRI detected the tumor in all 42 patients. MRI findings in group A and B patients included, respectively, contrast enhancement (11 and 17), mass effect (8 and 15), cystic component (10 and 7), peritumoral edema (1 and 7) and calcifications (13 and 8; confirmed by CT).

Pre and post resection ECoG monitoring was performed in 32 patients (15 in group A). In 12 patients in group A and 13 in group B resection of the epileptic zone was complete and all were seizure free postoperatively. In 3 patients (1 in group A and 2 in group B), there was a subtotal (90%-95%) tumor resection and a complete resection of the ECoG spiking zone: all of them were rendered seizure's free postoperatively. In all patients, adequate resection of the epileptogenic zone required tissue removal that extended beyond that which would have been necessary for tumor resection alone. In 7 patients, resection of the epileptic zone was incomplete, due to overlap of eloquent (motor or language) cortex and the epileptic zone. Postoperatively, these patients continued to experience seizures, but a 90-95% improvement in seizure's frequency was noted.

Surgical resection was complete in 17 (89.5%) patients in group A and in 18 (78.2%) patients in group B.

Mean postoperative follow-up time was 33.4 months. Postoperatively, 18 (94.7%) patients in group A and 20 (87%) in group B were classified as Engel's grade I and the others as Engel's grade II.

DISCUSSION

Haddad et al.¹² found that GG was an uncommon finding among the etiologies of epilepsy. That might be true if we considered epilepsy in all its presenting forms; however, if we considered only patients with refractory seizures, the situation might be different. The Cleveland Clinic reported⁵ that 12% of the patients operated on for refractory epilepsy over a 10-years period had low-grade tumors; all patients have had less than 30 seizures per month and a long history of epilepsy (more than 6 years).

The mean duration of epilepsy before surgery in patients with low-grade tumors was 10.8 years in our series, in agreement with others^{16,17}. This behavior differs from that seen in patients with high-grade brain tumors. In the latter, the high frequency of seizures usually leads to earlier investigation and diagnosis¹⁶. In group A patients, seizures began earlier than in group B. That difference reached statistical significance and is in agreement with findings in other centers^{6,8,18}. GG seems to be related to neural maturation and is frequently found in young children.

The higher prevalence of GG in this young population could have important clinical implications. Early surgical intervention might offer the best chance of relief of intractable epilepsy and might reduce neuropsychological and social disability.

In patients with low-grade brain tumor and refractory epilepsy, seizure's frequency can progressively decrease over time^{16,19}. This was not noted in our series. There was a high prevalence of partial seizures in group A and B. This was also noted in other studies of patients with refractory epilepsy and brain tumors, which found that 85% to 92% of them suffered partial seizures²⁰⁻²². Partial epilepsy might occur in patients with tumors in the temporal lobe and outside it as well²³. Extracranial EEG, although lacking adequate spatial resolution may be used as a screening tool²⁴. The presence of epileptic discharges consistently located within the same cerebral lobe, in consecutive exams, even in patients with a normal neurological examination, warrants further investigation including MRI^{16,25}. In our series, pre and post-

operative EEG data did not correlate with seizure outcome. According to some authors^{25,26}, 30% of refractory temporal lobe epilepsy have surface EEG recordings showing independent bitemporal spiking. This prevalence of bitemporal abnormalities increases as the duration of the EEG recordings increased. Other studies have also shown that surface EEG findings consisting of bilateral independent temporal foci, did not correlate with the effect of surgery in seizure's control^{26,27}.

MRI was abnormal in all patients in this series. Habitual findings consisted of hypointensity in the T1-weighted and hyperintensity in T2-weighted slices. On the other hand, CT was normal in seven patients, all of whom had GG (group A) within the temporal lobe. MRI was more sensitive than CT in the detection of structural lesions in the temporal lobe²⁸. MRI was also more effective in suggesting specific tumor types and is presently considered the gold-standard in imaging evaluation of patients with epilepsy²⁹. MRI findings such as the presence or absence of gadolinium enhancement, mass effect, and cystic components had no measurable influence on the seizure outcome following tumor resection in our series and in others^{7,24}.

The temporal lobe is the favorite location for GG (40% to 77% of the patients). It is often associated with neuronal migration disorders^{12,16,20}.

Ninety-four percent of our patients with GG have been rendered seizure-free after surgery. Morris et al. found that 74% of the patients operated on for refractory temporal lobe epilepsy and GG had excellent results in relation to seizure's control. This is especially true for young patients, with short duration of the epileptic syndrome and with absence of epileptic activity in postoperative EEG⁵. Secondary autonomous mirror foci may develop in patients with GG due to the presence of a prolonged refractory epileptic syndrome³⁰. Lesionectomy alone achieved seizure's control in 9 (64.2%) of 14 patients with an extratemporal lesion but in only 2 (22.2%) of 9 patients with a temporal lobe lesion¹³, suggesting that at least in temporal lobe lesions, resection of a cortical margin guided by ECoG might be useful. It is possible that secondary epileptic foci might be more prevalent within the temporal lobe where they tend to become autonomous more quickly than in other areas of the brain. Other studies^{25,31} identified incomplete tumor resection or tumor recurrence as causes of poor postoperative seizure control. Despite the small number of patients who had had incomplete resection in our

series, we believe that the presence of residual tumor is an important cause of postoperative seizures.

GG seems to be more indolent than other primary cerebral tumors, with longer history of epileptic seizures. In young patients, it could easily be confused with neuronal migration disorders if the lesion is located in the cortical surface^{11,32}. Our patients had a long history of seizures before diagnosis and received appropriate surgical treatment late. It would be necessary to develop a clinical paradigm to early identify patients with GG. Early diagnosis might provide a better chance of total tumor removal and remission of epilepsy^{1,33,34}.

Postoperative psychosis was found to be more common in patients bearing temporal lobe GG than in other temporal lobe pathology³⁵. No postoperative psychosis was noted in our series.

In our series, patients with GG were young (usually under 8 years old) and presented characteristically with complex partial seizures (94.7% of the patients), at a frequency of less than 16 seizures per month (usually less than 6), normal CT in one third of the patients, and MRI-defined tumor in all (hypointense in T1 and hyperintense in T2 slices). These features might be considered as suggestive of GG and could aid in the preoperative differential diagnosis from other low-grade tumors. Lesionectomy with cortical margins defined by intraoperative ECoG seems to be the best operative approach, especially in extra-temporal lobe lesions.

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