BRAIN TUMOR LOCATION INFLUENCES THE ONSET OF ACUTE PSYCHIATRIC ADVERSE EVENTS OF LEVETIRACETAM THERAPY: AN OBSERVATIONAL STUDY

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INTRODUCTION

The present retrospective study has explored possible correlations among brain lesion location, onset of psychiatric disorders and the use of antiepileptic drugs (AEDs) in a population of patients with brain tumor and epilepsy. A proportion of 30-50% of patients (pts) with primary brain tumors presents with an epileptic seizure as initial clinical manifestation, and up to 30% of these patients will later develop seizures (van Breemen et al., 2007). Tumor type greatly influences development of seizures. Management of seizures associated to tumors requires consideration of different aspects, including: i) high rate of recurrence after a first seizure; ii) increased sensitivity to the adverse effects of AEDs; iii) changes in clinical response in relation to the disease progression; iv) possible occurrence of disadvantageous interactions between AEDs and anticancer agents (Perucca, 2013). In recent years, a number of second-generation AEDs has been approved as initial monotherapy for focal seizures, namely oxcarbazepine, lamotrigine, topiramate, levetiracetam, and zonisamide. Available data suggest that these drugs can be more advantageous than older drugs in terms of improved tolerability and reduced risk of drug interactions (Fattore and Perucca, 2011; Pisani et al., 2013) and, consequently, they are frequently used for the treatment of epilepsy in patients with brain tumors. An additional aspect that can complicate the clinical picture of these pts is the development of psychiatric disorders.

PATIENTS AND METHODS

Tumors were classified as: i) "low grade" (World Health Organization grade I or II); ii) "high grade" (World Health Organization grade III or IV); iii) other solid intra-axial tumors without infiltration of brain parenchyma. Inclusion criteria were: 1) pts older than 18 years; 2) new diagnosis of brain tumor through neuroimaging techniques; 3) supra-tentorial location; 4) true diagnosis of tumor type through a histological analysis; 5) new and true diagnosis of epilepsy on the basis of both the clinical manifestations and the electroencephalographic (EEG) findings; 6) beginning of treatment with any AED; 7) no other concomitant causes apart from brain tumor, potentially responsible of acute seizures (for example: alcohol withdrawal; stroke; psychotropic drugs; electrolyte disturbance; previous brain lesions); 8) follow-up of at least six months. Patients with grade III-IV glioma were not included in the analysis, as they represent a substantially distinct entity in terms of histopathological and clinical features of these tumors (extreme aggressiveness, survival of 1 year in a high percentage of patients, large extent of resection). Patients with a previous history of seizures or psychiatric illness were excluded from the analysis. Surgery was performed after an individualized preoperative investigation and tailored to the patient's anatomical, radiological and clinical characteristics. The site of surgical resection was categorized as: unilobar temporal; unilobar frontal; posterior; and multilobar. Psychiatric disorders were classif[illegible] of Mental Disord[illegible] have been clinica[illegible]nxiety, and emotio[illegible]

. Logistic regression models of risk factor for PAE.

	Odds ratio	95% Confidences Indexes	p-value
Meningioma	0.65	0.25-1.70	0.4
LEV therapy	3.95	1.4-10.9	0.006
Frontal localization	3.43	1.40-8.55	0.008
No AED therapy	0.6	0.1-4.2	0.3
Intercept	0.06	0.02-0.22	<0.0001

Variable not in the equation: presence of seizures, sex, age, other lobar location, other AEDs.

Statistical analysis

All analyses were performed grouping patients according to the presence of PAE. Categorical data (male, presence of EEG abnormalities, type of pharmacological therapy, location of the tumor) were analyzed using the Pearson's Chi square test or the Fisher's Exact test, where appropriated, while continuous predictors (age) were analyzed using the Mann Whitney U test.

Table 1. Demographic and clinical features of patients with brain-tumor

	Pts with PAE (n=31)	Pts without PAE (n=252)	Overall (n=283)	p-value
Demographic factors				
Male	11 (35.5)	116 (46.0)	127 (44.8)	0.3
Age (years)	64.3±13.5	61.0±14.5	61.4±14.4	0.2
Clinical features				
EEG abnormalities	(74.2)	136 (54)	159 (56.2)	0.03
Seizures	23 (74.2)	152 (60.3)	175 (61.8)	0.1
Maningioma	24 (77.5)	222 (89.0)	246 (87.0)	0.09
Glial neoplasm	7 (22.5)	30 (11.0)	37 (13.0)	0.09
Left-sided lesion	16 (51.6)	92 (36.5)	108 (38.0)	0.10
Frontal lesion	23 (74.1)	121 (48.0)	144 (51.0)	0.006
Parietal lesion	4 (12.9)	58 (23.0)	62 (21.0)	0.25
Temporal lesion	3 (9.7)	54 (21.0)	57 (20.0)	0.15
Occipital lesion	1 (3.2)	19 (8.0)	20 (8.0)	0.7
Therapy				
CBZ	4 (12.9)	34 (13.5)	38 (13.4)	0.90
LEV	14 (45.1)	38 (15.0)	52 (18.4)	<0.0001
VPA	3 (9.7)	45 (17.9)	48 (16.9)	0.30
PB	2 (6.5)	7 (2.8)	9 (3.1)	0.25
OXC	4 (12.9)	24 (9.5)	28 (10.0)	0.50
No AED therapy	4 (12.9)	104 (41.2)	108 (38.1)	0.01

PAE= psychiatric adverse events; age is indicated as M±SD; other factors are expressed as numbers

DISCUSSIONS

Twenty of 303 potentially eligible patients were excluded because they were lost at follow-up. Thus, 283 patients were analyzed: 253 underwent surgical treatment and 30 were not eligible for tumor excision. Among the 253 surgical patients, 10 were treated with radiotherapy after surgery and 3 with chemotherapy after both surgery and radiotherapy; 10 pts with grade II astrocytoma located to eloquent areas (7 pts motor area, 3 pts speech area) underwent awake surgery. Tumor excision was not performed in 30 pts because of the presence of various unfavorable prognostic factors: old age, existing severe neurological symptoms, a Karnofsky performance-status score of < 60. Seizure diagnosis was made in 175/283 pts (61.8%): 1-3 months before tumor diagnosis in 63 pts, within the first month after tumor diagnosis in the remaining 112 pts. AED therapy was: carbamazepine in 38 pts (starting dose 200 mg/day with increases of 200 mg per week, maximal dose achieved 600-800 mg in 3 daily administrations), levetiracetam (LEV) in 52 (starting dose 1000 mg/day up to 1500-2500 mg/day achieved within 10 days, in 2 daily administrations), sodium valproate in 48 (starting dose 200 mg/day up to 1000 mg achieved within 10 days, in 2 daily administrations), phenobarbital in 9 (maximal dose of 100-150 mg from the beginning of treatment, one daily administration), oxcarbazepine in 28 (starting dose 300 mg/day with weekly increases of 300 mg, maximal dose achieved 900-1200 mg in 2-3 daily administrations). Clinical and demographic data of patients grouped according the occurrence of PAE are shown in Table 1. Overall, 31 pts developed PAE: 27 of 175 (15.4%) AED-treated-pts and 4 of 108 (3.7%) of AED-untreated-pts. All these patients underwent surgical treatment. PAE were: psychosis in 13 pts (42%), aggressive behavior in 11 (35.5%), emotional lability and depression in 4 (12.9%), and other behavioral abnormalities, such as agitation, anger/hostile behavior, personality changes in 3 (9.7%). None of the patients reported suicidal ideation.

CONCLUSION

Over the past 10 years a number of new AEDs has been extensively used to treat epileptic seizures and, among them, LEV is undoubtedly one of the most frequently employed not only among epileptologists but also among general neurologists, emergency physicians, neurointensivists and neurosurgeons. the present study strongly indicates that LEV is a risk factor for the development of acute PAEs in patients with frontal tumor. A prompt discontinuation of the drug is needed to clear psychiatric symptoms. Since patients with brain tumors show increased susceptibility to the adverse effects of AEDs (Glantz et al., 2000; Van Breemen et al., 2007; Soffietti et al., 2010; De Groot et al., 2012) and some AEDs negatively impact on mood and behavior, it is crucial to assess in this respect all patients with tumor-related epilepsy. Large prospective studies are needed to confirm our preliminary observations.

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