Original Communication

Brain tumor location influences the onset of acute psychiatric adverse events of levetiracetam therapy. An observational study

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Abstract

Purpose: To explore possible correlations among brain lesion location, development of psychiatric symptoms and the use of antiepileptic drugs (AEDs) in a population of patients with brain tumor and epilepsy.

Methods: The medical records of 283 patients with various types of brain tumor (161M/122F, mean age 64.9 years) were analysed retrospectively. Patients with grade III and IV glioma, previous history of epileptic seizures and/or psychiatric disorders were excluded. Psychiatric symptoms occurring after initiation of AED therapy were considered as treatment emergent psychiatric adverse events (TE-PAEs) if they fulfilled the following conditions: i) onset within 4 weeks after the beginning of AED therapy; ii) disappearance on drug discontinuation; iii) absence of any other identified possible concurrent cause. The possible influence of the following variables were analysed: a) AED drug and dose; b) location and neuroradiologic features of the tumor, d) location and type of EEG epileptic abnormalities, e) tumor excision already or not yet performed; g) initiation or not of radiotherapy.

Results: TE-PAEs occurred in 27 of the 175 AED-treated patients (15.4%). **Multivariate** analysis showed a significant association of TE-PAEs occurrence with location of the tumor in the frontal lobe (Odds ratio:5.56; 95% confidence interval: 1.95-15.82; p-value:0.005) and treatment with levetiracetam (Odds ratio:3.61; 95% confidence interval: 1.48-8.2; p-value: 0.001). Drug-unrelated acute psychiatric symptoms were observed in 4 of the 108 AED-untreated patients (3.7%) and in 7 of the 175 AED-treated patients (4%).

Conclusions: The results of the present study suggest that an AED alternative to levetiracetam should be chosen to treat epileptic seizures in patients with a brain tumor located in the frontal lobe to minimize the possible onset of TE-PAEs.

Key words: tumor frontal lobe location; epilepsy; levetiracetam; psychiatric adverse events;

Key Points Box:

- This study suggests that patients with a brain tumor located in the frontal lobe are at high risk to develop PAEs after LEV treatment.
- LEV should be carefully used in patients with frontal tumor and epilepsy because of the frequent onset of acute PAEs.
- Acute PAEs do not occur frequently in patients with frontal tumors when other AEDs are used.

INTRODUCTION

A proportion of 30-50% of patients with primary brain tumors presents with an epileptic seizure as initial clinical manifestation, and up to 30% of these patients will later develop seizures.[1] Tumor type greatly influences development of seizures. Low-grade gliomas, for example, are more frequently associated with epilepsy than high-grade tumors [1-4]. Noteworthy, epilepsy is an independent risk factor for poor quality of life in patients with brain tumors mainly as a consequence of the frequent occurrence of adverse events of antiepileptic drugs (AEDs) and/or the possible poor control of seizures [5]. A recent study suggests that patients with brain tumors and 'well-controlled epilepsy' have a comparable health-related quality of life (HRQOL) to that of subjects without epilepsy [6]. Management of seizures associated with brain 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 [7]. 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 and, consequently, they are frequently used for the treatment of epilepsy in patients with brain tumors [8-9]. An additional aspect that can complicate the management of epilepsy in patients with brain tumors is the development of psychiatric symptoms. These symptoms most commonly include mood changes, anxiety, suicidal ideation, hallucinations and other psychotic symptoms, and personality changes and may affect a percentage of patients of approximately 20-40% [10-11]. Psychiatric manifestations in this clinical context may be due to a single or even a multifactorial aetiology, which include a possible psychogenic nature, the type, location and progression of the tumor, an adverse event of AED therapy and other causes [12-14].

Aim of the present study was to investigate possible correlations among acute onset of psychiatric symptoms, treatment with specific AEDs and the location of brain tumor.

MATERIALS AND METHODS

Patients selection

This retrospective study examined clinical, radiological, pathological, and follow-up data of patients who underwent surgical evaluation of a brain tumor at the Department of Neurosciences of S. Anna Hospital, Como, between January 2008 and December 2016. 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) patients older than 18 years; 2) new diagnosis of brain tumor through neuroimaging techniques; 3) supra-tentorial location; 4) diagnosis confirmed by histology; 5) diagnosis of epilepsy

according to the practical clinical definition of epilepsy of the recent ILAE official report [15]; 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) implementation of a psychiatric assessment by a psychiatrist; 9) follow-up of at least six months. Patients with a previous history of seizures were excluded from the analysis. 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 (extreme aggressiveness, survival of 1 year in a high percentage of patients, large extent of resection). Thus, only patients with "low grade" brain tumors and solid intra-axial tumors without infiltration of brain parenchyma, scheduled for surgery or already operated and/or treated with radiotherapy and/or chemotherapy, were evaluated for this study.

Clinical-pathologic data collection

Clinical-pathologic data consisted of gender, age at diagnosis, histopathologic diagnosis, and side and lobe of lesion. 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. Extent of resection was categorized as gross macroscopic resection, subtotal resection (50–95% tumor excision), partial resection (<50% tumor excision) or **biopsy**.

AED therapy was started soon after the first seizure attributable to the tumor [15] and seizure occurrence was evaluated at the following time intervals: 0–1, 1–3, 3-6 months. After hospital discharge a regular intake of the prescribed therapy was strongly recommended to the patient and to the members of his family and an accurate interrogation on it has been made at each control day.

Psychiatric data collection

A psychiatric evaluation in a population of epileptic patients who are potential candidates for surgery is a common practice in our department, as it has been suggested in the literature [16]. In particular, in the present study only those patients who had been assessed by a psychiatrist once the diagnosis of brain tumor had been made were included in the analysis. Patients with previous psychiatric disorders or family history of psychiatric disorders were excluded from the analysis. Additional psychiatric evaluations were made at regular two-month intervals for at least a six month follow-up and at any time when a psychiatric disorder was evident or even suspected. The psychiatric evaluation was carried out through a clinical interview and administration of the following standard scales: Hospital Anxiety and Depression Scale (HADS), Mini Mental State Examination (MMSE), Dissociative Experiences Scale (DES). Psychiatric diagnosis was made according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) criteria. Psychiatric symptoms occurring after initiation of AED therapy were assessed by the same psychiatrist who had previously evaluated the patient and were considered as treatment emergent psychiatric adverse

events (TE-PAEs) only when the following conditions were met: i) occurrence within 4 weeks from the initiation of AED treatment; ii) recovery after drug discontinuation; iii) no intake of other drugs, apart AEDs; patients already on treatment with glucocorticoids for peritumoral oedema were also included; iiii) exclusion of any other identified possible concurrent cause, like for example additional personal/familiar stressful events due to worsening course of the patient clinical condition (occurrence of additional neurological signs/symptoms, headache, fever, etc.) or other occasional causes. The possible influence of the following variables on the onset of TE-PAEs was investigated: a) AED drug and dose, b) location and neuroradiologic features of the tumor, c) location and type of EEG epileptic abnormalities, d) tumor excision already or not yet effectuated.

Psychiatric manifestations occurring at any time in addition to those recorded at the initial evaluation (as new symptoms and/or sudden worsening of those already exhibited, requiring specific treatment with psychotropic drugs) in patients untreated with AEDs were coded as psychiatric disorders (PDs).

Ethics

Data storage and management were compliant with the Good Clinical Practice statement in accordance to the Declaration of Helsinki.

Statistical analysis

All analyses were performed grouping patients according to the presence/absence of TE-PAEs. 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. The variables that showed in the univariate analysis a p-value < 0.1 were used to build a regression logistic model in which the dependent variable was represented by the **dichotomous** presence/absence of TE-PAEs. Finally, the ROC analysis was performed to check the goodness of fit of the implemented logistic regression final model. Statistical significance was chosen at the 5 % level. All statistics were implemented using STATA version 12 (StataCorp, USA).

RESULTS

Patient cohort

Twenty of 303 potentially eligible patients were excluded because they were lost at follow-up **and 108 patients were not considered for analysis since they did not manifest any epileptic seizure.** Thus, data from **175** patients **fulfilling the inclusion criteria** were analyzed. Demographic and clinical data of these patients are given in Table 1.

Data on tumor and tumor treatment

Specific data on tumor type, size and location are shown on Table 1. **All 175** patients underwent surgical treatment. Among these patients, **7** were treated with radiotherapy within 12 months after surgery and **1** with chemotherapy after both surgery and radiotherapy; **6** patients with grade II astrocytoma located to eloquent areas (**4** motor area, **2** speech area) underwent awake surgery. Perilesional edema when associated with clinical signs/symptoms was treated with corticosteroids, more frequently i.v. dexamethasone at daily doses of 16-24 mg (**142** patients), or oral prednisone 25-50 mg/day (**33** patients).

Epileptic seizures and EEG features

Seizure diagnosis followed by AED treatment was made in 175: 1-3 months before tumor diagnosis in 63 patients, within the first month after tumor diagnosis in the remaining 112 pts (67 of these after tumor excision). Seizures occurred with motor manifestations with (88 patients; 27 of which with secondary generalized tonic-clonic seizures) or without (34 patients) consciousness involvement or with consciousness involvement only (brief confused states in 53 patients). All these patients underwent surgical treatment. An abnormal EEG activity was observed in **all** patients: polymorphic delta activity in **107**, interictal epileptiform discharges (spikes, sharp waves and/or spike-wave complexes) in **59**, periodic lateralized epileptiform discharges (PLEDs) in **9** patients (Table 1).

AED therapy

AED therapy was: carbamazepine in 39 (starting dose 200 mg/day with increases of 200 mg per week, maximal dose achieved 600-1000 mg in 3 daily administrations), levetiracetam in 52 (starting dose 1000 mg/day up to 1500-2500 mg/day achieved within 10 days, in 2 daily administrations), sodium valproate in 49 (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 26 (starting dose 300 mg/day with weekly increases of 300 mg, maximal dose achieved 900-1800 mg in 2-3 daily administrations) (Table 2).

Psychiatric manifestations

Psychiatric evaluation at first assessment showed a mild-to-moderate degree of mood and anxiety disorders in the majority of patients (**164/175**; HADS anxiety score: mean ± SD = **9.21±3.3**; HADS depression score: **8.51±3.7**). A cognitive impairment was detected in **16 (9.1%)** patients (MMSE score: **19.9+2.1**) and in the remaining patients the average MMSE score was normal **(26.0±1.4)**. No significant changes were detected in MMSE score during the follow-up. No patient exhibited dissociative or personality disorders at the first assessment and the average DES score in the entire population was **8.4±3.3**.

TE-PAEs. Overall, 27 of 175 (15.4%) AED-treated-patients developed TE-PAEs. These occurred in all the 27 patients after surgical treatment. TE-PAEs were: dissociative disorders in 12 patients (44.4%) (DES score: 34.8+4.3; HADS anxiety score:18.4±3.54; HADS depression score: 14.2±5.4); impulse control disorders with aggressive behaviour in 10

(37.0%) (DES score: 9.4±2.8; HADS anxiety score: 16.3±4,1; HADS depression score: 8.5±3.4); mood disorders with major depressive episodes in 4 (14.8%) (DES score: 9.2±3.3; HADS anxiety score: 8.0+2.2; HADS depression score: 19.1±1.1) and generalized anxiety disorders with agitation, anger/hostile behavior, or personality changes in 1 (3.7%) (DES score: 18.6±4.9; HADS anxiety score: 17.8+2.0; HADS depression score: 8.7±1.3). TE-PAEs occurred within the first week of AED treatment in 10 patients, within the second in 8, within the third week in 5, and within the fourth week in the remaining 4. Switch to another AED resulted in a gradual return of the patients toward the pre-drug conditions as assessed by the psychiatric interview and the corresponding reduction of the questionnaire scores toward the basal values (data not shown).

PDs. PDs were observed in 7 of the 175 AED treated patients (4%). PDs consisted in dissociative disorders and personality changes in **1 patient** (DES score: 30; HADS anxiety score: 16; HADS depression score: 8) and sudden worsening of the basal depressive condition with major depressive episodes in the **6** patients (DES score: 7 (**2** patients), 8 (**2** patients), 9 (2 patients); HADS anxiety score: 8 (**4** patients), and 10 (**2** patients); HADS depression score: 18 (4 patients), 19 (2 patients). In all the **7** patients PDs were observed after surgical treatment.

None of the **34** patients with psychiatric manifestations (27 with TE-PAEs and **7** with PDs) reported suicidal ideation.

Statistical data

Univariate analysis showed that the occurrence of TE-PAEs was associated with location of the tumor in the frontal lobe and treatment with levetiracetam (LEV) (Table 1). No significant differences were seen for the other tested variables (Table 1).

Multiple regression logistic analysis confirmed that frontal lobe location of brain tumor and LEV therapy were risk factors for the development of TE-PAEs in our patients (Table 2).

A check of the goodness of fit demonstrated that the regression model was representative of the screened data (area under the ROC curve = 0.77).

Overall, 52 patients were treated with LEV (Table 1). TE-PAEs occurred in 14 and the tumor was located in the frontal lobe, left (8) or right (6), in all these patients. In the remaining 38 patients without TE-PAEs, tumor location was in the left (16) or right (7) temporal lobe, left (3) or right (3) occipital lobe, left (2) or right (3) parietal lobe, left (2) or right (2) frontal lobe.

The total daily LEV dose was 2071.43±319.44 mg (mean±SD) in the first group and 2065.79±307.17 mg in the second group respectively, given in 2 daily administrations in both groups; a paired t test did not show any statistically significant difference.

DISCUSSION

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 reasons of the large use of LEV rely on its various favourable characteristics: 1) low interaction potential, 2) no production of active metabolites, 3) short elimination half-life, 4) no detrimental effects on sleep architecture, 5) no hematologic adverse effects [17-18]. Additionally, LEV is of a proven efficacy in epileptic patients with brain tumors [19] and, as it is available also as intravenous formulation, it can be also used as loading dose for seizure prophylaxis during and early after craniotomy [20]. Thus, in this clinical condition LEV could represent an ideal choice and in a recent systematic review it has been proposed as a first-line drug [21]. However, the same authors of this review underline the need for further research to gain a deeper knowledge especially about the toxicological profile of the drug. Noteworthy, the drug is not devoid of important PAEs as depression, psychosis and aggressiveness [22]. Our study strongly suggests that patients with a brain tumor located in the frontal lobe are at high risk to develop PAEs after LEV treatment. The mechanism of action of LEV is distinct from that of other AEDs, its main functional binding site in the brain being the synaptic vesicle glycoprotein 2A (SV2A), which is ubiquitous in the brain. Interestingly, a recent study provided preliminary evidence that the expression of synaptic vesicle 2A (SV2A) in tumor and peri-tumor zones may predict responsiveness to the anti-seizure effect of LEV in patients with glioma [23]. Different studies have reported that in this population of patients side effects associated with LEV are infrequent and substantially include dizziness, fatigue, and somnolence [19,24]. However, the fact that a proportion of approximately 10% of LEV-treated patients manifests PAEs is worthy of clinical attention [18,22]. Our study suggests that: i) LEV should be carefully used in patients with frontal tumor and epilepsy because of the frequent onset of acute PAEs; ii) close clinical monitoring is indicated when the tumor is in the frontal region; iii) acute PAEs do not occur frequently in patients with frontal tumors when other AEDs are used. Available studies indicate that patients developing PAEs following LEV therapy exhibit a particular clinical profile. Mula et al. found that patients with a previous history of febrile convulsions or status epilepticus, a previous psychiatric history and a family psychiatric history are prone to develop PAEs during LEV therapy [22, **25**]. Additionally, LEV-related PAEs can occur with specific features. Self-reported aggressiveness, for example, is reported as “always” a problem by 9.8% of the patients on LEV treatment and is not an isolated symptom but associated to depressed mood [**26**]. In another recent study, LEV has been reported to be an independent risk factor for the development of post-operative depression in patients with drug-resistant focal epilepsy; the use of carbamazepine reduced this risk [**27**]. The observations deriving from the present investigation give an additional knowledge on LEV-related PAEs. In our analysis, cases with previous personal and/or familiar psychiatric history, and patients with a previous history of epilepsy were excluded. Additionally, our results seem to indicate the absence of any influence of LEV starting dose

and titration schedule (which were the same in all patients), and the final LEV dose on the onset of TE-PAEs (Table 1). These developed shortly after LEV initiation and rapidly disappeared after LEV discontinuation. Concerning the other variable studied, namely EEG features, tumor features, tumor excision effectuated or not, co-treatment or not with steroids, none of these have shown statistically significant differences between patients with and without TE-PAEs. The main finding of our study, therefore, is that patients on LEV therapy with a frontal location of a brain tumor are at **a higher** risk**, as compared to patients treated with other AEDs,** to develop TE-PAEs. **This suggests** that other features, apart from a given specific profile of the patient [22, **25**], may be relevant for the development of TE-PAEs. To the best of our knowledge, this observation has not been reported in previous studies. Concerning the involvement of frontal lobe, it is known that abnormal activity of some specific structures, like for example the middle, the superior and the supramarginal frontal gyrus, is associated to peculiar symptoms of schizophrenia, in particular processing and negative symptoms [**28-30**]. It can be hypothesized that LEV interferes with specific frontal circuits, possibly already damaged by the tumor, contributing to reduce further the activity of frontal lobe and to trigger acute TE-PAEs.

Our results should be considered bearing in mind the following two limitations: 1) the retrospective design; 2) the limited sample size. Another important aspect potentially influencing TE-PAE onset, i.e. seizure evolution after AED treatment, has not been analysed in the present study because of the short period time between seizure diagnosis and the initiation of AED therapy and the equally short follow-up of the patients. In this respect, in fact, it is known that psychoses may occur in a percentage of patients rendered seizure-free by therapy. The phenomenon, known as alternative psychosis/forced normalization, has been described with various AEDs [**31**], this suggesting that it is more likely to be related to the clinical patient phenotype rather than a specific characteristic of a given drug. A recent review underlines the complexity of the matter concerning the behavioural adverse effects of AEDs in patents with epilepsy and lists numerous influencing variables related to both the patient and the medication features [**32**]. These variables include: age, epilepsy type, learning disability, previous psychiatric history, drug dosage, titration rate, efficacy in controlling seizures, and concurrent AEDs. A number of methodological limitations in drawing conclusions from the available literature data has been is also mentioned, including variation in study design, treatment group, and assessment tools [**32**].

In conclusion, regardless of the limits above indicated of the present study, our results suggest that LEV is a risk factor for the development of acute TE-PAEs in patients with a tumor located in the frontal lobe. A prompt discontinuation of the drug leads to a rapid disappearance of the psychiatric manifestations, consisting in a large percentage of our patients in dissociative disorders. These observations are in line with the findings of a very recent study, in which *(a)* a statistically significant association was found in a population of epileptic patients between the use of LEV and AED-induced psychotic disorders and *(b)* no patients with these disorders exhibited a chronic course of the psychiatric

condition [**33**]. Since patients with brain tumors show increased susceptibility to the adverse effects of AEDs [**34**] and some AEDs negatively impact on mood and behavior[14], it is crucial to assess in this respect all patients with tumor-related epilepsy. Large prospective studies are needed to confirm our preliminary observations.

Disclosure of Conflict of Interest

MM has received consultancy fees from UCB Pharma, Eisai, Pfizer and Elsevier and has also received supports from Bial and Special Products Ltd. Vincenzo Belcastro, Laura Rosa Pisani, Paolo Casiraghi, Silvio Bellocchi, Gaetano Gorgone, Francesco Pisani declare that they have not conflict of interest. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines. This manuscript received no funding.

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Table 1. Demographic and clinical data of epileptic patients (n=175) exhibiting or not TE-PAEs

	Pts with TE-PAEs n=27	Pts without TE-PAEs n=148	p
Demographic factors			
Male	11 (40.7)	67 (45.3)	0.8
Female	16 (59.3)	81 (54.7)	
Age (years ±SD)	62.6±14.4	61.8±13.9	0.4
Clinical features			
Tumor type			
- Meningioma	24 (88.9)	126 (85.1)	0.8
- Glial neoplasm	3 (11.1)	22 (14.7)	
Surgery resection			
- Partial	2 (7.4)	8 (5.4)	0.7
- Subtotal	15 (55.6)	99 (66.9)	1.0
- Gross total	10 (37.0)	41 (27.7)	0.3
Tumor location			
- Left-sided lesion	16 (59.3)	82 (55.4)	0.8
- Right-sided lesion	11 (40.7)	66 (44.6)	
- Frontal lesion	21 (77.8)	59 (39.8)	<0.01
- Parietal lesion	3 (11.1)	37 (25.0)	0.1
- Temporal lesion	2 (7.4)	29 (19.6)	0.2
- Occipital lesion	1 (3.7)	23 (15.5)	0.1
EEG abnormalities			
- Polimorphic Delta activity	17 (63.0)	90 (60.8)	1.0
- Interictal epileptiform discharges	9 (33.3)	50 (33.8)	1.0
- PLEDs	1 (3.7)	8 (5.4)	1.0
AED therapy			
CBZ	5 (18.5)	34 (23.0)	0.8
LEV	14 (51.9)	38 (25.7)	<0.001
VPA	4 (14.8)	45 (30.4)	0.1
PB	1 (3.7)	8 (5.4)	1.0
OXC	3 (11.1)	23 (15.5)	0.8

TE-PAEs= treatment emergent psychiatric adverse events; age is indicated as M+SD; other factors are expressed as numbers and percentages (in brackets). CBZ= carbamazepine, LEV= levetiracetam, VPA= sodium valproate, PB= phenobarbital, OXC= oxcarbazepine. All patients underwent surgical treatment. For other details see the result section.

Table 2. Logistic multiple regression model of risk factor for TE-PAEs.

	Odds ratio	95% Confidences Indexes	p-value
LEV therapy	3.61	1.48-8.2	0.001
Frontal location	5.56	1.95-15.82	0.005
Intercept	0.04	0.01-0.1	<0.0001

Variables not in the equation: presence of seizures, sex, age, other lobar locations, other AEDs, already or not yet resected tumor, type and lateralization of EEG.