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Short communication

Status epilepticus management in patients with brain tumors. A cohort study

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ABSTRACT

Purpose: Status epilepticus (SE) represents a neurological emergency with significant morbidity and mortality. SE in patients with primary brain tumors received only limited attention to date; detailed analysis of treatment flow is lacking, especially as compared to other SE causes. This study aims to describe the frequency and treatment flow of tumor-related SE and compare it to other SE etiologies.

Methods: Retrospective cohort study based on an institutional SE registry (SERCH) comprising adult SE (excluding post-anoxic causes), treated between January 2013 and December 2022, comparing SE management, frequency of refractory SE, and clinical outcome, among four patients' groups stratified by SE etiology: Non-neoplastic, Gliomas, Brain metastases, Other brain tumors.

Results: We analyzed 961 episodes in 831 patients (Non-neoplastic: 649, Gliomas: 85, Metastases: 77, Other brain tumors: 20). Although tumor-patients presented more often with focal episodes and less consciousness impairment than non-neoplastic patients, administration of benzodiazepines as first-line treatment (>75% across all groups), and utilization of second-line ASM were similar across groups. Treatment adequacy was marginally higher in glioma patients compared to the non-neoplastic population (p: 0.049), while refractory SE was comparable in all groups (p: 0.269). No significant differences in clinical outcomes were observed (mortality: non-neoplastic (89/649, 13.7%), glioma (8/85, 9.4%), metastases (14/77, 18.2%), other tumors (5/20, 25.0%), p: 0.198; non-neoplastic vs. glioma, p: 0.271)

Conclusion: Tumor-associated SE represents 1/5 of all SE episodes, and is managed similarly to other SE causes. Treatment responsiveness and short-term clinical outcomes also exhibit comparable results.

1. Introduction

Status epilepticus (SE) carries a significant risk of morbidity and mortality[1]. Treatment involves the sequential administration of anti-seizure medications (ASM), starting with benzodiazepines, and moving progressively to general anesthetics, and the outcome is essentially determined by the patient's underlying biological background[2].

Approximately 3–12% of all SE cases are linked to brain tumors[3,4]. The likelihood of developing epilepsy, as the initial tumor symptoms or later in the disease progression, varies considerably across different neoplasms and their locations. Overall, SE among individuals with primary brain tumors has received limited attention. While some cohorts (most of them relatively small) provided evidence on SE frequency and outcomes, including the identification of predictive variables[3–8], to the best of our knowledge an analysis of treatment patterns is lacking, particularly in comparison to patients with other SE causes. This study aims to delineate the frequency of brain tumor-related SE, explore the treatment course, and draw comparisons with patients experiencing other tumor types (including brain metastases) or non-oncological etiologies.

2. Methods

This quality assessment study focuses on a cohort of consecutive adults diagnosed with SE (excluding post-anoxic), identified from the CHUV SE registry (SERCH) over a period of 10 years, between January

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2013 to December 2022, comprising a total of 831 patients. The registry is approved by the local ethics committee (CER-VD, 116/13), with consent waiver for the study (quality assessment involving anonymized procedures and treatments that are part of standard care, as of Swiss law).

Upon admission, demographics, history of prior seizures, SE etiology (including "potentially fatal", defined as leading to death within a short timeframe if not specifically treated), and seizure type were prospectively documented; the Status Epilepticus Severity Score (STESS: age, previous seizure history, seizure type, and level of consciousness impairment before treatment start) was calculated[1]; detailed information about pharmacological treatment (time to initiation, time and initial dose of each compound) were prospectively recorded, along with the necessity for intubation, and frequency of refractory SE (RSE: persistence of SE despite first- and second-line treatments). Patients were subsequently divided into four groups based on etiology: non-neoplastic, glioma, brain metastases, other brain tumors. Clinical outcomes at hospital discharge were prospectively categorized into patient return to baseline, new disability, or mortality.

For this analysis, treatment adequacy was defined as the appropriate sequential administration of first- and second-line treatment, starting with clonazepam (at least 1 mg), diazepam (10 mg), lorazepam (4 mg), or midazolam (0.1 mg/kg); followed by levetiracetam, valproate, or phenytoin (each at least 20 mg/kg), phenobarbital (15 mg/kg), lacosamide (5 mg/kg), or briviact (1 mg/kg), excluding the use of anesthesia during the first 2 treatment steps[2]. For practical purposes, we only analyzed the three most frequently used ASM across the groups.

2.1. Statistics

Calculations were performed using the RStudio software (version 2023.12.0 + 369). Categorical variables were presented as frequencies (percentages), while continuous variables were expressed as mean ± standard deviation (SD) or median (range), as appropriate. Categorical variables were analyzed using Pearson's chi-square or 2-sided Fisher's exact tests as appropriate across the groups, analyzing SE episodes (except for mortality, where patients were used). We also calculated differences between the most important neoplastic group (i.e. gliomas), and non-neoplastic etiologies. Given the exploratory nature of this study, no correction for multiple comparisons was performed. Significance was set at $p < 0.05$.

3. Results

Over a period of 10 years, 961 SE episodes occurring in 831 patients were entered in the registry. Demographics and SE characteristics are described in Table 1. A total of 206 SE episodes (21.4% of all SE episodes) were linked to 182 patients with brain tumors (21.9% of all

Table 1
Characteristics of Status epilepticus episodes stratified into different etiologies. Bold values are significant.

Total 961 episodes (831 patients)		**Non neoplastic 755 episodes (649 patients)**	**Neoplastic Glioma 95 episodes (85 patients)**	**Brain metastases 90 episodes (77 patients)**	**Other 21 episodes (20 patients)**	**P Across all groups**	**P Non-neoplastic vs. Glioma**
Age	Mean (SD)	62.9 (±19.2)	61.3 (±15.9)	64.4 (±11.6)	69 (±18)	**<0.001** (ANOVA)	0.762 (*t*-test)
Gender (%)	F	315 (41.7)	37 (38.9)	51 (56.7)	12 (57.1)	**0.021** (Chi[2])	0.605
	M	440 (58.3)	58 (61.1)	39 (43.3)	9 (42.9)		
Potentially fatal etiology (%)		297 (39.3)	79 (83.2)	85 (94.4)	11 (52.3)	**<0.001** (Fisher)	**<0.001**
Previous seizures (%)		395 (52.3)	53 (55.8)	38 (42.2)	12 (57.1)	0.237 (Chi[2])	0.523
Consciousness before treatment (%)	Alert/somnolent	286 (38.1)	58 (61.1)	54 (60)	7 (33.3)	**<0.001** (Chi[2])	**<0.001**
	Stupor/coma	464 (61.9)	37 (38.9)	36 (40)	14 (66.7)		
Seizure type (%)	Focal aware	120 (15.9)	30 (31.6)	26 (29.5)	4 (19.0)	**<0.001** (Fisher)	**<0.001**
	Focal unaware	191 (25.4)	27 (28.4)	27 (30.7)	6 (28.6)		
	Generalised convulsive	370 (49.1)	35 (36.8)	32 (36.4)	11 (52.3)		
	NCSEC	52 (6.9)	0 (0)	1 (1.1)	0 (0)		
	Other	20 (2.7)	3 (3.2)	2 (2.3)	0 (0)		
STESS score (%)	0–2	342 (45.3)	52 (54.7)	40 (44.4)	9 (42.9)	0.357 (Chi[2])	0.082
	3–6	413 (54.7)	43 (45.3)	50 (55.6)	12 (57.1)		
Intubation for SE treatment (%)	No	521 (69.0)	73 (76.8)	75 (83.3)	14 (66.7)	0.070 (Chi[2])	0.298
	Yes (for SE treatment)	124 (16.4)	13 (13.7)	8 (8.9)	2 (9.5)		
	Yes (airways protection)	106 (14.0)	9 (9.5)	7 (7.8)	5 (23.8)		
1–2 steps used adequately* (%)	Yes	279 (37.4)	45 (47.4)	34 (43.4)	9 (42.9)	0.259 (Chi[2])	**0.049**
BZD as first drug (%)		602 (79.7)	81 (85.3)	69 (88.1)	16 (76.2)	0.541 (Chi[2])	0.200
2nd line ASM (%)	LCM	58 (8.5)	13 (15.1)	4 (5.0)	0 (0)	0.402 (Fisher)	0.458 (Chi[2])
	VPA	87 (12.7)	13 (15.1)	9 (11.3)	1 (5.9)		
	LEV	313 (45.6)	46 (53.5)	43 (53.8)	11 (64.7)		
Refractory SE (%) (persistent SE despite 1st- and 2nd-line ASM)		409 (54.2)	50 (52.6)	51 (56.7)	7 (33.3)	0.269 (Chi[2])	0.776
Clinical outcomes (%) (calculated using number of patients)	Back to baseline	318 (49.0)	36 (42.4)	26 (33.8)	8 (40.0)	0.061 (Chi[2])	0.130
	New handicap	242 (37.3)	41 (48.2)	37 (48.1)	7 (35.0)		
	Death **	89 (13.7)	8 (9.4)	14 (18.2)	5 (25.0)		

Legend: ASM: anti-seizure medication. NCSEC: non-convulsive Status epilepticus in coma. SE: Status epilepticus.
* clonazepam 1 mg, or diazepam10mg, or lorazepam 4 mg, or midazolam 0.1 mg/kg, followed by levetiracetam 20 mg/kg, or valproate 20 mg/kg, or phenyntoin 20 mg/kg, or phenobarbital 15 mg/kg, or lacosamide 5 mg/kg, or brivaracetam 1 mg/kg; AND correct sequence, AND no anesthesia at the first 2 steps.
** Mortality was calculated on number of patients.

patients; 85 with glioma and 77 with brain metastasis). Other brain tumors included meningiomas (11), lymphomas (7), neuroectodermal tumors (1), neuroepithelial tumor (1), and cerebral lipoma (1). Brain tumors were newly diagnosed at SE admission in 33 patients (18%).

Brain tumor subjects exhibited milder consciousness impairment at SE onset, although they had a higher likelihood of potentially fatal etiologies compared to non-neoplastic patients. Glioma-SE was predominantly observed in males, contrasting with the other tumor subgroups. Patients with gliomas and metastases experienced generalized convulsive SE less frequently when compared to non-neoplastic subjects. There was no difference in the BZD administration as first-line treatment (>75% for all groups), nor for 2nd line ASM, with levetiracetam being by far the most common across all groups, followed by valproate and lacosamide. Treatment adequacy was marginally significantly higher in glioma patients than in the general population. Finally, no notable disparities in clinical outcomes were identified when comparing the four subgroups, including between low-grade (15 patients; back to baseline: 33.3%, handicap: 46.7%, death: 0) and high-grade gliomas (70 patients; back to baseline: 40%, handicap: 48.6%, death: 11.4%; p-value:0.450). Comparing mortality alone across the four groups also revealed no significant differences (p-value across all groups: 0.198; p-value for non-neoplastic versus glioma: 0.271, both chi-square).

4. Discussion

In this large adult cohort, the prevalence of brain tumor-related SE episodes was 21.4%, half of which was associated to primary brain tumors. This finding contrasts to prior analyses that identified brain tumors as a relatively rare cause of SE, with the highest documented prevalence being 12%[3,4,9,10]. The discrepancy between different studies may be due to underlying differences in the studied cohorts, and the considerably larger dataset of the present one. The male predominance in glioma patients mirrors the distribution of these tumors in the population. Our cohort confirms that brain tumor patients exhibit a relatively high frequency of focal SE[5,10,11] (this is reflected by the less severe consciousness impairment compared to non-neoplastic patients).

Our analysis did not reveal significant differences in the treatment flows employed between non-neoplastic and neoplastic SE episodes (only glioma patients demonstrated a marginally higher adherence to treatment compared to the non-neoplastic population). Benzodiazepines represented the initial treatment in over 3/4 of patients across all groups, with a notable proportion (85.3%) observed in the glioma group. The observed overall modest adequacy to treatment guidelines (slightly under 50%, using a relatively liberal definition) in our cohort underlines the need of increased awareness of treatment protocols.

Levetiracetam emerged as the most frequently used 2nd line ASM, followed by valproate and lacosamide, emphasizing their clinical significance in managing SE across both neoplastic and non-neoplastic etiologies[12]. A recent study also demonstrated the increasing trend in the use of newer ASMs particularly levetiracetam and lacosamide, in the management of both adult and children SE, while confirming the decline of older ASM[13]. The widespread use of new-generation ASM lacking significant pharmacokinetic interactions, likely contributes to the alignment of treatment strategies across oncological and non-oncological SE patients. Phenytoin for example, formerly a crucial molecule in SE management, is no longer a treatment of choice in oncological patients, due to the risks of interactions potentially compromising oncological treatments.

Short-term clinical outcomes were comparable across the various etiological groups; we observed a 9.4% mortality for glioma patients. Notably, this rate remained tendentially lower than in non-neoplastic patients (13.7%). The high mortality rate observed in the group of other neoplastic etiologies (25%) was primarily attributed to the presence of lymphoma patients. However, the relatively small number in this group precludes drawing generalized conclusions. Previous studies have presented variable data, with some showing similar or lower[4] and others indicating higher mortality rates[6]. Nevertheless, in the long term, mortality surpasses that of other etiologies[4], reflecting the progressive nature of the underlying neoplasm. A recent study revealed an overall mortality among brain tumor patients of 7.3%, with the highest incidence observed in those with metastases (mortality at one year was estimated at 65.9%)[8].

The major limitation of our study is its retrospective design, preventing a detailed analysis of data apart from those collected for the purpose of the SE registry. For example, glioma grade classification was not available, and we inferred low grades in patients lacking potentially fatal etiologies. However, all data were collected prospectively by 2 authors (JN, AOR), reinforcing the internal validity. Given the heterogeneity of the group with other tumor-related etiologies, no detailed analysis was undertaken. Finally, this assessment cannot be readily generalized to pediatric populations or environments with different health policies, such as developing countries. Conversely, treatment flow comparisons to other SE etiologies, especially at this large scale, adds new data to the existing literature.

5. Conclusion

Our findings suggest that tumor-associated SE, representing 1/5 of SE episodes, although more inclined to manifest as focal SE with limited consciousness impairment, are treated similarly to other SE patients, with comparable treatment responsiveness (evaluated by the likelihood of developing refractory SE) and short-term clinical outcomes.

Statement of ethics

The registry is approved by the local ethics committee (CER-VD, 116/13), with consent waiver for the study (quality assessment involving anonymized procedures and treatments that are part of standard care, as of Swiss law).

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Declaration of competing interest

None.

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