Journal of the Neurological Sciences 407 (2019) 116538

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Clinical characteristics, EEG findings and implications of status epilepticus in patients with brain metastases

Jonah Fox[a,*,1], Shaun Ajinkya[a,1], Adam Greenblatt[a], Peter Houston[b], Alain Lekoubou[a], Scott Lindhorst[c], David Cachia[c], Adriana Olar[b,c,2], Ekrem Kutluay[a,2]

[a] Department of Neurology, Medical University of South Carolina, Charleston, SC, USA
[b] Department of Pathology, Medical University of South Carolina, Charleston, SC, USA
[c] Department of Neurosurgery, Medical University of South Carolina, Charleston, SC, USA

ARTICLE INFO

Keywords:
Epilepsy
Morbidity
Complications
Mortality

ABSTRACT

Purpose: To evaluate the clinical implications of status epilepticus in patients with metastases to the brain as well as associated demographic, clinical, EEG and radiographic features.
Methods: Retrospective chart review of 19 patients with metastases to the brain who subsequently developed status epilepticus.
Results: Of the patients who developed status epilepticus only 36.8% had a prior history of seizures since diagnosis of brain metastases. Status epilepticus most commonly occurred in the setting of a new structural injury to the brain such as new metastases, increase in size of metastases or hemorrhage. 57.9% of patients had either refractory or super-refractory status epilepticus. Focal non-convulsive status epilepticus was the most common subtype occurring in 42.1% of patients. 31.6% of patients died within 30 days of the onset of status epilepticus.
Conclusion: Status epilepticus eventually resolved with treatment in all patients with brain metastases; however, it is associated with poor outcomes as nearly one-third was deceased within 30-days of onset. Nevertheless, no patients died during status epilepticus. Thus, status epilepticus may be indicative of an overall poor clinical status among patients with brain metastases.

1. Introduction

Seizures are a significant source of morbidity in patients with metastases to the brain (MB) and occur in approximately 15–35% of individuals afflicted [1,2]. In the general population, the overall case fatality rate in patients with status epilepticus (SE) is approximately 20% [3]; however, those who survive may suffer from a permanent change in their clinical condition due to neuronal injury and death, as well as changes to neuronal networks [4,5]. While brain tumors of various types are collectively responsible for approximately 2–12% of SE, there is some evidence that they may be more treatment responsive but generally associated with a poorer short-term prognosis relative to other causes of SE [6,7]. Therefore, we hypothesized that SE in patients with MB would also be treatment responsive and associated with a poor short-term prognosis. Thus, we performed a retrospective analysis on a cohort of patients with both SE and MB to evaluate treatment responsiveness and prognosis as well as other associated demographic, clinical, EEG, and radiographic features.

2. Methods

This study was approved by the Medical University of South Carolina (MUSC) Institutional Review Board for human research.

2.1. Data collection and inclusion criteria

A retrospective chart review was performed of adult patients with MB at a tertiary medical center between April 8, 2006 and December 14, 2018. Data collection was completed on May 1, 2019. Inclusion criteria consisted of a diagnosis of MB, the absence of prior history of seizures prior to initial presentation of MB and age greater than 18 years. The diagnosis of MB was confirmed by histopathological

Abbreviations: MB, metastases to the brain; SE, Status epilepticus

* Corresponding author at: Department of Neurology, Medical University of South Carolina, Charleston, SC, USA.
E-mail address: foxjo@musc.edu (J. Fox).

[1] Jonah Fox and Shaun Ajinkya are joint first authors.
[2] Adriana Olar and Ekrem Kutluay are joint last authors.

https://doi.org/10.1016/j.jns.2019.116538
Received 6 July 2019; Received in revised form 19 September 2019; Accepted 15 October 2019
Available online 16 October 2019
0022-510X/

analysis via tissue biopsy or resection in 73.7% of patients, while for the remainder it was made based on radiographic evidence and clinical history in the context of a known primary per review by experienced neuro-oncologists and neuro-radiologists. The data included basic demographic characteristics, MRI results, findings on EEG, clinical details including treatment modalities and the dates of critical clinical events. SE, when convulsive and not captured on EEG, was determined to be present if it was sufficiently described in the chart upon review by a neurologist. For example, if a patient was described to have rhythmic shaking of the right upper extremity and had an EEG that showed left hemispheric interictal discharges it would be counted as focal SE. All non-convulsive status epilepticus (NCSE) cases were captured on EEG. Refractory SE was defined as seizures which persisted despite administration of two properly chosen and dosed antiepileptic drugs including benzodiazepines [8]. Super-refractory SE was defined as continued or recurrent seizures which lasted a minimum of 24 h following administration of anesthetics (e.g. propofol or midazolam) [8].

2.2. Statistical analysis

Continuous variables were described by mean and standard deviation if normally distributed and by median and interquartile range (IQR) if non-normally distributed. Categorical variables were described by frequencies and percentages. The categories of initial symptoms of MB, cancer treatment, SE provoking factors, and SE treatment were not mutually exclusive. We used Wilcoxon rank-sum testing to compare the "chart documented period" (CDP) between patients who were deceased and those who were not. CDP refers to the duration of time that a particular patient's clinical status was able to be assessed by chart review. All analyses performed with Stata 11 (StataCorp LLC, College Station, TX).

3. Results

19 patients fit our criteria. Mean CDP from diagnosis of MB and time of SE was 323.9 days (median 154, range 12–1221) and 159 days (median 60, range 4–1133), respectively. 68.4% of patients died during the CDP. There was no significant difference in duration of CDP in days between patients who were alive (median 110.5, IQR 19–167) and patients who were deceased (median 60, IQR 25–193) from the time of SE diagnosis (Wilcoxon rank sum $p = .79$). Median duration from diagnosis of MB to SE was 60 days (IQR 0–200).

Table 1 describes the demographics of SE patients. 52.6% of patients were female, with a mean age of 63.9. Frontal (47.4%) and parietal (36.8%) lobe locations were the most common for the largest tumor present. The median number of CNS lesions on initial presentation was 2.5 (IQR 1–4), while the most common primary tumor type was lung (57.9%). The median largest dimension of CNS lesion at presentation was 2.7 cm (IQR 2–3.3).

Clinical characteristics of SE are described in Table 2. Of patients with MB and SE only approximately one-third (36.8%) had a prior history of seizures since their diagnosis of MB. Several patients (15.8%) presented with SE who had no prior known diagnosis of MB. A majority of patients (57.9%) had either refractory (42.1%) or super-refractory (15.8%) SE. Focal NCSE (42.1%) was the most common subtype (Table 3), followed by generalized SE (31.6%). Structural injury (i.e. new MB, hemorrhage or increased size of MB) was the most common (42.1%) etiology of SE. Duration of the SE showed an approximate U-shaped pattern with approximately equal fractions exhibiting SE less than 30 min or greater than 24 h. Benzodiazepine pushes and levetiracetam were the most common treatments overall. The largest subgroup of patients was discharged home (42.1%) while an equal number of patients were discharged to rehab (26.3%) and hospice (26.3%). Only 1 patient died during hospitalization however 31.6% of patients died within 30 days of SE onset.

In approximately 68.4% of patients, seizure activity was captured on EEG however for the rest it was terminated prior to hook up. Focal discharges were captured in nearly two-thirds of patients, while lateralized periodic discharges were captured in approximately 10%. Brief ictal rhythmic discharges were captured in 15.8%. Interestingly, in a patient with miliary metastases generalized epileptiform activity was present during seizure activity.

Table 1
Demographic characteristics of patients with metastatic brain cancer and status epilepticus.

	N (%)
Age (years, mean (SD))	63.9 (10.5)
Female sex	10 (52.6)
Initial symptoms of metastases	
Altered mental status	6 (31.6)
Seizures	10 (52.6)
Motor symptoms	4 (21.1)
Sensory symptoms	2 (10.5)
Headache	4 (21.1)
Gait symptoms	1 (5.3)
Nausea and vomiting	2 (10.5)
Not Stated in chart	3 (15.8)
Largest tumor site on presentation with metastases	
Frontal	9 (47.4)
Parietal	7 (36.8)
Temporal	1 (5.3)
Occipital	1 (5.3)
Thalamus	1 (5.3)
Hemorrhagic metastases	
Yes	8 (42.1)
No	10 (52.6)
Unknown	1 (5.3)
Size of largest dimension of tumor at presentation [cm, median (IQR)]	2.7 (2–3.3)
Number of tumors at presentation (median (IQR))	2.5 (1–4)
Primary tumor	
Lung	11 (57.9)
Breast	1 (5.3)
Melanoma	2 (10.5)
Gastrointestinal	1 (5.3)
Renal	2 (10.5)
Other	2 (10.5)
Treatment	
Steroids	19 (100.0)
Chemotherapy/Immunotherapy	14 (73.7)
Radiation	15 (79.0)
Surgery	14 (73.7)

4. Discussion

To the best of our knowledge there is little previously published information on the course, clinical features, EEG findings and prognostic implications of SE in patients with MB. Interestingly, most patients with MB who developed SE did not have a prior history of seizures since their diagnosis of MB and several patients were diagnosed with MB only after initially presenting with SE. This is dissimilar to findings previously reported in patients with glioma and SE where most patients had a history of well controlled epilepsy [9]. It may be that this difference is simply related to the relative longer survivability and increased prevalence of seizures in low grade glioma patients relative to patients with MB. However, unlike previously reported findings in glioma patients most patients in our cohort with MB had focal NCSE as opposed to focal SE with secondary generalization [9,10]. We suspect that this may be due to differences in the size and location of tumors, as well as potential histological differences, between patients with glioma and MB which likely result in a difference in the tendency of a seizure to secondary generalize. It is also likely that NCSE is underdiagnosed in patients with MB [11,12].

The most common location for the largest tumor site in patients with MB and SE was the frontal lobe and parietal lobe. However, it is

Table 2
Clinical Characteristics of Status Epilepticus in patients with metastases to the brain.

	N (%)
Category of status epilepticus	
Status epilepticus	8 (42.1)
Refractory status epilepticus	8 (42.1)
Super refractory status epilepticus	3 (15.8)
Duration of status epilepticus	
Less than 30 min	5 (26.3)
30 min to under 1 h	3 (15.8)
1 h to under 5 h	2 (10.5)
5 h to under 24 h	1 (5.3)
24 h and greater	5 (26.3)
Not Stated	3 (15.8)
Seizures before development of status epilepticus	7 (36.8)
Provoking factors:	
Infection	3 (15.8)
Metabolic abnormality	3 (15.8)
Medication noncompliance	2 (10.5)
Structural injury	8 (42.1)
Treatments used for status epilepticus	
Benzodiazepine push	18 (94.7)
Divalproex	3 (15.8)
Lacosamide	4 (21.1)
Levetiracetam	17 (89.5)
Phenytoin/Fosphenytoin	11 (57.9)
Anesthetics:	
Midazolam	3 (15.8)
Propofol	8 (42.1)
Ketamine	1 (5.3)
Discharge Disposition:	
Home	8 (42.1)
Rehab	5 (26.3)
Hospice	5 (26.3)
Deceased	1 (5.3)

Table 3
Electroencephalographic Characteristics of Status Epilepticus in patients with metastases to the brain.

	N (%)
Routine EEG	19 (100.0)
EEG continuous monitoring	18 (94.7)
EEG findings:	
Focal slowing	5 (26.3)
Hemispheric slowing	8 (42.1)
Generalized slowing	15 (78.9)
Focal discharges	12 (63.2)
Lateralized periodic discharges	2 (10.5)
Generalized discharges	1 (5.2)
Brief Ictal rhythmic discharges	3 (15.8)
Seizures captured	13 (68.4)
Generalized epileptiform activity present during seizure	1 (7.6)
Type of status	
Focal SE	4 (21.1)
Generalized SE	6 (31.6)
Focal NCSE	8 (42.1)
Generalized NCSE	1 (5.3)

difficult to interpret this information as these locations are also the most common sites for MB in the general population [13]. Though a meta-analysis of glioma patients found that frontal lobe tumors may result in an increased risk for seizures [14]. It has been reported that among patients with brain metastases, tumors located in the temporal and occipital lobe are associated with an increased risk for seizures [15]. It is yet unknown if the relationship between tumor location and risk for SE is different than that for seizures as no study has yet had sufficient sample size to perform an appropriate statistical analysis.

In most patients, a potential provoking factor for SE was identified. The most common provoking factor for SE was a structural injury such as an increase in the size or number of metastases as well as hemorrhage. In the patients for whom no structural change was identified there was often another inciting factor such as infection or metabolic abnormality. Prior studies on patients with glioma or MB have similarly found that SE tends to occur in the context of disease progression or initial presentation [9,10,16].

Given the small sample size it was not possible to perform a logistic regression to identify particular factors independently associated with outcome. However, we found that approximately 31.6% of patients died within 30 days of SE onset, though only one patient died during their hospitalization. A study on SE in gliomas patients found a much more favorable prognosis with zero patients deceased during SE or within three weeks after SE but six of twenty died within three months [9]. The relative worse prognosis among patients with MB and SE, also specifically NCSE, compared to those with primary brain tumors and SE is consistent with previously reported findings [10,17]. Generally, however it has been demonstrated that those with SE due to cancer tend to respond to treatment better than those with other etiologies though they have a higher short-term mortality [6,7].This however may be due to underlying disease progression of their underlying cancer diagnosis.

The duration and refractoriness of SE in patients with MB was highly variable. Nearly half of patients remained in SE for up to one hour or less while approximately one quarter of patients were in SE for more than 24 h. Eventually however, SE in all patients was terminated though 15.8% were super-refractory. The duration and refractoriness of SE in our cohort was not dissimilar to that found in the general population of patients with SE of various causes [18].

Some limitation of this study includes the relatively small sample size as well as the retrospective design. In addition, some patients that had SE of relatively short duration were not hooked up to EEG quickly enough for it to be captured. Further, a significant percentage of our patients had at some point resective surgery and it is difficult to ascertain how that may have impacted their risk for SE. However, to the best of knowledge there is little previously published on the clinical features, EEG findings and implications of SE in patients with MB.

5. Conclusions

Our results suggest that among most patients with MB that SE eventually resolves with appropriate treatment. However, approximately one-third are deceased within 30-days of onset, but it is typically not due to SE directly. It may be that SE is indicative of an overall poor clinical status among patients with MB due to underlying disease progression or complications arising from brain metastasis such as intratumoral bleeding. In addition, a substantial portion of patients with MB who develop SE had no prior history of seizures suggesting, particularly for NCSE, that a high index of suspicion is warranted.

Declaration of Competing Interest

None.

Acknowledgement

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References

[1] D.J. Englot, E.F. Chang, C.J. Vecht, Epilepsy and brain tumors, Handb. Clin. Neurol. 134 (2016) 267–285.
[2] V. Chan, A. Sahgal, P. Egeto, T. Schweizer, S. Das, Incidence of seizure in adult patients with intracranial metastatic disease, J. Neuro-Oncol. 131 (2017) 619–624.
[3] G. Logroscino, D.C. Hesdorffer, G. Cascino, W.A. Hauser, A. Coeytaux, B. Galobardes, A. Morabia, P. Jallon, Mortality after a first episode of status epilepticus in the United States and Europe, Epilepsia 46 (Suppl. 11) (2005) 46–48.
[4] E. Trinka, H. Cock, D. Hesdorffer, A.O. Rossetti, I.E. Scheffer, S. Shinnar, S. Shorvon, D.H. Lowenstein, A definition and classification of status epilepticus – report of the ILAE task force on classification of status Epilepticus, Epilepsia 56 (2015)

1515–1523.
[5] R.C. Scott, What are the effects of prolonged seizures in the brain? Epileptic Disord. 16 (2014) S6–S11 Spec No 1.
[6] Y. Arik, F.S. Leijten, T. Seute, P.A. Robe, T.J. Snijders, Prognosis and therapy of tumor-related versus non-tumor-related status epilepticus: a systematic review and meta-analysis, BMC Neurol. 14 (2014) 152.
[7] A. Neligan, S.D. Shorvon, Frequency and prognosis of convulsive status epilepticus of different causes: a systematic review, Arch. Neurol. 67 (2010) 931–940.
[8] S. Hocker, W.O. Tatum, S. LaRoche, W.D. Freeman, Refractory and super-refractory status epilepticus–an update, Curr. Neurol. Neurosci. Rep. 14 (2014) 452.
[9] K.M. Knudsen-Baas, K.N. Power, B.A. Engelsen, S.E. Hegrestad, N.E. Gilhus, A.M. Storstein, Status epilepticus secondary to glioma, Seizure 40 (2016) 76–80.
[10] R. Cavaliere, E. Farace, D. Schiff, Clinical implications of status epilepticus in patients with neoplasms, Arch. Neurol. 63 (2006) 1746–1749.
[11] M. Spindler, L.M. Jacks, X. Chen, K. Panageas, L.M. DeAngelis, E.K. Avila, Spectrum of nonconvulsive status epilepticus in patients with cancer, J. Clin. Neurophysiol. 30 (2013) 339–343.
[12] S. Blitshteyn, K.A. Jaeckle, Nonconvulsive status epilepticus in metastatic CNS disease, Neurology 66 (2006) 1261–1263.
[13] G. Minniti, E. Clarke, G. Lanzetta, M.F. Osti, G. Trasimeni, A. Bozzao, A. Romano, R.M. Enrici, Stereotactic radiosurgery for brain metastases: analysis of outcome and risk of brain radionecrosis, Radiat. Oncol. 6 (2011) 48.
[14] J. Zhang, L. Yao, S. Peng, Y. Fang, R. Tang, J. Liu, Correlation between glioma location and preoperative seizures: a systematic review and meta-analysis, Neurosurg. Rev. 42 (2018) 603–618.
[15] A. Wu, J.D. Weingart, G.L. Gallia, M. Lim, H. Brem, C. Bettegowda, K.L. Chaichana, Risk factors for preoperative seizures and loss of seizure control in patients undergoing surgery for metastatic brain Tumors, World Neurosurg. 104 (2017) 120–128.
[16] P.L. Moots, R.J. Maciunas, D.R. Eisert, R.A. Parker, K. Laporte, B. Abou-Khalil, The course of seizure disorders in patients with malignant gliomas, Arch. Neurol. 52 (1995) 717–724.
[17] L.V. Marcuse, G. Lancman, A. Demopoulos, M. Fields, Nonconvulsive status epilepticus in patients with brain tumors. Seizure - European, J. Epilepsy 23 (2014) 542–547.
[18] D. Dubey, J. Kalita, U.K. Misra, Status epilepticus: refractory and super-refractory, Neurol. India 65 (2017) S12–s17.