Journal of the Neurological Sciences 400 (2019) 34–38

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

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

Seizures in patents with primary central nervous system lymphoma: Prevalence and associated features

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ARTICLE INFO

Keywords:
PCNSL
Epilepsy
Morbidity
Complications

ABSTRACT

Objective: Primary central nervous system (CNS) lymphoma (PCNSL) is a rare, aggressive, yet highly chemosensitive form of non-Hodgkin lymphoma which is associated with significant morbidity. Very little is known about the long-term risk for and features of seizures associated with this condition.

Methods: We performed a retrospective and longitudinal analysis of 36 patients with pathologically and radiographically confirmed primary CNS lymphoma to evaluate the incidence, prevalence and features associated with seizures. Demographic, radiographic, histological and electroencephalographic (EEG) data were included as part of the study.

Results: One-third of patients with primary CNS lymphoma had clinical seizures of which two-thirds occurred at time of initial presentation, while the remainder developed during a mean follow-up time of 1.49 years. The incidence rate of first seizure in PCNSL was 224.4 per 1000 persons, per year. There was a trend towards association with seizures in patients with cortical lesions relative to patients with subcortical lesions. EEG revealed epileptiform discharges in 44.4% of patients with both PCNSL and clinical seizures which suggests that it is a useful diagnostically in a substantial proportion of patients.

Conclusions: A significant percentage of patients with primary CNS lymphoma develop comorbid seizures during their disease course. Increased awareness and collaboration between neuro-oncologists and epileptologists may enhance and improve care for these patients.

1. Introduction

Primary central nervous system (CNS) lymphoma (PCNSL) is a rare and highly aggressive extra-nodal non-Hodgkin lymphoma which constitutes approximately 1.9–4.0% of all newly diagnosed primary central nervous system tumors [1,2]. PCNSL most commonly presents as an intracerebral mass; however, it may also involve the eyes, spinal cord, meninges or cranial nerves. Immunodeficiency, secondary to human immunodeficiency virus (HIV), solid-organ transplant immunosuppression, or other causes, is the only known significant risk factor for the development of PCNSL, and infection with Epstein-Barr virus (EBV) may play a role in oncogenesis among the immunocompromised [3,4]. When untreated, patients with PCNSL have a survival of months from the time of diagnosis; however, PCNSL is highly responsive to chemotherapy, particularly high-dose methotrexate-based therapy, and up to 20–30% of patients survive 5-years or longer [2,5,6]. Thus, there are a significant percentage of patients with PCNSL who will survive for an extended period of time and thus have an extensive opportunity to develop potential complications.

Seizures are a frequent and well-studied complication of other types CNS tumors such as gliomas and metastases, however, there are very limited published data on seizures among patients with PCNSL [7]. Prior studies have identified the incidence of seizures in 11–14% of immunocompetent and 14–27% of immunocompromised patients at the time of initial presentation with PCNSL [8–10]. We evaluated the longitudinal risk for seizures in patients with PCNSL as well as any potential associated features.

Abbreviations: PCNSL, Primary CNS Lymphoma

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https://doi.org/10.1016/j.jns.2019.03.011
Received 29 December 2018; Received in revised form 12 March 2019; Accepted 13 March 2019
Available online 14 March 2019
0022-510X/

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

In this retrospective study we performed a chart review of adult patients with a pathologically confirmed diagnosis of PCNSL at a large tertiary medical center from 1/1/2013 until 11/28/2018. All patients underwent a complete evaluation for evidence of extra-CNS disease including ophthalmological evaluation, serum and urine protein electrophoresis, lumbar puncture, positron emission tomography scan, testicular ultrasound in male patients, bone marrow biopsy, as well as chest, abdominal and pelvis computed tomography imaging. Data collection finished on 12/2/2018. Inclusion criteria included a diagnosis of PCNSL, confirmed by histopathological evaluation, no prior history of seizures before presentation for PCNSL, age greater than 18 years and consistent longitudinal follow-up at our institution for a minimum of one year. Exclusion criteria were any extra-CNS involvement. Data collected included age, sex, if the patient was deceased, cortical location of lesion, EBV status, integrity of immunological function, presenting symptoms, pathology and EEG results. All electroencephalograms (EEGs) and pathology specimens were interpreted by board-certified neurophysiologists and pathologists, respectively, at our tertiary medical center.

2.2. Statistical analysis

For the purposes of epidemiological calculations, follow-up time was determined between the last time seen by neuro-oncology and the initial presentation. The time of first seizure was determined via chart review. Incidence was calculated by using the raw number of first seizures as the numerator and the person-time contributed by each subject as the denominator. A person contributed person-time to the calculation until first seizure, death, or the ending of their follow-up period. Demographic variables were stratified by presence vs. absence of seizures. Fisher's exact test/chi square tests were used for categorical variables and *t*-tests or Wilcoxon rank-sum test (if normality assumption not met by Shapiro-Wilk test) was used for continuous variables. All analyses were performed by Stata 11 (StataCorp LLC, College Station, TX).

3. Results

The sample included 36 patients with a confirmed tissue diagnosis of PCNSL without radiographic or pathological evidence of extra-CNS disease and no prior history of seizures (Table 1). Of that total, 12 (33.3%) had seizures, which would be representative of the period prevalence of the sample during our course of follow-up. In total, 14 (38.9%) died during the period for which they were followed. Subjects were followed for a mean of 1.49 years. The subjects generated 53.5 person-years; this yielded an incidence rate of first seizure in PCNSL of 224.4 per 1000-person years. Of those patients who had seizures 66.7% presented with them while the remainder developed seizures later during their disease. Of the four patients who had seizures after diagnosis, mean time to seizure was 4.5 months after initial diagnosis. Three of the four patients had received treatment with high-dose methotrexate-based chemotherapy regimens while one had never initiated treatment. Two were associated with progression of disease, one was associated with hygroma after resection, and one had an unclear etiology with no apparent changes in metabolic testing or imaging around the time of the complaint.

Mean age of patients with seizures was 57.8 while among those without seizure was 66.3. In addition, there was a trend towards association of cortical location among patients with seizure however it did not meet statistical significance ($p = .16$, Wilcoxon rank-sum). The location of subcortical lesions in patients who also had seizures included the right caudate, left centrum semiovale and left greater than right splenium of the corpus callosum. There was no evidence of influence of immunodeficiency on the incidence of seizures ($p = 1.00$, Fisher's exact test). Seizures, as a mono-variate, were not associated with patient mortality ($p = .47$, Fisher's exact test) (Table 1).

With respect to cytopathology, data was scant for many observations, but all were CD20 positive, and 29 of 36 (80.6%) were MUM-1 positive (Table 2). 31 of 33 (93.9%) contained CD-3 T-cell infiltrate. Bcl-6, Ki67% and histological subtype (activated B-cell (ABC), germinal center (GC) or uncategorized) had no evidence of impact on seizure prevalence (Table 2). CSF yielded a diagnosis of PNCSL in only 5% of the 20 patients who were assessed by this method and 16 patients did not get CSF analysis.

Among patients with cortical lesions the most common location was the frontal lobe which was found in 50% of patients with cortical lesions (Table 3). The next most frequent location for lesions were in the parietal lobe which was detected in 30% of patients with cortical lesions.

EEG was performed in 75% of patients with clinical seizures of

Table 1
Sample demographic characteristics of adult patients with primary central nervous system lymphoma by the presence or absence of seizures.

	Seizures ($n = 12$)	No seizures ($n = 24$)	p-Value
	N (%)	N (%)	
Age (years) [Mean (SD)]	57.8 (17.9)	66.3 (9.78)	0.59**
Female Sex	4 (33.3)	11 (45.8)	0.72
Deceased	6 (50.0)	8 (33.3)	0.47
Cortical location of lesion	9 (75.0)	11 (45.8)	0.16
Multiple CNS sites at presentation	4 (33.3)	15 (62.5)	0.16
Laterality			
Left	4 (33.3)	7 (29.2)	
Right	7 (58.3)	16 (66.7)	
Midline	1 (8.3)	1 (4.2)	
EBV positive*	4 (36.4)	10 (43.5)	1.00
Immunocompromised	2 (16.7)	3 (12.5)	1.00
Presenting symptoms†			
AMS/confusion	3 (25.0)	9 (37.5)	
Seizure	8 (66.7)	0 (0.0)	
Fatigue	1 (8.3)	2 (8.3)	
Headache	2 (16.6)	6 (25.0)	
Focal weakness/hemiparesis	2 (16.6)	6 (25.0)	

Abbreviations: AMS – altered mental status, CNS – central nervous system, EBV – Epstein-Barr virus, n,N – number, SD – standard deviation.

* Only 34 patients had EBV data.

† These do not add up to 100% and are not mutually exclusive.

** Used Wilcoxon rank-sum test. All other *p*-values refer to the Fisher's exact test.

Table 2
Cytopathology characteristics of adult patients with primary central nervous system lymphoma by the presence or absence of seizures.

	Seizures (n = 12)	No seizures (n = 24)	p-Value
	N (%)	N (%)	
Bcl-6**	9 (81.8)	11 (61.1)	0.41
Ki-67 (MIB-1) (%) (Mean (SD))	65.8 (33.2)	51.2 (39.2)	0.43*
ABC vs. GC or uncategorized	11 (91.7)	18 (75.0)	0.38

Abbreviations: ABC – activated B-cell subtype, GC – germinal center, N – number, SD – standard deviation.

* Used Wilcoxon rank-sum test. All other *p*-values refer to the Fisher's exact test.

** Only 29 patients had data.

Table 3
Lesion localization of adult patients with primary central nervous system lymphoma involving the cortex by the presence or absence of seizures.

	Seizures (n = 9)	No seizures (n = 11)	p-Value
	N (%)	N (%)	
Temporal vs. other	1 (11.1)	3 (27.3)	0.59
Frontal vs. other	4 (44.4)	6 (54.6)	1.00
Parietal vs. other	4 (44.4)	2 (18.2)	0.34

Abbreviation: N – number.
All p-values refer to the Fisher's exact test.

Table 4
Characteristics of seizures of adult patients with primary central nervous system lymphoma.

	Seizures (n = 12)
	N (%)
Clinical semiology	
Focal with retained awareness	2 (16.7)
Focal with lost awareness	2 (16.7)
Focal not otherwise specified	1 (8.3)
Secondary generalized	6 (50.0)
Generalized	1 (8.3)
EEG Performed	9 (75.0)
Interictals*	
"Right hemisphere epileptiform discharges"	1 (10.0)
"Left parasagittal sharp wave complexes"**	1 (10.0)
Right frontotemporal LPDs**	1 (10.0)
Left LPDs	1 (10.0)
None reported	5 (55.5)

Abbreviation: EEG – electroencephalogram, LPD – lateralized periodic discharge, n,N – number.
* Out of the 9 who had seizures and EEG.
** Patient with subcortical lesions.

which 44.4% had epileptiform discharges (Table 4). In total, 12 patients (33.3%) of our sample had continuous EEG monitoring. Of these, 5 (41.7% of those monitored) had a prior history of clinical seizures since PCNSL diagnosis, with 2 (16.7% of those monitored) having seizure activity recorded during monitoring. The indications for ordering continuous EEG monitoring in these patients were clinical concern for non-convulsive status epilepticus due to encephalopathy (9, 75% of those monitored) followed by concern for convulsive status epilepticus (3, 25% of those monitored). Captured epileptiform discharges included: "right hemisphere epileptiform discharges"; "left parasagittal sharp wave complexes"; right frontotemporal lateralized periodic discharges (LPDs); and left LPDs (Fig. 1). Of the patients with subcortical lesions and seizures, two out of three had epileptiform discharges. Generally, the location of epileptiform discharges appeared to grossly correspond to the location of the primary lesion (Table 5). Among all patients with seizures, the most common semiology was secondary generalized seizures (50.0%), followed by focal with retained awareness (16.7%) and focal with lost awareness (16.7%). Of note, the EEG recordings were of variable length and included both routine studies as well as long-term monitoring.

4. Discussion

In our cohort, the incidence of seizures in patients with PCNSL was 224.4 per 1000-person years. Seizures occurred in two thirds of patients at initial presentation. Furthermore, there was a trend towards a significant association between patients with cortical PCNSL lesions and seizures. Given that cortical structures are thought to be more liable relative to subcortical structures to initiate epileptic activity, it has been speculated that one of the reasons why PCNSL patients are less likely to have seizures relative to patients with other types of brain tumors is due to the increased tendency for PCNSL to involve the subcortex relative to cortex [11–13]. Though cortical involvement may be less common in PCNSL, it is still common; for instance, a prior study which reviewed the imaging findings of 100 patients with newly diagnosed PCNSL found that 44 patients had at least one cortical lesion [14]. In our cohort we found that 20 out of 36 patients (56%) had a cortical lesion of whom 45% had seizures, compared to 3 (18.8%) of those who did not have a cortical lesion (p = .10; data not shown). It has been previously shown that patients with gliomas that involve the cortex are also at an increased risk for seizures [15].

The pathology available for our cohort does not suggest an effect of BCL-6, Ki-67 or histological subtype on the likelihood of seizures in patients with PCNSL. However, it is conceivable that particular genetic aberrations specific to certain variants of PCNSL may produce an increased likelihood for seizures. For instance, there is some evidence to suggest that IDH mutation status may influence the tendency for diffuse glioma patients to develop seizures by increasing glutamate activity on the NMDA receptor [16]. Additional research on whether a similar phenomenon exists in patients with PCNSL may be the subject of future studies.

Among the patients with seizures, 25% of patients with cortical temporal lesions developed seizures; 40% of patients with cortical frontal lesions developed seizures; and 67% of patients with parietal cortical lesions developed seizures. Previously published data on glioma patients suggests that frontal lobe lesions may be the most likely to produce seizures while the occipital lobe is the least likely [17]. However, given that gliomas and PCNSL are distinct entities that have unique histopathological characteristics it may be that the relationship between cortical location and epileptogenic potential may be distinct. Also, PCNSL is typically a highly infiltrative neoplasm that has been characterized as a "whole brain disease" with extensive CNS involvement that may be significantly underestimated by MRI [18].

The semiology of seizures in patients with PCNSL was found to be most frequently secondary generalized seizures which occurred in 50% of cases with seizure. This was followed by focal with retained awareness in 16.7% and focal with lost awareness in 16.7%. EEG was performed in 9 of the 12 patients with clinical seizures of whom 44.4% had epileptiform discharges. This suggests that EEG is useful for detecting epileptiform discharges in a significant percentage of patients with PCNSL. It should be noted that not all EEGs in this sample were of equal duration.

Weaknesses of this study included the low sample size which resulted in insufficient power to detect statistically significant differences between groups and the retrospective nature of the study. An additional weakness is the variable length of EEG recordings which may make it difficult to draw significant practical conclusions from our results; however we do show that in a substantial number of patients there are abnormal EEG findings in this patient cohort. Also, given that the mean follow-up time was only 1.49 years it is possible that we missed additional patients who may have developed seizures later on in the course of their disease. Our study's strength is that PCNSL is a very rare condition and to the best of our knowledge there are no previous studies which evaluated the prevalence and associated characteristics of seizures in patients with this condition.

5. Conclusions

PCNSL is a rare primary brain malignancy which is associated with seizures in one-third of patients of whom the onset may occur at variable stages in their disease course. Therefore, neuro-oncologists and other providers involved in the care for patients with PCNSL should be mindful that patients who do not present with seizures may develop them later. EEG appeared to be a useful diagnostically in a significant percentage of patients of whom epileptic discharges were found. Future prospective studies involving larger cohorts and with more

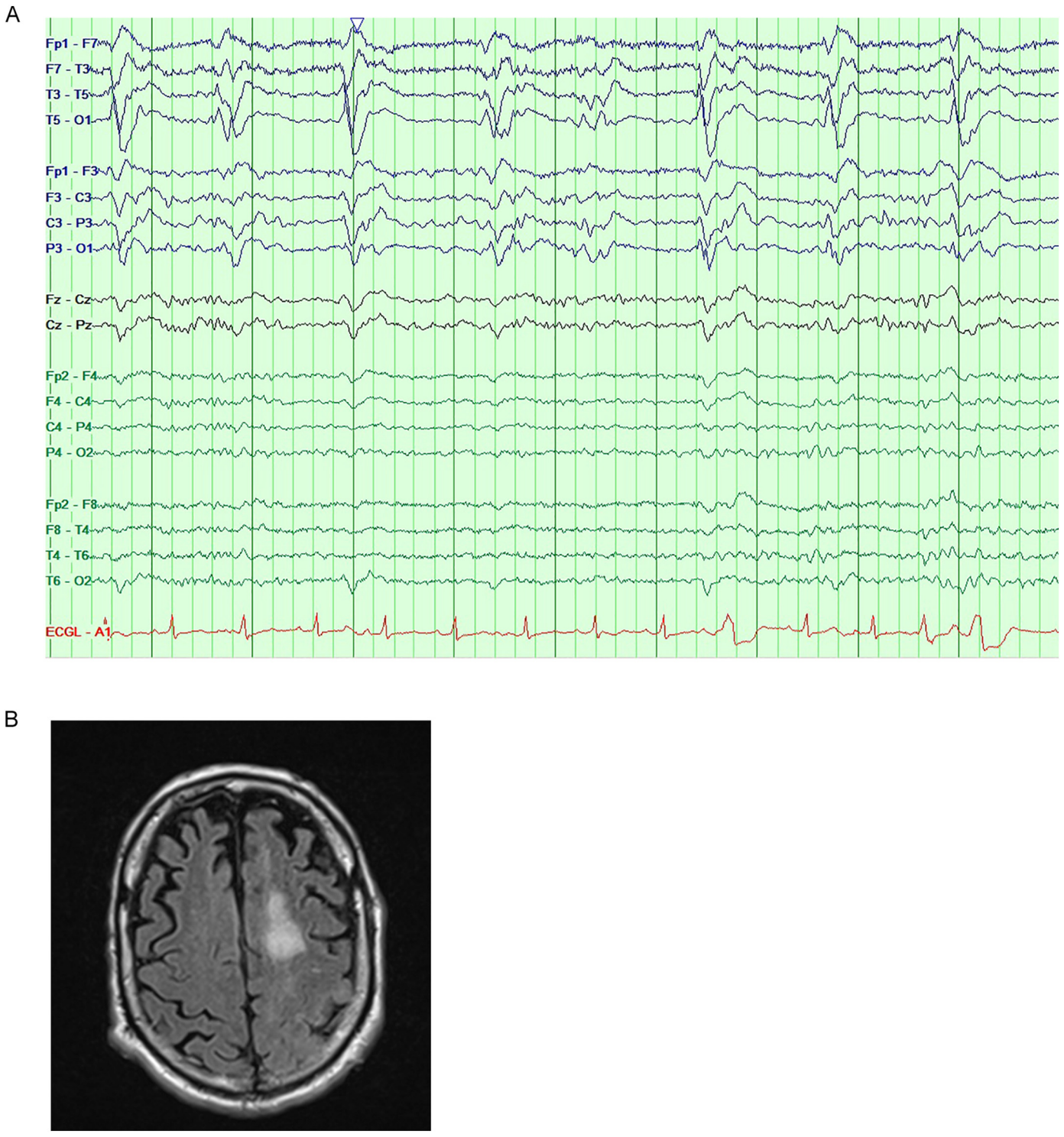

Fig. 1. EEG and MRI findings of a patient with PCNSL who had seizures at presentation and was connected to continuous EEG monitoring approximately 1 month from time of diagnosis due to concern for non-convulsive seizures. MRI showed some progression of disease though he had only recently began to receive high-dose methotrexate-based therapy a few days previously. (a) Interictal EEG (High frequency filter: 70 Hz, low frequency filter: 0.1 Hz, notch filter: on, and montage: longitudinal bipolar) of patient revealed lateralized periodic discharges over the left hemisphere with temporal maximum. (b) MRI T2 signal hyperintensity in the left centrum semiovale.

histopathological data is required to better understand the relationship between these conditions.

Declarations of interest

None.

Acknowledgement

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

Table 5
Location of primary lesion in adult patients with primary central nervous system lymphoma and associated interictals found on electroencephalogram.

Primary lesions location	Interictals
Left frontal lobe	Right hemisphere epileptiform discharges
Left greater than right of the splenium of corpus callosum	Left parasagittal sharp wave complexes
Right Frontal lobe	Right frontotemporal LPDs
Left centrum semiovale	Left LPDs

Abbreviation: LPD – lateralized periodic discharge

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