SHORT REPORT

RUNNING HEAD: EEG in CNS-GvHD

EEG characteristics of central nervous system graft-versus-host disease

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ABSTRACT

In this multicenter retrospective study, we analyzed the EEG characteristics of 17 patients with possible CNS graft-versus-host disease (pCNS-GvHD). All EEGs were abnormal. Most (11/17 patients) showed background activity slowing. Sporadic epileptiform discharges were rare (2 patients) and observed only in chronic pCNS-GvHD. Sporatic non-epileptiform discharges, often generalized, frontally predominant, and triphasic, were common (15/17 patients). Two patients presented generalized rhythmic delta activity, one showed lateralized rhythmic delta activity, and one exhibited lateralized periodic discharges. Background activity slowing was statistically associated with higher one-year overall mortality (P=0.026). These findings suggest that EEG may serve as a prognostic tool in CNS-GvHD.

NEW & NOTEWORTHY

This retrospective study is the first to describe EEG features of central nervous system involvement in graft-versus-host disease (CNS-GvHD). It shows CNS-GvHD consistently associates with EEG abnormalities at peak disease severity. Epileptiform discharges are rare and mostly occur in chronic CNS-GvHD. Finally, it identifies a statistically significant association between background rhythm frequency and one-year survival, suggesting EEG as a potential prognostic tool for CNS-GvHD.

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Keywords: Allogeneic hematopoietic stem cell transplantation - Central nervous system graft-versus-host-disease (CNS-GvHD) - EEG - Encephalitis - Transplantation

INTRODUCTION

Graft-versus-host disease (GvHD) is a severe complication of allogeneic hematopoietic stem cell transplantation (allo-HSCT).[1] Central nervous system (CNS) was initially thought to be exempt of GvHD but, over the past years, there has been a growing evidence of the existence of CNS involvement in both acute and chronic GvHD.[2-4] In a recent retrospective international multicenter study, the authors provided the first comprehensive description of the clinical, biological, radiological and histopathological characteristics as well as the response to treatment and prognosis of a large cohort of 66 patients diagnosed with both acute and chronic possible CNS-GvHD (pCNS-GvHD), based on predetermined criteria (Table 1).[5] However, EEG characteristics of CNS-GvHD remain unstudied.

MATERIAL AND METHODS

We reviewed the patients included in our initial study and identified those who had at least one EEG recording during the disease. For each patient identified, the local investigator was asked to retrieve the EEG tracing and complete a questionnaire to characterize the patient's status at the time of recording. If the patient had multiple recordings, the EEG with the fewest factors likely to interfere with the EEG, performed without sedation and as close as possible to the peak clinical severity of the disease, was requested. Each EEG was then independently analyzed by two neurologists, and data were compiled in a file according to the American Clinical Neurophysiology Society's Standardized Critical Care EEG Terminology (2021 Version),[6] with adaptations to describe sporadic non-epileptiform discharges, and the 2017 multinational revised glossary of terms most commonly used by clinical electroencephalographers.[7] Extracted data were then compared, and discrepancies were resolved by consensus.

The primary objective of the study was to describe the EEG characteristics of pCNS-GvHD. Secondary objectives included the comparison of EEG characteristics between acute and chronic pCNS-GvHD and the identification of EEG features associated with one-year survival following pCNS-GvHD onset.

Categorical variables were reported as counts and percentages, while continuous variables were presented as medians with interquartile ranges. Subgroup comparisons were performed using Fisher’s exact test when both variables were binary, and the Cochran-Armitage test for trend when one variable was binary and the other was ordered categorical. Kaplan–Meier curves were used to describe survival. Analyses were conducted using the maximum available data, and no imputation of missing data was performed. All tests were two-sided and considered significant at an α threshold of 0.05. Statistical analyses were performed using Prism 10 (https://www.graphpad.com).

The study was approved by the University Hospital of Liège Ethics Committee (reference: 2024/33).

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RESULTS

Patients' characteristics

Among the 66 patients included in the initial study, 39 patients (59%) underwent at least one EEG recording. A recording was retrieved and analyzed for 17 of these 39 patients (44%); these patients were included in this study (Figure 1).

The characteristics of the 17 included patients and the conditions under which the EEG recordings were obtained are presented in Table 2. Most patients (13/17, 76%) were male, and the median age at the time of pCNS-GvHD onset was 64 years (58–67.5). pCNS-GvHD occured before day 100 following allo-HSCT or donor lymphocyte infusion (acute pCNS-GvHD) in six patients (35%) and after day 100 (chronic pCNS-GvHD) in 11 patients (65%). Neurological presentation consisted of extralimbic encephalitis in 11 patients (65%), encephalomyelitis in three (18%), rhombencephalitis in two (12%), and demyelinating disease with focal neurological deficits in one patient (6%). Four patients (35%) experienced at least one seizure during the course of the disease, including two patients within 24 hours prior to the EEG recording. Three patients (18%) were on antiseizure medication at the time of the EEG. Median time between the onset of CNS-GvHD and the EEG was 35 days (10.5-61), and six patients (35%) had intercurrent factors at the time of the recording. Most EEG (13/17, 76%) were recorded at the peak of clinical disease severity, while the remaining were captured during disease progression. At the time of EEG recording, four patients were in the intensive care unit, including two who were intubated; however, none of the patients were receiving sedation. One-year survival from the onset of the neurological condition was 53% for the patients included in this analysis.

EEG characteristics

EEG characteristics of the 17 included patients are summarized in Table 3. Most recordings (10/17, 59%) revealed slowing of the background activity in theta frequencies, usually between 6 and 8 Hz. Six patients (36%) had a background rhythm in alpha frequencies, while one had a background rhythm in the delta band. All tracings showed a continuous, symmetrical background activity of normal voltage, but the physiological posterior dominance was observed in only three patients (18%). Sporadic epileptiform discharges were identified in two patients: one displaying left frontocentral lateralized sharp waves, and the other exhibiting both generalized sharp waves and right frontotemporal lateralized spikes. Neither patient had a documented history of CNS pathology prior to allo-HSCT; however, the second patient had experienced a seizure within the 24 hours preceding the EEG recording. Fifteen patients (88%) exhibited non-epileptiform discharges, most often generalized (14/17 patients, 82%), frontally predominant, and frequently triphasic in morphology (11 patients, 65%). Finally, rhythmic or periodic patterns (RPPs) were observed in four patients. Two patients presented with brief, blunt, generalized (frontally predominant) rhythmic delta activity (GRDA). One patient had very brief sharply contoured right frontal lateralized rhythmic delta activity (LRDA), and another exhibited long right temporal lateralized periodic discharges (LPDs) with blunt morphology. None of the RPPs exhibited an epileptiform morphology. No seizures or status epilepticus were recorded. Of note, none of the EEG recordings was normal.

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Factors associated with one-year survival following pCNS-GvHD onset

Background activity slowing was statistically associated with an increased risk of one-year mortality in a linear manner (100% survival if >= 9 Hz, 50% if 5 < 9 Hz, 0% if <= 5 Hz, *P*=0.026). In contrast, the presence of neither sporadic epileptiform discharges, RPPs, nor lateralized discharges were statistically associated with one-year mortality (*P*=0.47, 0.29, >0.99, respectively).

Comparison between acute and chronic pCNS-GvHD

None of the evaluated features (background activity slowing, presence of epileptiform discharges, RPPs, or lateralized discharges) were significantly more frequent in acute or chronic pCNS-GvHD (*P*=0.2, 0.51, 0.58, 0.3, respectively). However, sporadic epileptiform discharges were observed only in chronic pCNS-GvHD.

DISCUSSION

This study provides the first description of EEG characteristics in CNS-GvHD. Epileptiform discharges were rarely observed despite severe neurological impairment. In our initial cohort of 66 patients, only ten (15%) had seizures, and none experienced refractory status epilepticus.[5] Hence, CNS-GvHD does not appear to be highly associated with seizure occurrence, indicating that prophylactic antiepileptic treatment may not be indicated, contrary to recommendations for other neurological complications in patients with hematologic malignancies, such as Immune Effector Cell-Associated Neurotoxicity Syndrome.[8]

Despite the rare occurrence of epileptiform discharges, all EEGs were abnormal, indicating cerebral dysfunction. However, EEGs were performed near the peak severity of the disease, and data from earlier recordings are lacking. Furthermore, no patients with isolated myelopathy were included. While not an initial study objective, no unique patterns specific to CNS-GvHD emerged from the analysis. Further studies are needed to assess the sensitivity of EEG in the early stages of the disease and its specificity in distinguishing CNS-GvHD from other neurological complications occurring in transplanted patients, such as opportunistic infections or drug toxicity.[9,10]

No EEG characteristics significantly differentiated acute from chronic CNS-GvHD despite prior data indicating that these are distinct entities, exhibiting different clinico-radiological presentations and prognoses.[5] Although not reaching statistical significance, epileptiform discharges occurred exclusively in chronic pCNS-GvHD. This observation should be further investigated in larger, prospective studies.

In this analysis, background activity slowing was significantly associated with increased one-year overall mortality following the diagnosis of pCNS-GvHD in a linear manner, potentially providing an objective biomarker for prognosis. Given the exploratory nature of the study and the small number of patients included, further studies are needed to confirm the role of EEG as prognostic assessment tool for patients with CNS-GvHD.

We must acknowledge that the patients included in this study had substantial pre-existing medical histories, having, by definition, undergone intensive therapeutic interventions and commonly presenting with multiple comorbidities. Although stringent selection criteria were applied and patient records meticulously reviewed to ensure that pCNS-GvHD was the most plausible etiology of the clinical

manifestations observed, the contribution of intercurrent factors to the EEG abnormalities cannot be definitively excluded and remains a potential confounding element.

In conclusion, CNS-GvHD appears to be systematically associated with abnormal EEG findings at the peak severity of the disease. The occurrence of epileptiform discharges in this context is rare, and some preliminary data from this work suggest that they may be more likely to occur in chronic forms of the disease. Finally, EEG could prove to be a valuable tool for determining the prognosis of patients with this complication.

SUPPLEMENTARY MATERIAL

No additional supplementary material is available for this article.

DATA AVAILABILITY

Data requests should be sent to Nicolas Lambert. Data access must be approved by the Belgian data protection authority. For more information, see https://www.dataprotectionauthority.be/citizen

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DISCLOSURES

NL has received speaker honoraria from Novartis. SGP has received speaker honoraria from Sanofi, Roche, Merck, and Biogen and has participated on Merck and Bristol Myers Squibb advisory boards. JDS has received consulting fees from Cycle Pharmaceuticals, UCB, and TG Therapeutics. None of these are related to or have any impact on the data presented in this manuscript. The remaining authors declare no competing interests. This research received no targeted funding.

AUTHOR CONTRIBUTIONS

NL and OB conceived and designed research, NL and OB analyzed data, all authors interpreted results of experiments, NL drafted manuscript, all authors edited, revised, and approved final version of manuscript.

REFERENCES

1 Zeiser R, Blazar BR. Acute Graft-versus-Host Disease - Biologic Process, Prevention, and Therapy. *N Engl J Med*. 2017;377(22):2167-2179. doi:10.1056/NEJMra1609337

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2 Grauer O, Wolff D, Bertz H, et al. Neurological manifestations of chronic graft-versus-host disease after allogeneic haematopoietic stem cell transplantation: report from the Consensus Conference on Clinical Practice in chronic graft-versus-host disease. *Brain*. 2010;133(10):2852-2865. doi:10.1093/brain/awq245

3 Cuvelier GDE, Schoettler M, Buxbaum NP, et al. Toward a Better Understanding of the Atypical Features of Chronic Graft-Versus-Host Disease: A Report from the 2020 National Institutes of Health Consensus Project Task Force. *Transplant Cell Ther*. 2022;28(8):426-445. doi:10.1016/j.jtct.2022.05.038

4 Mathew NR, Vinnakota JM, Apostolova P, et al. Graft-versus-host disease of the CNS is mediated by TNF upregulation in microglia. *J Clin Invest*. 2020;130(3):1315-1329. doi:10.1172/JCI130272

5 Lambert N, Forte F, El Moussaoui M, et al. Central nervous system manifestations in acute and chronic graft-versus-host disease. *Brain*. Published online October 23, 2024. doi:10.1093/brain/awae340

6 Hirsch LJ, Fong MWK, Leitinger M, et al. American Clinical Neurophysiology Society's Standardized Critical Care EEG Terminology: 2021 Version. *J Clin Neurophysiol*. 2021;38(1):1-29. doi:10.1097/WNP.0000000000000806

7 Kane N, Acharya J, Benickzy S, et al. A revised glossary of terms most commonly used by clinical electroencephalographers and updated proposal for the report format of the EEG findings. Revision 2017 [published correction appears in Clin Neurophysiol Pract. 2019 Jun 15;4:133. doi: 10.1016/j.cnp.2019.06.001]. *Clin Neurophysiol Pract*. 2017;2:170-185. Published 2017 Aug 4. doi:10.1016/j.cnp.2017.07.002

8 Rees JH. Management of Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS). In: Kröger N, Gribben J, Chabannon C, Yakoub-Agha I, Einsele H, eds. *The EBMT/EHA CAR-T Cell Handbook*. Cham (CH): Springer; February 7, 2022.141-145.

9 Colombo AA, Marchioni E, Diamanti L, et al. Neurological Complications Involving the Central Nervous System After Allogeneic Hematopoietic Stem Cell Transplantation During a Period of Evolution in Transplant Modalities: A Cohort Analysis. *Transplantation*. 2017;101(3):616-623. doi:10.1097/TP.0000000000001257

10 Balaguer-Rosello A, Bataller L, Piñana JL, et al. Noninfectious Neurologic Complications after Allogeneic Hematopoietic Stem Cell Transplantation. *Biol Blood Marrow Transplant*. 2019;25(9):1818-1824. doi:10.1016/j.bbmt.2019.05.024

FIGURE LEGENDS

Figure 1. Flowchart describing patients' inclusion.

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Table 1. Inclusion criteria for the initial study aimed at describing the clinical, biological, and radiological characteristics of pCNS-GvHD. To be included, patients had to be at least 18 years old, have undergone an allogeneic hematopoietic stem cell transplant prior to the onset of neurological symptoms, have at least two supportive criteria, and no exclusion criteria.

Supportive criteria (at least two are needed for inclusion)	Exclusion criteria
Brain or spinal cord lesions visible on MRI at a neuroanatomical site compatible with the symptomatology	Differential diagnosis deemed more probable to explain the clinical observations, including: ○ CNS infections ○ CNS infiltration by neoplastic lesions ○ Toxic, endocrine, metabolic, or deficiency-associated CNS disorders ○ Stroke or intracranial hemorrhage without radiological or histopathological evidence of vasculitis ○ Peripheral nervous system disorder responsible for the whole clinical picture ○ Neurological disease already present before allo-HSCT and potentially responsible for the whole symptomatology
CSF WBC count > 5 cells/mm^3 or protein level > 0.45 g/L	
Concomitant (within 30 days before or after) acute or chronic extra-neurological GvHD flare	
Clinical response to immunosuppressive therapy	
Parenchymal, perivascular, or vascular mural lymphocyte infiltrates on histopathology	

Adapted from Lambert et al., *Brain*, 2024[5]

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Table 2. Patients' characteristics and conditions under which EEG recordings were collected.

Characteristics	
Male sex at birth, No. (%)	13 (76%)
History of chemotherapy or radiation therapy prior to allo-HSCT procedure, No. (%)	12 (71%)
Intravenous chemotherapy	12 (71%)
Intrathecal chemotherapy	3 (18%)
Radiation therapy	2 (12%)
Conditioning regimen for allo-HSCT	
Myeloablative, No. (%)	3 (18%)
TBI-based, No. (%)	4 (24%)
Age at pCNS-GvHD onset (years), median ($IQ_{25–75}$)	64 (58–67.5)
Neurologic syndrome[a], No. (%)	
Extra-limbic encephalitis	11 (65%)
Encephalomyelitis	3 (18%)
Brainstem encephalitis	2 (12%)
Multifocal demyelinating disease with neurologic deficits	1 (6%)
Delay between allo-HSCT or DLI and pCNS-GvHD onset (days), median ($IQ_{25–75}$)	188 (90-571)
≤ 100 days (acute pCNS-GvHD), No. (%)	6 (35%)
> 100 days (chronic pCNS-GvHD), No. (%)	11 (65%)
One-year overall survival from pCNS-GvHD onset, No. (%)	9 (53%)
Seizure during the course of the disease, No. (%)	4 (24%)
Seizure within 24 hours preceding EEG recording, No. (%)	2 (12%)
Delay (days) between pCNS-GvHD onset and EEG recording, median ($IQ_{25–75}$)	35 (10.5-61)
Patient's status at EEG recording, No (%)	
Hospitalized	16 (94%)
Intensive care unit	4 (24%)
Endotracheal intubation	2 (12%)
Ongoing immunosuppression for pCNS-GvHD treatment	4 (24%)
Ongoing antiseizure medication at EEG recording, No. (%)	3 (18%)
Levetiracetam, No. (%)	1 (6%)
Sodium valproate, No. (%)	2 (12%)
Intercurrent factor at EEG recording, No. (%)	6 (35%)
Acute kidney injury, No. (%)	1 (6%)
Ongoing infection, No. (%)	2 (12%)
Severe anemia, No. (%)	2 (12%)
Hepatic disease, No. (%)	2 (12%)
Ongoing treatment with opioids, No. (%)	1 (6%)
Ongoing treatment with benzodiazepins, No. (%)	1 (6%)

As patients may have multiple characteristics, numbers may not sum to group totals, or percentages add to 100%.

[a]The neurological presentations were categorized into the following syndromes: meningitis, limbic encephalitis, extra-limbic encephalitis, brainstem encephalitis, myelitis, encephalomyelitis, multifocal demyelinating disease with neurologic deficits, and CNS angiitis.

Allo-HSCT stands for allogeneic hematopoietic stem cell transplantation and DLI for donor lymphocyte infusion.

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Table 3. EEG characteristics.

Background	
Predominant background frequency when most awake, No. (%)	
Alpha >= 9 Hz	3 (18%)
Alpha 8 =< 9 Hz	3 (18%)
Theta 6 =< 8 Hz	8 (47%)
Theta 5 =< 6 Hz	1 (6%)
Theta 4 =< 5 Hz	1 (6%)
Delta 3 =< 4 Hz	1 (6%)
Delta < 3 Hz	0 (0%)
Symmetry, No. (%)	17 (100%)
Continuity, No. (%)	17 (100%)
Posterior Dominant Rhythm, No. (%)	3 (18%)
Reactivity to eye opening/closure, No. (%)[a]	3 (27%)
Sporadic epileptiform discharges	
Presence of sporadic epileptiform discharges, No (%)	2 (12%)
Spikes	1 (6%)
Polyspikes	0 (0%)
Sharp waves	2 (12%)
Localization, No (%)	
Generalized	1 (9%)
Lateralized	2 (12%)
Sporadic non-epileptiform discharges	
Presence of sporadic non-epileptiform discharges, No (%)	15 (88%)
Sharply contoured	7 (41%)
Bold	9 (53%)
Localization, No (%)	
Generalized	14 (82%)
Lateralized	4 (24%)
Number of phases, No (%)	
1	5 (29%)
2	1 (6%)
3	11 (65%)
Rhythmic and periodic patterns (RPPs)	
Presence of RPPs, No (%)	4 (24%)
Generalized rhythmic delta activity (GRDA)	2 (12%)
Lateralized rhythmic delta activity (LRDA)	1 (6%)
Lateralized periodic discharges (LPDs)	1 (6%)

As patients may have multiple characteristics, numbers may not sum to group totals, or percentages add to 100%.

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66 patients included in the initial retrospective cohort of pCNS-GvHD

27 patients did not have any EEG recorded during the course of the disease

39 patients with pCNS-GvHD who had at least one EEG recording

22 patients for whom no EEG could be retrieved:

- 14 patients for whom the local investigator or the associated neurophysiology department did not follow up on our request
- 6 patients for whom the EEG recording had not been preserved
- 2 patients for whom the EEG was outsourced

17 patients included in this analysis

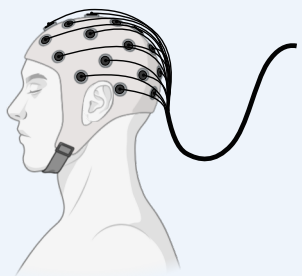
EEG characteristics of central nervous system graft-versus-host disease

Methods

Multicenter retrospective study

Population: 17 patients with probable central nervous system graft-versus-host disease

One EEG retrieved for each patient and analysed by two neurologits



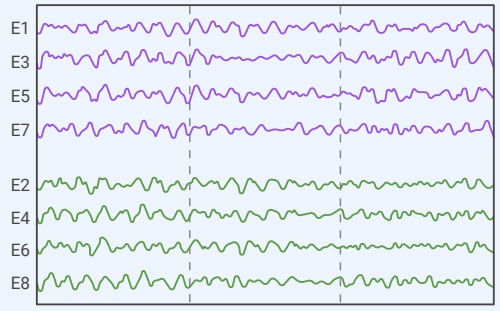
EEG characteristics

All EEGs were abnormal

59% showed background activity slowing

88% showed sporadic non-epileptiform discharges

12% showed sporadic epileptiform discharges



Prognosis

One year survival statistically associated with background activity frequency

No association between epileptiform discharges or lateralized discharges and mortality