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Epilepsy after acute central nervous system complications of pediatric hematopoietic cell transplantation: A retrospective, multicenter study

Luca Bergonzini [a,b,1], Davide Leardini [c,1], Roberta Rao [b], Thomas Foiadelli [d], Maura Faraci [e], Maria Margherita Mancardi [f], Giulia Nobile [f], Alessandro Orsini [g], Salvatore Savasta [d,h], Francesca Gottardi [b,c], Anna Fetta [a,b], Tommaso Mina [i], Gabriella Casazza [j], Maria Cristina Menconi [j], Dario Pruna [k], Rosa Maria Mura [l], Antonio Piroddi [m], Paola Rucci [n], Riccardo Masetti [b,c], Duccio Maria Cordelli [a,b,*]

[a] IRCCS Istituto delle Scienze Neurologiche di Bologna, U.O.C. Neuropsichiatria dell'età pediatrica, Member of the ERN EpiCare, Bologna, , Italy
[b] Department of Medical and Surgical Sciences (DIMEC), Alma Mater Studiorum - University of Bologna, Bologna, Italy
[c] Pediatric Hematology and Oncology, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy
[d] Clinica Pediatrica, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy
[e] HSCT Unit, Department of Pediatric Hematology-Oncology, IRCCS Istituto G. Gaslini, Genova, Italy
[f] Unit of Child Neuropsychiatry, member of the ERN EpiCare, IRCCS Gaslini, Genova, Italy
[g] Pediatric Neurology, Pediatric Department, AOUP Santa Chiara Hospital, Pisa, Italy
[h] Dipartimento di Scienze Mediche e Salute Pubblica, Università di Cagliari, Italy
[i] Pediatric Hematology and Oncology, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy
[j] Pediatric Hematology and Oncology, Azienda Ospedaliero Universitaria Pisana, Pisa, Italy
[k] Pediatric Neurology and Epileptology Unit, Pediatric Department, ARNAS G. Brotzu/ASL, Cagliari, Italy
[l] Paediatric Hematology and Oncology Unit, Pediatric Hospital "Microcitemico A. Cao", Cagliari, Italy
[m] Bone Marrow Transplant Center, Pediatric Hospital "Microcitemico A. Cao", Cagliari, Italy
[n] Department of Biomedical and Neuromotor Sciences (DIBINEM), Alma Mater Studiorum - University of Bologna, Bologna, Italy

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ABSTRACT

Background: Acute central nervous system (CNS) complications are common and well described among pediatric patients undergoing haematopoietic cell transplantation (HCT). However, their long-term outcomes are not known. The aim of this study is to describe the incidence, characteristics, and risk factors of long-term epilepsy in pediatric patients with acute CNS complications of HCT.

Methods: This retrospective study included pediatric patients who developed acute CNS complications from autologous or allogeneic HCT between 2000 and 2022. Clinical, therapeutic and prognostic data including long-term outcomes were analyzed. A diagnosis of epilepsy was provided if unprovoked seizures occurred during follow-up.

Results: Ninety-four patients (63 males, 31 females, median age 10 years, range 1–21 years) were included. The most common acute CNS complications were posterior reversible encephalopathy syndrome ($n = 43$, 46 %) and infections ($n = 15$, 16 %). Sixty-five patients (69 %) had acute symptomatic seizures, with 14 (16 %) having one or more episodes of status epilepticus (SE). Nine patients (9.6 %) were diagnosed with long-term focal epilepsy during the follow-up (5-year cumulative incidence from the acute complication, 13.3 %). Acute symptomatic SE during neurological complications of HCT was associated with an increased risk of long-term epilepsy (OR=14, 95 % CI 2.87–68.97).

Conclusions: A higher occurrence of epilepsy has been observed in our cohort compared to the general population. Acute symptomatic SE during HCT was associated with a higher risk of long-term epilepsy. Pediatric patients with CNS complications during HCT could benefit from specific neurological follow-up. Further studies are needed to characterize mechanisms of epileptogenesis in pediatric patients undergoing HCT.

* Corresponding author at: Department of Medical and Surgical Sciences (DIMEC), IRCCS Istituto delle Scienze Neurologiche di Bologna, U.O.C. Neuropsichiatria dell'età pediatrica, Via Massarenti 9, 40138, Bologna, Italy.
E-mail address: ducciomaria.cordelli@unibo.it (D.M. Cordelli).
[1] These authors contributed equally to this work.

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1. Introduction

Hematopoietic cell transplantation (HCT) is a potentially curative strategy for many oncological, hematological, metabolic, and immunological diseases in children [1,2]. HCT is a multi-stage procedure that consists in (1) a conditioning regimen based upon chemotherapy or radiotherapy; (2) the infusion of hematopoietic stem cells collected from the patients or from a third-party donor; (3) the subsequent regeneration of a new hematopoietic and immune system [1]. HCT is associated with a large spectrum of possible neurologic complications that significantly contribute to its morbidity and mortality rates [3–8]. Literature data describe acute symptomatic seizures in up to 73 % of patients who develop acute neurological complications from HCT [5,6]. Seizures are often repeated or long lasting, presenting as acute status epilepticus in up to 50 % of patients, and mostly are the first manifestation of underlying neurological complications, such as central nervous system (CNS) infections, cerebrovascular or metabolic events, and neurotoxicity of immunosuppressive agents manifesting as posterior reversible encephalopathy syndrome (PRES) [6,9]. Little is known about the long-term sequelae of neurological complications in pediatric patients undergoing HCT, probably due to the lack of long-term neurological follow-up. Specifically, comprehensive epidemiological data about the occurrence of epilepsy in these patients is lacking. The primary aim of this study is to describe the occurrence of epilepsy following neurologic complications in pediatric patients undergoing HCT and to identify possible factors predisposing to epilepsy in these patients.

2. Methods

2.1. Study design and participants

This multicenter observational retrospective study involved five Italian university centers for pediatric oncology, hematology, and neurology (Supplementary Figure 1). Patients who underwent HCT for any indication from January 1st, 2000 to December 31st 2022, who experienced neurological complications within 100 days from transplantation and with available long-term follow-up data were enrolled in the study. Inclusion criteria were 1) the occurrence of at least one known neurological complication from HCT within 100 days of transplantation; 2) age between 1 month-21 years at the time of HCT. Exclusion criteria were 1) a history of epilepsy before HCT; 2) neurological involvement of the underlying condition prior to HCT; 3) death before the resolution of the acute neurological complication; 4) lack of follow-up for more than three months after HCT. Informed consent by legal guardians, patients' assent or substitutes were gathered. The institutions involved in the study received approval for data collection by local ethic committees.

2.2. Assessment methods

Clinical data were extracted from medical reports. Demographic data and medical history were analyzed, specifically with regards to any underlying hematologic, oncologic, or neurologic conditions before HCT. Several transplant features were considered, such as source of stem cells, donors, conditioning regimen, and GvHD prophylaxis. Clinical outcomes of HCT included incidence of GvHD, viral reactivation and bloodstream bacterial infections. GvHD diagnosis and grading was based the Glucksberg criteria [10]. Neurological complications were defined as the development of neurological signs or symptoms consistent with known neurological complications from HCT and requiring the evaluation of consultant child neurologists or other diagnostic and therapeutic procedures. Neurological complications were categorized as PRES, drug related neurotoxicity, CNS infections, cerebrovascular events, metabolic events, encephalopathy of unknown etiology. Patients with paroxysmal events of non-epileptic origin were excluded. The definition and classification of seizures and SE was performed in accordance with the latest International League Against Epilepsy (ILAE) classification position paper and guidelines [11,12]. Data concerning video-EEG recordings and neuroimaging were collected by accessing local electronic EEG and imaging software. Medical reports of both brain computerized tomography (CT) scans and magnetic resonance imaging (MRI) techniques were considered. Patients with a diagnosis of epilepsy during follow-up were identified by consulting clinical practice software and related medical records. Epilepsy was defined as the enduring predisposition to generate epileptic seizures, with related neurobiological, cognitive, psychological, and social consequences, according to an ILAE Task Force [13]. Drug resistant epilepsy was defined as failure of adequate trials of two tolerated, appropriately chosen and used anti-seizure medications (whether as monotherapies or in combination) to achieve sustained seizure freedom [14].

2.3. Statistical analysis

Descriptive statistics were provided for the study population. Patients were classified into those who developed epilepsy (group 1) and those who did not (group 2). Shapiro–Wilk's and Levene's tests were used to assess the normality of data distribution and homogeneity of variance. Comparisons between group 1 and 2 were investigated with *t*-test for continuous variables (or Mann–Whitney when appropriate) and chi-square tests for nominal variables. Logistic regression models were used to identify possible risk factors for epilepsy. The significance level was set to 0.05, and all tests were two-tailed. Statistical analyses were conducted with JASP (version 0.17.1.0) and SPSS (version 26.0) for Mac and Windows.

3. Results

3.1. Demographic and clinical features

Overall, 94 patients (63 males, 31 females; median age: 10 years, interquartile range: 6.5 years, range: 1–21 years) who underwent HCT were analyzed in the study. Fig. 1 shows the eligibility assessment process.

The main demographic and clinical features of the two groups are listed in Tables 1 and 2. Leukemia and non-oncological conditions (i.e.: thalassemia, sickle cell disease, Fanconi anemia, primary immune deficiency) were the most frequent indications to HCT (48 % and 45 %, respectively). Half of the patients received HCT from a matched unrelated donor (MUD) (51 %) and myeloablative conditioning regimen (MAC) was the most frequently performed (n = 80, 88 %). Total body irradiation (TBI) conditioning was performed in 20 % of subjects (n = 19). Bone marrow was the main source of stem cells (n = 57, 62 %). Prophylaxis with anti-seizure medications (ASMs) was administered to

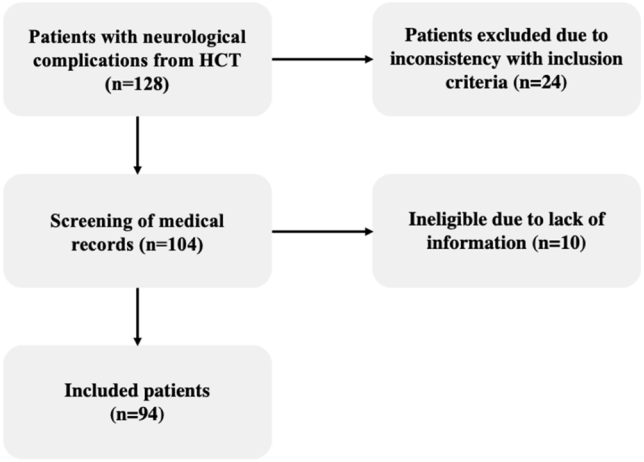

Fig. 1. Eligibility assessment process. HCT: hematopoietic cell transplantation.

Table 1
Demographic, clinical and HCT features.

Characteristics	Total ($n = 94$)
Age at HCT – yrs. (IQR)	10.0 ± 6.5
Male – n. (%)	63 (67)
Underlying condition - n. (%)	
Leukaemia	45 (48)
Lymphoma	4 (4)
Solid tumour	3 (3)
Non-oncological conditions	42 (45)
Donors – n. (%)	
Autologous	5 (5.3)
Identical sibling	21 (22.4)
MUD	48 (51)
Haploidentical	20 (21.3)
Source of stem cells – n. (%)	
Bone Marrow	57 (62)
Peripheral blood	29 (31.5)
Umbilical cordon	9 (10)
Conditioning regimen – n. (%)	
MAC	80 (88)
RIC	11 (12)
NA	3
Acute toxicity	
CMV reactivation	46 (49)
EBV	16 (17)
aGVHD	60 (64)
Follow-up (y.)	
Median	15.8
Interquartile range (IQR)	17.2

HCT: hematopoietic cell transplantation; MUD: matched unrelated donor; MAC: myeloablative conditioning regimen; RIC: reduced intensity conditioning regimen; NA: not available; CMV: cytomegalovirus; EBV: Epstein-Barr virus; aGVHD: acute graft-versus-host disease.

Table 2
Neurological complications and outcomes.

Characteristics	Total ($n = 94$)
CNS complications – n. (%)	
PRES	43 (46)
Infections	15 (16)
Drug-related toxicity	8 (10)
Cerebrovascular	6 (6)
Metabolic	3 (3)
Other	19 (20)
Acute symptomatic seizures - n. (%)	65 (69)
Focal onset seizures	37 (57)
Unknown onset seizures	28 (43)
Acute symptomatic Status Epilepticus – n. (%)	14 (15)
With prominent motor symptoms	10 (71)
Without prominent motor symptoms (NCSE)	4 (29)
Acute neuroimaging – n. (%)	79 (84)
Normal - n. (%)	15 (19)
Alteration – n. (%)	64 (81)
Follow-up neuroimaging – n. (%)	29 (31)
Resolution – n. (%)	14 (48)
Persistent alteration – n. (%)	15 (51)
Interictal EEG after the acute complication – n. (%)	44 (47)
Focal slowing	13 (30)
Diffuse slowing	10 (23)
Focal epileptiform discharges	15 (34)
ICU – n. (%)	24 (26)
ASMs after complication – n. (%)	28 (30)
Evolution to epilepsy - n. (%)	9 (9.6)
Death - n. (%)	35 (37)

CNS: central nervous system; PRES: posterior reversible encephalopathy syndrome; NCSE: not-convulsive status epilepticus, EEG: electroencephalogram; ICU: intensive care unit, ASM: anti-seizure medication.

22 % of patients ($n = 21$). Acute neurological complications occurred within 100 days from transplantation and were PRES ($n = 43$, 46 %), infections ($n = 15$, 16 %), drug related neurotoxicity ($n = 9$, 10 %), cerebrovascular events ($n = 6$, 6 %), metabolic events ($n = 3$, 3 %), or other events, ranging from headache to undefined encephalopathies ($n = 19$, 20 %). Seizures occurred in 69 % ($n = 65$) of patients, with either focal ($n = 37$, 57 %) or unknown ($n = 28$, 43 %) onset. Status epilepticus (SE) was observed in 15 % of cases ($n = 14$), Supplementary Table S1 describes its occurrence among acute neurological complications. Acute seizures and SE were treated with benzodiazepines, ASMs or anesthetics as per usual clinical practice, according to international guidelines for acute seizures and SE. Overall, 26 % of patients ($n = 24$) required intensive treatment in the pediatric intensive care unit; 30 % of patients ($n = 28$) were prescribed ASMs considering the acute and post-acute neurological clinical picture. After the acute complication, an abnormal interictal EEG was observed in 40 % of cases ($n = 36$). Eventually, 9.6 % of patients ($n = 9$) were diagnosed with focal-onset epilepsy during the follow-up.

An underlying causal lesion (e.g. mesial temporal sclerosis) was ascertained in 44 % of subjects ($n = 4/9$). Thirty percent of cases ($n = 3/9$) were drug-resistant, all of them had structural focal epilepsy. The median post-transplant follow-up was 15 years (range: 6 months −18 years). The onset of epilepsy ranged from 83 days to 4 years after the acute neurological complication (median: 342 days), and the five-year cumulative incidence of epilepsy from the acute event was 13.3 % (95 % CI: 7.2 % to 24.6 %) (Fig. 2). Five-year overall survival for the whole cohort was 62.7 % (95 % CI: 52.9 % to 72.5 %). Five-year overall survival did not differ between patients developing and not developing epilepsy (77.8 %, 95 % CI: 50.6 %−100.0 % vs 61.2 %, 95 % CI: 50.8 % −71.5 %; $p = 0.367$).

3.2. Association with epilepsy

We compared the characteristics of patients developing and not developing epilepsy during the follow-up (Table 3 and Supplementary Table S2). The two groups did not show significant differences in terms of demographic features (e.g. age and sex), underlying conditions, and transplant-related variables (Supplementary Table S2). No difference in terms of epilepsy onset was observed based on the conditioning regimen, the type of HCT, the use of ASMs (either prophylactic or as a treatment for seizures). Notably, the occurrence of seizures in the acute phase of neurological complications was not significantly higher among those who were diagnosed with epilepsy during the follow-up (89% vs 67 %, $p = 0.178$). Acute symptomatic SE was observed more frequently in patients who would later be diagnosed with epilepsy (56% vs 11 %, $p < 0.001$), regardless of SE semiology or the underlying neurological complication. Indeed, PRES, infections, pharmacological neurotoxicity, cerebrovascular events, metabolic disorders, or other complications

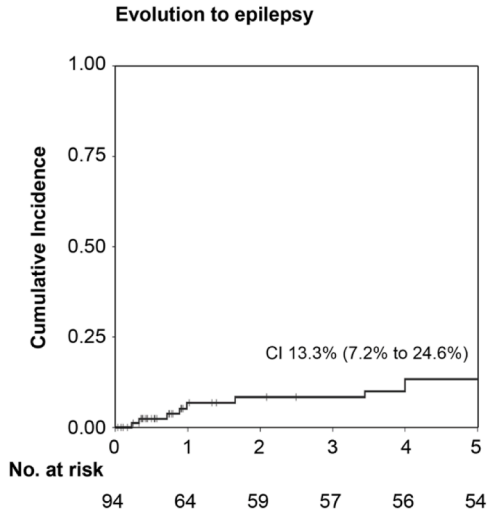

Fig. 2. Five-year cumulative incidence of epilepsy.

Table 3
Comparison of neurological variables between patients with and without epilepsy.

Characteristics	Epilepsy (*N* = 9)	No epilepsy (*N* = 85)	*p -value*
CNS complications – n. (%)			
PRES	5 (55)	38 (45)	0.534
Infection	1 (11)	14 (16)	0.676
Drug-related toxicity	2 (22)	7 (8)	0.175
Cerebrovascular	0	6 (7)	0.410
Metabolic	0	3 (4)	0.567
CNS involvement of the underlying pathology	0	2 (2)	0.642
Other	1 (11)	15 (18)	0.676
Acute symptomatic seizures - n. (%)	8 (89)	57 (67)	0.178
Focal onset seizures	4 (50)	33 (58)	0.673
Unknown onset seizures	4 (50)	24 (42)	
Acute symptomatic Status Epilepticus – n. (%)	5 (56)	9 (11)	**<0.001**
With prominent motor symptoms	4 (80)	6 (67)	0.597
Without prominent motory symptoms (NCSE)	1 (20)	3 (33)	
Interictal EEG after the acute complication – n. (%)	6 (67)	38 (45)	
Focal slowing	1 (17)	12 (32)	0.457
Diffuse slowing	1 (17)	9 (24)	0.703
Focal epileptiform discharges	3 (50)	12 (32)	0.376
Acute neuroimaging – n. (%)	8 (89)	71 (84)	
Normal - n. (%)	2 (25)	13 (18)	0.647
Abnormal – n. (%)	6 (75)	58 (82)	
Control neuroimaging – n. (%)	6 (67)	26 (31)	0.034
Resolution – n. (%)	2 (33)	13 (57)	0.311
Persistent alteration – n. (%)	4 (67)	10 (43)	
Missing	3		
ICU – n. (%)	4 (44)	10 (24)	0.119
ASMs after complication – n. (%)	5 (56)	23 (29)	0.107
Death	2 (22)	33 (38)	0.327

CNS: central nervous system; PRES: posterior reversible encephalopathy syndrome; NCSE: not-convulsive status epilepticus, EEG: electroencephalogram; ICU: intensive care unit, ASM: anti-seizure medication.

were unrelated with a higher risk of developing epilepsy. Logistic regression was performed to estimate the strength of association of SE with epilepsy. The logistic regression model correctly classified 91.4 % of cases (Nagelkerke R^2=0.247). The occurrence of SE during neurological complications from HCT was associated with an increased likelihood of developing epilepsy over the follow-up (OR=14, 95 % CI 2.87–68.97). The five-year cumulative incidence of epilepsy differed significantly between patients with or without acute symptomatic SE (45.3 %, 95 % CI 23.2 %−88.4 % vs. 7.3 %, 95 % CI: 2.8 %−18.9 %; $p < 0.001$) (Fig. 3). Mortality rate did not differ significantly between the 2 groups (22% vs 38 %, $p = 0.327$).

4. Discussion

The present work describes the occurrence of epilepsy (i.e. recurrent unprovoked seizures) in 9.6 % of patients that experienced acute central nervous system complications from HCT (5-year cumulative incidence: 13.3 %). Data were collected over 20 years of clinical practice at 5 university centers for pediatric oncology, hematology, and neurology. The occurrence of acute symptomatic SE was associated with the development of unprovoked seizures during a median follow-up of 15 years. All subjects developed epilepsy before the age of 18, all of them had focal onset epilepsy. A clear structural etiology (e.g. mesial temporal sclerosis) was identified in 44 % cases. Drug resistant epilepsy was exclusively observed in patients with a clear underlying structural etiology. Previous reports have shown that acute symptomatic seizures occur in up to 15.4 % of pediatric patients undergoing HCT, and in up to 75 % of patients with neurological complications from the procedure, with large variability due to inter-study differences in terms of transplantation type, ethnicity, patients' age, conditioning regimen, follow-up duration, and trial design [5,6]. Conversely, there is a paucity of data about the risk of developing long-term epilepsy in these patients [6,15,16]. Our findings indicate that the occurrence of epilepsy in this cohort of patients is higher than in the general pediatric population. Indeed pooled estimates from a meta-analysis of international studies indicate that the annual cumulative incidence of epilepsy in the 18 year-old or younger people is 85.29 per 100,000 (0.08529 %, 95 % CI: 59.54–122.19) [17]. We found a higher cumulative incidence of epilepsy in this study (5-year cumulative incidence: 13.3 %). The reason for this difference is related to the stringent inclusion criteria of our study, in which patients have a history of neurological complications of HCT. Considering the relatively high incidence of epilepsy among these patients, it is relevant to explore the underlying possible mechanism and associated factors.

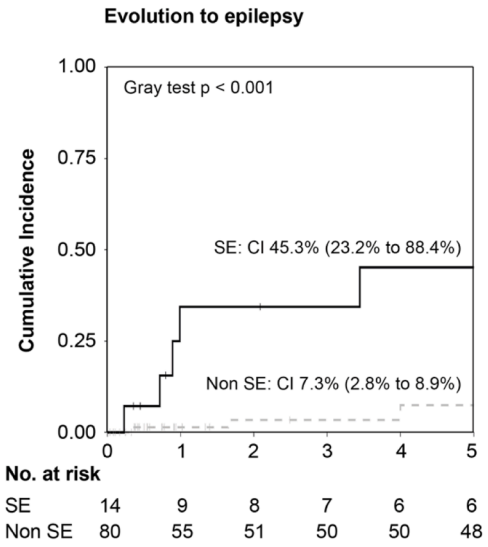

Fig. 3. Cumulative incidence and Status Epilepticus.

4.1. Epileptogenesis models

Epileptogenesis is the process through which previously normal brain networks are functionally altered toward increased seizure susceptibility, thus having an enhanced probability of generating spontaneous recurrent seizures [18–20]. As for the mechanisms of epileptogenesis, various models from experimental and clinical evidence have been described. Acquired epilepsies typically develop in three phases: (1) the occurrence of brain damage, such as traumatic brain injury, stroke, or infections leads to (2) epileptogenesis over a latent period with no evidence of overt clinical seizures, which is followed by the occurrence of (3) long-term unprovoked seizures and epilepsy, with further ongoing epileptogenesis [20,21]. In the present study, the onset of clinical epilepsy, namely, the first unprovoked, clinically evident seizures, occurred within a range of 83 days to 4 years after the acute brain insult during HCT. This is consistent with literature reports, describing a latent period ranging from few days to years in patients with acquired epilepsy secondary to previous brain insults [18,22,23]. Some Authors suggest that long latent periods to overt clinical seizures after brain injuries may represent a phase during which seizures are unrecognized, often subclinical/nonconvulsive or undetected by scalp EEG, rather than being non-existent [18,22]. Studies on EEG findings during the latent period of acquired human brain insults are lacking [24]. No significant association was found between post-acute scalp EEG interictal findings and the development of epilepsy in this study, although several limitations should be acknowledged due to the retrospective design.

The primary drive to epileptogenesis is a series of cellular alterations

(such as cell death, gliosis, neurogenesis, axonal and dendritic plasticity, rearrangement of the extracellular matrix, angiogenesis) and molecular mechanisms that underlie a network reorganization and lead to persistent hyperexcitability with reduced seizure threshold [25,26]. Patients undergoing HCT are at risk of several complications, such as drug-related neurotoxicity (chemotherapy, immunosuppressants, and anti-infective agents), metabolic disturbances (electrolyte imbalances, blood glucose abnormalities), organ failure, intracranial infections, and cerebrovascular events that ultimately can converge in common molecular mechanisms underpinning hyperexcitability and acute seizures [27]. However, this study didn't identify significant associations between the occurrence of acute seizures alone after HCT and the development of long-term unprovoked seizures and epilepsy. Therefore, it could be hypothesized that mechanisms leading to acute seizures may not be sufficient *per se* to cause long-term persistent disruption of neuronal circuitries. This is consistent with literature data from smaller cohorts that do not show an overlap between the incidence of acute seizures and long-term epilepsy in these patients [6,22]. For sure, event-related factors (pathogenesis, severity, location) and patient-related factors (genetic background, age, sex, comorbidities), play a pivotal role in causing different outcomes in terms of epileptogenesis after brain injuries [20,21]. However, this intra and inter-individual variability may not fully explain the big picture.

4.2. Status epilepticus

Status epilepticus was significantly associated with the development of epilepsy in this study. This evidence is consistent with models that acknowledge different rates of epileptogenesis between various brain insults, being the highest after acute provoked seizure associated with SE, rather than after seizures alone, stroke, or severe traumatic brain injury [20]. The epileptogenic role of SE is well acknowledged since experimental models of epileptogenesis are typically triggered by inducing SE and SE is considered as an acute brain insult that increases the risk of developing acquired epilepsy [28]. The mechanisms through which SE acts as an epileptogenic injury are several. First, SE leads to loss of GABAergic interneurons, reactive synaptogenesis and axonal sprouting of glutamatergic neurons, and reorganization of glutamate and GABA receptor subunits, which cause an increase in neuronal synchronization and excitability during periods of increased network activity [29–32]. Also, SE is known to cause microglial activation causing inflammatory processes that alter glioneuronal communication through multiple mechanisms such as dysfunction of glial K channels and gap junctions, disruption of K and adenosine homeostasis [28,33–37]. As a result, the activation of microglia causes the release of inflammatory mediators such as damage-associated molecular patterns (high mobility group box-1 [HMGB1], adenosine triphosphate, S100b), cytokines (IL-1b, TNF-a, IL-6), chemokines, and related effector pathways (COX-2/PGE2 and complement factors) that contribute to hyperexcitability and epilepsy progression after SE [28,38,39]. Moreover, both SE and inflammation lead to the disruption of the blood-brain barrier due to glutamate release, blood pressure rise, derailed autoregulation of cerebral blood flow, inflammatory molecules, and oxidative stress[28]: this contributes to albumin extravasation, which hampers homeostatic astrocytic functions and induces excitatory synaptogenesis by activating the TGF-b/ALK5 signaling, ultimately contributing to the development of epilepsy [28,40–43]. Eventually, SE activates four signaling pathways involved in cell survival and neurotransmission, potentially contributing to epileptogenesis (i.e.: Janus kinase/signal transducer and activator of transcription [JAK/STAT], mammalian target of rapamycin complex [mTORC], BDNF/tyrosine receptor kinase B [trkB]/phospholipase Cc1 [PLCc1], and IL-1R1/Toll-like receptor 4) [28]. Despite the specific mechanisms of SE-induced epileptogenesis have been extensively described, it is challenging to determine to what extent they contribute to epileptogenesis in the real-life setting, since SE is often caused by other underlying acute brain injuries [21]. In this study, acute SE was associated with long-term epilepsy regardless of its semiology [12]. This is consistent with previous findings highlighting worse functional outcomes in terms of a higher rate of later epilepsy among children with nonconvulsive SE undergoing long-term EEG monitoring in the pediatric intensive care unit [22,44].

4.3. Other modifiers

As said, several modifiers could play a role in determining the onset of clinical epilepsy after one epileptogenic injury, and the pathways leading to long-term epilepsy after acquired brain insults likely differ between patients. Age susceptibility for brain insults may play a role in the drive to epilepsy [22,45]: Zhang and colleagues identified younger age (< 18 yrs) as an independent risk factor for seizures after allo-HCT [5]. Indeed, the immature brain exhibits increased excitation and diminished inhibition with a higher propensity for seizures and epileptogenesis in infancy and early childhood [23]. All subjects with epilepsy after HCT were younger than 18 at the time of epilepsy onset in this study. Lower median age at transplant was not associated with higher risk of developing epilepsy.

Multiple mechanisms favor epileptogenesis, one of which is neurotoxicity [46]. Several neurotoxic agents are used during HCT, both as part of the conditioning regimen and to prevent GvHD. Busulfan and cyclosporine (Cyclosporine capsules) have been previously associated with variable rates of acute seizures and long-term epilepsy (1.3–40 % and 2.1–26 %, respectively) [47–50]. Patients treated with Busulfan or cyclosporine (Cyclosporine capsules) in this study did not show higher risk of acute seizures and SE or long-term epilepsy. Future studies on neurological complications should also include the analysis on the gut microbiota, considering its crucial role in the genesis of many HCT-related complications and the known effect of the gut-brain axis [51–54].

4.4. Limitations

The present study has several limitations. The retrospective, multicenter design and the wide time span considered limited the retrieval of clinical data. Therefore, the occurrence of epilepsy might have been underestimated. The small number of epilepsy diagnoses limited our ability to identify other possible clinical predictors and to provide a detailed characterization of the epilepsy phenotypes. Moreover, no standardized, shared protocol for the management of acute neurologic complications or follow-up was available among the five centers involved in the study.

5. Conclusions

Epilepsy occurred in 9.6 % of pediatric patients with a history of neurologic complications following HCT. The 5-year cumulative incidence from the acute neurological complication was 13.3 %. The occurrence of SE during the neurological complication was associated with a higher risk of developing epilepsy during a median follow-up of 15 years. Patients undergoing HCT and experiencing acute neurological complications could benefit from a specific neurological post-HCT follow-up, especially when acute SE occurs. Factors influencing the path to epileptogenesis are still debated. Future studies are needed to better identify the pathophysiological mechanisms driving epileptogenesis in this population.

Declaration of competing interest

The Authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.seizure.2024.08.001.

References

[1] Balassa K, Danby R, Rocha V. Haematopoietic stem cell transplants: principles and indications. Br J Hosp Med 2019;80:33–9.
[2] Copelan EA, Chojecki A, Lazarus HM, Avalos BR. Allogeneic hematopoietic cell transplantation; the current renaissance. Blood Rev 2019;34:34–44.
[3] Duléry R. Neurological complications. In: Carreras E, Dufour C, Mohty M, Kröger N, editors. The EBMT handbook: hematopoietic stem cell transplantation and cellular therapies. Cham (CH): Springer; 2019.
[4] Bonardi M, et al. Brain imaging findings and neurologic complications after allogenic hematopoietic stem cell transplantation in children. Radiographics 2018; 38:1223–38.
[5] Zhang X, et al. Epileptic seizures in patients following allogeneic hematopoietic stem cell transplantation: a retrospective analysis of incidence, risk factors, and survival rates. Clin Transplant 2013;27:80–9.
[6] Cordelli DM, et al. Etiology, characteristics and outcome of seizures after pediatric hematopoietic stem cell transplantation. Seizure 2014;23:140–5.
[7] Zama D, et al. Risk factor analysis of posterior reversible encephalopathy syndrome after allogeneic hematopoietic SCT in children. Bone Marrow Transplant 2014;49: 1538–40.
[8] Masetti R, et al. PRES in children undergoing hematopoietic stem cell or solid organ transplantation. Pediatrics 2015;135:890–901.
[9] Antonini G, et al. Early neurologic complications following allogeneic bone marrow transplant for leukemia: a prospective study. Neurology 1998;50:1441–5.
[10] Glucksberg H, et al. Clinical manifestations of graft-versus-host disease in human recipients of marrow from HL-A-matched sibling donors. Transplantation 1974;18: 295–304.
[11] Scheffer IE, et al. ILAE classification of the epilepsies: position paper of the ILAE Commission for Classification and Terminology. Epilepsia 2017;58:512–21.
[12] Trinka E, et al. A definition and classification of status epilepticus - report of the ILAE task force on classification of status epilepticus. Epilepsia 2015;56:1515–23.
[13] Fisher RS, et al. ILAE Official Report: a practical clinical definition of epilepsy. Epilepsia 2014;55:475–82.
[14] Kwan P, et al. Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. Epilepsia 2010; 51:1069–77.
[15] Vesole AS, et al. Drug-resistant epilepsy development following stem cell transplant and cyclosporine neurotoxicity induced seizures: case report in an adult and analysis of reported cases in the literature. Epilepsy Behav Case Rep 2018;10: 8–13.
[16] Lin P, Tian X, Wang X. Seizures after transplantation. Seizure 2018;61:177–85.
[17] Fiest KM, et al. Prevalence and incidence of epilepsy. Neurology 2017;88:296–303.
[18] Dudek FE, Staley KJ. The time course of acquired epilepsy: implications for therapeutic intervention to suppress epileptogenesis. Neurosci Lett 2011;497: 240–6.
[19] Goldberg EM, Coulter DA. Mechanisms of epileptogenesis: a convergence on neural circuit dysfunction. Nat Rev Neurosci 2013;14:337–49.
[20] Pitkänen A, Lukasiuk K, Dudek FE, Staley KJ. Epileptogenesis. Cold Spring Harb Perspect Med 2015;5:a022822.
[21] Pitkänen A, et al. Epileptogenesis in experimental models. Epilepsia 2007;48: 13–20.
[22] Löscher W, Hirsch LJ, Schmidt D. The enigma of the latent period in the development of symptomatic acquired epilepsy — traditional view versus new concepts. Epilepsy Behav 2015;52:78–92.
[23] Rakhade SN, Jensen FE. Epileptogenesis in the immature brain: emerging mechanisms. Nat Rev Neurol 2009;5:380.
[24] Löscher W, Brandt C. Prevention or modification of epileptogenesis after brain insults: experimental approaches and translational research. Pharmacol Rev 2010; 62:668–700.
[25] Jutila L, et al. Neurobiology of epileptogenesis in the temporal lobe. Adv Tech Stand Neurosurg 2002;27:5–22.
[26] Pitkänen A, Lukasiuk K. Molecular and cellular basis of epileptogenesis in symptomatic epilepsy. Epilepsy Behav 2009;14(Suppl. 1):16–25.
[27] Wang Z, Zhao M, Gao S. Epileptic seizures after allogeneic hematopoietic stem cell transplantation. Front Neurol 2021;12:675756.
[28] Klein P, et al. Commonalities in epileptogenic processes from different acute brain insults: do they translate? Epilepsia 2018;59:37–66.
[29] Houser CR, Esclapez M. Vulnerability and plasticity of the GABA system in the pilocarpine model of spontaneous recurrent seizures. Epilepsy Res 1996;26: 207–18.
[30] Tsunashima K, Schwarzer C, Kirchmair E, Sieghart W, Sperk G. GABA(A) receptor subunits in the rat hippocampus III: altered messenger RNA expression in kainic acid-induced epilepsy. Neuroscience 1997;80:1019–32.
[31] Brooks-Kayal AR, Shumate MD, Jin H, Rikhter TY, Coulter DA. Selective changes in single cell GABA(A) receptor subunit expression and function in temporal lobe epilepsy. Nat Med 1998;4:1166–72.
[32] Loup F, Wieser HG, Yonekawa Y, Aguzzi A, Fritschy JM. Selective alterations in GABAA receptor subtypes in human temporal lobe epilepsy. J Neurosci 2000;20: 5401–19.
[33] Devinsky O, Vezzani A, Najjar S, De Lanerolle NC, Rogawski MA. Glia and epilepsy: excitability and inflammation. Trends Neurosci 2013;36:174–84.
[34] Seifert G, Steinhäuser C. Neuron-astrocyte signaling and epilepsy. Exp Neurol 2013;244:4–10.
[35] Vezzani A, Aronica E, Mazarati A, Pittman QJ. Epilepsy and brain inflammation. Exp Neurol 2013;244:11–21.
[36] Foiadelli T, et al. Neuroinflammation and status epilepticus: a narrative review unraveling a complex interplay. Front Pediatr 2023;11.
[37] Fetta A, et al. Cannabidiol in the acute phase of febrile infection-related epilepsy syndrome (FIRES). Epilepsia Open 2023;8:685–91.
[38] Ravizza T, et al. High Mobility Group Box 1 is a novel pathogenic factor and a mechanistic biomarker for epilepsy. Brain Behav Immun 2018;72:14–21.
[39] Parker TM, Nguyen AH, Rabang JR, Patil A-A, Agrawal DK. The danger zone: systematic review of the role of HMGB1 danger signalling in traumatic brain injury. Brain Inj 2017;31:2–8.
[40] Braganza O, et al. Albumin is taken up by hippocampal NG2 cells and astrocytes and decreases gap junction coupling. Epilepsia 2012;53:1898–906.
[41] Friedman A, Heinemann U. Role of blood-brain barrier dysfunction in epileptogenesis. In: Noebels JL, Avoli M, Rogawski MA, Olsen RW, Delgado-Escueta AV, editors. Jasper's Basic Mechanisms of the Epilepsies. Bethesda (MD): (National Center for Biotechnology Information (US); 2012.
[42] Weissberg I, et al. Albumin induces excitatory synaptogenesis through astrocytic TGF-β/ALK5 signaling in a model of acquired epilepsy following blood-brain barrier dysfunction. Neurobiol Dis 2015;78:115–25.
[43] Gorter JA, van Vliet EA, Aronica E. Status epilepticus, blood–brain barrier disruption, inflammation, and epileptogenesis. Epilepsy Behav 2015;49:13–6.
[44] Wagenman KL, et al. Electrographic status epilepticus and long-term outcome in critically ill children. Neurology 2014;82:396–404.
[45] Masetti R, et al. Acute myeloid leukemia in infants: biology and treatment. Front Pediatr 2015;3.
[46] Rubio C, Rosiles-Abonce A, Taddei E, Rubio-Osornio M. Neurotoxicity and epileptogenesis. In: Sabuncuoglu S, editor. Neurotoxicity - New Advances. IntechOpen; 2022. https://doi.org/10.5772/intechopen.103687.
[47] Vassal, G. et al. Dose-dependent Neurotoxicity of High-Dose Busulfan in Children: A Clinical and Pharmacological Study.
[48] Gaggero R, et al. Intractable epilepsy secondary to cyclosporine toxicity in children undergoing allogeneic hematopoietic bone marrow transplantation. J Child Neurol 2006;21:861–6.
[49] Caselli D, et al. Risk of seizures in children receiving busulphan-containing regimens for stem cell transplantation. Biol Blood Marrow Transplant 2014;20: 282–5.
[50] Eberly AL, Anderson GD, Bubalo JS, McCune JS. Optimal prevention of seizures induced by high-dose Busulfan. Pharmacotherapy 2008;28:1502–10.
[51] Masetti R, et al. Gut microbiome in pediatric acute leukemia: from predisposition to cure. Blood Adv 2021;5:4619–29.
[52] Masetti R, et al. The gut microbiome in pediatric patients undergoing allogeneic hematopoietic stem cell transplantation. Pediatr Blood Cancer 2020;67:e28711.
[53] Masetti R, et al. Febrile neutropenia duration is associated with the severity of gut microbiota dysbiosis in pediatric allogeneic hematopoietic stem cell transplantation recipients. Cancers 2022;14:1932.
[54] Masetti R, et al. Gut microbiota diversity before allogeneic hematopoietic stem cell transplantation as a predictor of mortality in children. Blood 2023;142:1387–98.