Central nervous system disorders following haematopoietic stem cell transplantation: a prospective case–control observational study from the Infectious Diseases Working Party and the Transplant Complications Working Party of EBMT

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Summary

Background **CNS disorders (CNSD) after haematopoietic stem cell transplantation (HSCT) are a significant complication, although there are few specific studies on it. The major objective of this prospective case–control observational study was to characterise infectious and non-infectious CNSD (iCNSD and niCNSD, respectively) after HSCT.**

eClinicalMedicine 2026;93: 103792
Published Online 26 February 2026
https://doi.org/10.1016/j.eclinm.2026.103792

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Methods Patients were eligible for the CNSD group if they underwent HSCT between January 2021 and December 2022 at 20 centres in 11 countries and developed either an iCNSD or a niCNSD at any time after the start of conditioning prior to HSCT, up to the study termination (June 2023). Data were collected by local investigators and sent to the EBMT Leiden Study Unit, Leiden, Netherlands. For each case, two controls surviving the same period after HSCT without CNSD as the respective case were selected. Primary endpoints of this study were (1) percentage of iCNSD and niCNSD, including different causes, (2) characteristics of CNSD (e.g., percentage of patients with an abnormal brain imaging pattern), and (3) the course (e.g., mortality and overall survival [OS] = at different time points). This study is registered at ClinicalTrials.gov (NCT04737785).

Findings 237 patients (84 cases and 153 controls) were included, of whom 98 (41%) were female and 139 (59%) were male. The frequency of CNSD after HSCT was estimated at 2.9% (84 of 2910 transplanted patients, 95% CI 2.3–3.6%). Among cases, 21 (25%) had a proven/probable iCNSD, 47 (56%) had a proven/probable niCNSD, and 16 (19%) had a possible or unclassified CNSD. Human herpes virus-6 (meningo-)encephalitis was the most frequent proven/probable iCNSD (n = 9, 43%). In patients with proven/probable niCNSD, vascular pathologies were dominant (n = 15, 32%). In a multivariable Cox regression analysis, CNSD at the inclusion time point (HR 2.96, 95% CI 1.13–7.74, p = 0.027) remained the only significant predictor of inferior OS. Causes of death in the CNSD group were the CNSD (n = 15/36, 42%, eight with proven/probable iCNSD, five with proven/probable niCNSD and two with possible/unspecified CNSD), other HSCT-related causes (n = 7, 19%), relapse/progression (n = 5, 14%), or other (including multifactorial reasons, n = 9, 25%). Relapse/progression was the most frequent cause of death among controls (n = 17/25, 68%).

Interpretation CNSD represent a serious complication after HSCT with an estimated 2.9% frequency and non-infectious causes prevailing over CNS infections. Patients with a CNSD after HSCT have a reduced OS, with the CNSD itself being the main cause of death.

Funding None.

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Keywords: Haematopoietic stem cell transplantation; Central nervous system; Infection; Non-infectious disorder; Survival

Research in context

Evidence before this study

Novel comprehensive prospective studies on central nervous system (CNS) complications after haematopoietic stem cell transplantation are lacking. The majority of studies on this complication are quite old, focused on distinct causative pathogens and do not include a control group. The evidence before this study was assessed by searching the database pubmed.gov (focused on English-language), using search terms such as "central nervous system complication" (or related terms such as "CNS disorder", "encephalitis", etc.) and "stem cell transplantation" covering a period from 2010 until now (1st June 2025).

Added value of this study

We performed a prospective case–control observational study on infectious and non-infectious CNS complications after haematopoietic stem cell transplantation. For each case, two controls surviving the same period after transplant without CNS complication as the respective case were selected and included if exclusion/inclusion criteria were fulfilled. Our study shows that the spectrum of CNS infections after haematopoietic stem cell transplantation has significantly been changed in recent years with lower percentages of CNS fungal infection and Epstein–Barr virus encephalitis. We also found that a CNS complication after transplantation still confers an inferior overall survival, with the CNS complication being the main cause of death.

Implications of all the available evidence

CNS complications after haematopoietic stem cell transplantation are still clinically relevant and associated with a poor prognosis. Therefore, a high level of vigilance is of the utmost importance in the clinical routine, and adequate diagnostics and treatment should be initiated in a timely manner.

Introduction

Few data have been published on central nervous system disorders (CNSD) after haematopoietic stem cell transplantation (HSCT).[1,2] The majority of these studies are old, retrospective in design, and focused on distinct causative agents of infectious CNSD (iCNSD) such as viral encephalitis/meningoencephalitis,[3,4] fungal CNS infections,[5,6] or neurotoxoplasmosis.[7]

A previous prospective study without a control group conducted by the Infectious Diseases Working Party (IDWP) of EBMT group evaluated the characteristics, spectrum, and outcome of both iCNSD and non-infectious CNSD (niCNSD) after HSCT.[3] A total of 163 episodes of CNSD following autologous or allogeneic HSCT between 2000 and 2002 were included. Among patients with proven/probable iCNSD (n = 34), viral (35%), fungal iCNSD (29%) and *Toxoplasma* spp. (27%) were the most prevalent, while bacteria (9%) were identified less frequently in this study recruiting patients more than 20 years ago.[3] Among niCNSD patients (n = 105), metabolic/drug-induced abnormalities (27%) and cerebral vascular events (21%) were the most frequent.

However, the diagnostics and the treatment of CNSD used in these studies and other older analyses do not reflect the current standard of care. For example, the broad availability of cerebrospinal fluid (CSF) polymerase chain reaction (PCR) and CSF next-generation sequencing (NGS) in an increasing number of centres, besides neuroimaging by magnetic resonance imaging (MRI), has been introduced in the clinical routine.[8,9] Additionally, novel effective treatment options have been introduced in clinical practice for selected CNSD, such as isavuconazole for invasive cerebral fungal infection.[5] The way HSCT is conducted has also significantly changed in recent years. Haploidentical transplantation has been established as a routine procedure of stem cell transplantation,[10] and novel conditioning regimens and graft-*versus*-host disease (GvHD) treatment strategies[11] have been developed.

Finally, in previous studies on CNSD after HSCT, the likelihood of CNSD was frequently not classified despite increasing efforts to standardise diagnostics and classify the probability (e.g., proven vs probable vs possible), mainly for different infectious diseases such as cytomegalovirus (CMV) disease,[12] invasive fungal disease,[13] and other CNS infections.[14]

Due to this lack of representative data on CNSD in the current era of HSCT and the comparably low incidence of these disorders, a prospective case–control observational study was urgently warranted. We performed a prospective, comprehensive observational study on infectious and non-infectious CNSD after HSCT. To get further insights into potential risk factors for CNSD after HSCT and to compare the outcome of patients with vs without a CNSD after transplantation, we included a control group with patients who survived for the same period after HSCT without CNSD, matching the respective case with CNSD.

Methods

Study design and participants

This was a prospective case–control observational study from the IDWP and the Transplant Complications Working Party (TCWP) of EBMT. All active EBMT centres (n = 599) were invited to participate in this prospective observational study. A survey was launched in June 2020 in which 94 centres declared interest. Finally, 20 centres from 11 countries participated and included patients. This study is registered at ClinicalTrials.gov (NCT04737785).

Primary objectives of this study were (1) the spectrum of iCNSD and niCNSD, (2) characteristics of CNSD (e.g., diagnostic criteria such as CSF and brain imaging patterns and timing after HSCT), and to determine (3) the course of the CNSD, including its outcome, including overall survival (OS) at different time points (day +30, day +100, last follow-up). Secondary objectives included (1) clinical symptoms and treatment, (2) the cumulative incidence of new-onset CNSD of both cases and controls, and (3) patient and transplant characteristics of cases and controls, including potential CNSD risk factors.

We hypothesised that the spectrum of CNSD has changed in recent years and that patients with a CNSD at study inclusion have an inferior survival compared to those without CNSD at this timepoint.

Patients were eligible for the CNSD group if they underwent autologous or allogeneic HSCT between January 2021 and December 2022 and developed either an iCNSD or a niCNSD at any time after the start of conditioning prior to HSCT, up to the study termination (June 2023). Follow-up data were obtained until April 2023 for cases and until June 2023 for controls. Patients with any iCNSD were included, while patients with a non-infectious or unspecified CNSD were included only if the respective abnormality was considered to be relevant (Common Terminology Criteria for Adverse Events Version 5.0> 1°). In contrast, terminal sedation or CNS disturbances due to multi-organ failure prior to death, usually coming in the late course of the underlying disease (e.g., acute leukaemia), were excluded. Further requirements for both cases and controls included the availability of essential patient and transplant data as well as written informed consent from participating patients.

Principal investigators of participating centres were urged to include all patients fulfilling inclusion and exclusion criteria to minimise bias for selective inclusion.

Ethics

Approvals from the coordinating ethics committee (Landesärztekammer Brandenburg, Cottbus, Germany, vote S (bB)/2021, 9th February 2021) and votes from local ethics committees of participating centres were obtained. Written informed consent was obtained from

all participants for inclusion in the EBMT database. Additional study-specific informed consent was obtained if required by the local ethics committees.

Procedures

To estimate the frequency of CNSD, all patients after HSCT were monitored for the occurrence of both iCNSD and niCNSD in participating centres and included if the inclusion/exclusion criteria were fulfilled. Controls developing a CNSD after study inclusion were not included in the estimation of the frequency.

We intended to select two controls for each case (i.e., an HSCT recipient at study inclusion defined by CNSD onset) and collect their data. Hereby, two patients transplanted subsequently to the respective case were included when inclusion/exclusion criteria were fulfilled as controls if they did not develop a CNSD between conditioning prior to HSCT and study inclusion and had survived until the inclusion time point of their respective CNSD case (defined as the same delay between transplantation and CNS disorder onset of the corresponding case). Cases and controls were matched by centre, type of HSCT (i.e., autologous vs allogeneic), and age category (children vs adults). Cases and controls were evaluated regularly until the last follow-up. Reasons for not including cases or controls besides matching characteristics are summarised in the Supplementary Material. Controls developing a CNSD after study inclusion could not enter the case group and were also included in the final analysis (details are shown in the Supplementary Material). Following their recruitment, both cases and controls were prospectively followed. New-onset CNSD after study inclusion and during the prospective follow-up occurred in both cases and controls, as could be expected.

As both cases and controls were recruited prospectively, development of CNSD after inclusion in controls could not be anticipated at inclusion and was not a reason to disqualify them from the control group. Development of the new CNSD after inclusion was recorded and compared both in cases and in controls.

Diagnostics and treatment of CNSD were conducted in accordance with local standards of care. Patients' follow-up was recorded 30 and 100 days after study inclusion—i.e., defined by CNSD onset in cases (day 0) and the corresponding period in controls—and at the last follow-up. All cases and controls were identified locally by treating physicians and recorded in the EBMT database. They were followed up for at least four months from study inclusion if surviving.

Patient and study data were collected by local investigators and sent to the EBMT Leiden Study Unit, Leiden, Netherlands.

Outcomes

Primary endpoints of this study were (1) percentage of iCNSD and niCNSD, including different causes, (2) characteristics of CNSD (e.g., percentage of patients with an abnormal brain imaging pattern), and (3) the course (e.g., mortality and OS at different time points). Secondary endpoints included (1) percentage of patients with different clinical symptoms and treatment, (2) the cumulative incidence of new-onset CNSD of both cases and controls and (3) the percentage of patients with distinct characteristics (cases and controls, including potential CNSD risk factors).

As applicable, the strength of evidence for CNSD (proven vs probable vs possible) was defined according to previously published criteria (Table S1 and the section on the classification process in the Supplementary Material). CNSD onset times were calculated as the time from HSCT until the appearance of CNS-related symptoms (with times from the start of conditioning prior to HSCT being negative; for details of onset times calculation, please see Supplementary Material).

For cases, study inclusion (i.e., day 0) was defined as the date of onset of CNS symptoms. For controls, study inclusion was defined as the same number of days after HSCT as the CNSD onset occurred in their matched case patient.

Patients' survival time was calculated as the time from study inclusion to death or the last follow-up, whichever occurred first. New-onset CNSD was defined as the first occurrence of a CNSD after study inclusion or reoccurrence of a previous CNSD in cases after previous CNSD resolution.

The onset was defined either as acute (e.g., CNS bleeding) or non-acute (e.g., progressive over several days, such as in the case of encephalopathy).

Statistics

Based on the aforementioned survey, the target number of patients with a CNSD at inclusion was calculated to be 150 in a two-year period (2021–2022), with 130 of these cases analysed. This proposed sample size resulted in a total number of 400 prospectively enrolled and analysed patients (130 cases and 270 controls). Due to lower patient accrual than expected, enrolment was terminated after the inclusion of 84 patients with a CNSD and 153 controls.

Descriptive statistics were calculated via absolute and percentage frequencies for categorical variables and interquartile ranges (IQR) for continuous variables. The numbers of missing values per variable were counted. CNSD types were classified as one of: (1) proven/probable iCNSD; (2) proven/probable niCNSD; or (3) possible iCNSD/niCNSD or unclassified CNSD. Characteristics of the three different CNSD types were compared via the X^2 test for categorical variables, or Fisher's exact test if the minimal expectancy requirement was failed, and the Wilcoxon rank sum test for continuous variables. The same tests were used whenever comparing variables across subgroups.

P-values (two-sided) <0.05 were considered statistically significant. Statistical analyses were performed using R, version 4.4.1 (R Core Team, 2024). Missing data were excluded from the analyses without imputation.

OS was analysed via the Kaplan–Meier method. The association of different variables with OS upon univariable analysis was assessed by the log-rank test. Variables found to be associated with OS were included in a multivariable Cox proportional hazard (PH) model; their impact on the outcome was assessed using the Wald test. Candidate independent variables included, among others, the presence of CNSD at the inclusion time point (i.e., cases vs controls), HSCT type (autologous vs allogeneic), age category (<18 vs ≥18 years), stem cell source, recipient/donor relationship, and use of T cell depletion pre-HSCT (please see Table S14 for the full list of predictor variables). The impact of a new-onset CNSD on OS was assessed in a time-dependent Cox PH model. The potential effect of centre was examined as a random-effect (frailty) term. The multivariable Cox PH model was stratified by set to account for matching (each set contained one case and the matched controls). A complete-case analysis was used for the final Cox PH model; sensitivity analyses were performed by re-estimating the model while excluding individual predictors in turn to evaluate the stability of the model's estimates. It was ensured that the model had an adequate number of events per variable.

New-onset (i.e., post-inclusion) CNSD were analysed via Aalen-Johansen models, taking death without new-onset CNSD as a competing risk. For controls, new-onset CNSD was assessed over three time periods following study inclusion: <30 days, 30–99 days and ≥100 days post-inclusion. For cases, this was assessed across two: <100 days and ≥100 days. The association between new-onset CNSD and independent variables was assessed via Gray's test. Those associated with the outcome were included in a multivariable cause-specific Cox PH model, stratified by matched set.

Roled of the funding source

There was no funding for this prospective study.

Results

By taking the 84 cases as a proportion of the 2910 transplanted patients across the 20 participating centres in the study timeframe, the frequency of CNSD after HSCT was estimated at 2.9% (95% CI 2.3–3.6%). CNSD were significantly more frequent for allogeneic HSCT than autologous HSCT: 80/1735 vs 4/1175, translating to estimated frequencies of 4.6% (95% CI 3.7–5.7%) vs 0.3% (95% CI 0.1–0.9%), with $p < 0.0001$ (via the X^2 test). Furthermore, CNSD were more frequent for children than adults: 29/670 vs 55/2238, giving estimated frequencies of 4.3% (95% CI 2.9–6.2%) vs 2.5% (95% CI 1.9–3.2%), $p = 0.016$.

Characteristics of cases (n = 84) and controls (n = 153) are shown in Table 1 and Tables S2–S4. The analysis encompassed 98 (41%) females and 139 males (59%) with no significant differences between cases and controls (Table 1). The majority of patients underwent allogeneic HSCT (n = 228, 96%) and were adults (n = 156, 66%). Cases were statistically significantly more frequently hospitalised (75/83 patients, 90%) than controls (88/153 patients, 58%, $p < 0.0001$). In addition, a grade II-IV Eastern Cooperative Oncology Group (ECOG) status at study inclusion was more frequently present in cases (63/82 patients, 77%) than in controls (42/153, 27%, $p < 0.0001$).

The spectrum of proven/probable iCNSD (n = 21, 25%), proven/probable niCNSD (n = 47, 56%), and possible iCNSD/niCNSD or unclassified CNSD (n = 16, 19%) is shown in Fig. 1. Characteristics (e.g., causative agent/type, diagnostic criteria, likelihood, and outcome) of all 84 individual cases are summarised in Table S5 with reasons for not including distinct patients also shown in the Supplementary Material. Classification of proven/probable iCNSD was mainly based on CSF PCR (n = 15, 72%) and, to a lesser extent, on CNS tissue studies (e.g., brain biopsy or autopsy; n = 3, 14%, cases N. 35, 65 and 73 in Table S5) or other methods (n = 3, 14%). Proven/probable niCNSD—e.g., vascular pathologies, drug-related changes and metabolic encephalopathy—were mainly diagnosed based on neuroimaging findings (n = 15, 32%); the administration of a distinct drug together with the clinical course, e.g., neurological improvement after cessation of a presumable causative drug (n = 13, 28%); laboratory measurements, such as in the case of metabolic encephalopathy (n = 4, 8%); or other methods/the combination of different methods (n = 15, 32%, Table S5).

CNSD in children (n = 29, 35%) mainly included proven/probable niCNSD (n = 19, 65.5%), followed by possible/unclassified CNSD (n = 8, 27.5%) and finally proven/probable iCNSD (n = 2, 7%). Conversely, adults (n = 55, 65%) had proven/probable niCNSD in 28 cases (51%), followed by proven/probable iCNSD (n = 19, 34.5%) and finally possible/unclassified CNSD (n = 8, 14.5%, $p = 0.016$, Table S6).

Table 2 presents the CSF characteristics and brain imaging patterns of patients with a proven or probable iCNSD compared to those with a proven or probable niCNSD or a possible or unclassified CNSD. Brain MRI showed abnormalities presumably associated with the CNSD in 15 of 21 evaluable patients (71%) with proven/probable iCNSD, in 24 of 32 patients (75%) with proven/probable niCNSD, and in 5 of 10 patients (50%) with possible/unclassified CNSD.

The median onset time of CNSD after HSCT for patients with CNSD was 31 days (IQR 15–57 days, n = 84). Among the 84 case patients, 73 had an onset time less than 100 days, and 11 had an onset time greater than or equal to 100 days. These two subgroups

Parameter	Patients with a CNSD at inclusion (cases, N = 84)	Patients without a CNSD at inclusion (controls, N = 153)	p
Diagnosis			0.97
Acute leukaemia (n, %)	42 (50.0%)	76 (49.7%)	
MDS/MPN (n, %)	15 (17.9%)	30 (19.6%)	
Bone marrow failure (n, %)	9 (10.7%)	12 (7.8%)	
Inherited disorders (n, %)	5 (6.0%)	12 (7.8%)	
Lymphoma (n, %)	5 (6.0%)	9 (5.9%)	
Other (n, %)[a]	8 (9.5%)	14 (9.2%)	
Type of HSCT			
Allogeneic (n, %)[b]	80 (95.2%)	148 (96.7%)	0.72
Autologous (n, %)	4 (4.8%)	5 (3.3%)	
Recipient age, years (median, IQR)	35.9 (14.1–56.0)	38.9 (12.3–58.3)	0.90
Age category			1
Children (<18 years, n, %)	29 (34.5%)	52 (34.0%)	
Adult (≥18 years, n, %)	55 (65.5%)	101 (66.0%)	
Recipient sex			
Male (n, %)	45 (53.6%)	94 (61.4%)	0.30
Female (n, %)	39 (46.4%)	59 (38.6%)	
Donor/recipient sex matching (only allo-HSCT case recipients and their allogeneic HSCT controls)[b]			0.26
Female/female (n, %)	16 (20.0%)	18 (12.4%)	
Female/male (n, %)	17 (21.2%)	25 (17.2%)	
Male/female (n, %)	21 (26.2%)	39 (26.9%)	
Male/male (n, %)	26 (32.5%)	63 (43.4%)	
Recipient/donor HLA matching (only allo-HSCT case recipients and their allogeneic HSCT controls)[b]			0.049
Missing	5	7	
HLA-matched sibling (n, %)	23 (30.7%)	49 (35.5%)	
Mismatched relative (n, %)	26 (34.7%)	27 (19.6%)	
Unrelated (n, %)	26 (34.7%)	62 (44.9%)	
Stem cell source			0.29
BM (n, %)	29 (34.5%)	57 (37.3%)	
PB (n, %)	53 (63.1%)	96 (62.7%)	
CB ± BM (n, %)	2 (2.4%)	0 (0.0%)	
Disease status at inclusion			
Missing	25	47	1
CR (n, %)	45 (76.3%)	81 (76.4%)	
Other (n, %)[c]	14 (23.7%)	25 (23.6%)	
Conditioning type			
Missing	6	6	0.18
Standard (n, %)	43 (55.1%)	96 (65.3%)	
RIC (n, %)	35 (44.9%)	51 (34.7%)	
TBI-containing conditioning (only allo-HSCT case recipients and their allogeneic HSCT controls)[b]			1
Missing	1	1	
No (n, %)	66 (83.5%)	120 (83.3%)	
Yes (n, %)	13 (16.5%)	24 (16.7%)	
T cell depletion (only allo-HSCT case recipients and their allogeneic HSCT controls)[b,d]			0.83
Missing	4	6	
No (n, %)	49 (64.5%)	86 (61.9%)	
Yes (n, %)	27 (35.5%)	53 (38.1%)	
Patient location at inclusion[e]			<0.0001
Missing	1	0	
Outpatient (n, %)	8 (9.6%)	65 (42.5%)	
In hospital (n, %)	75 (90.4%)	88 (57.5%)	

(Table 1 continues on next page)

Parameter	Patients with a CNSD at inclusion (cases, N = 84)	Patients without a CNSD at inclusion (controls, N = 153)	p
(Continued from previous page)			
ECOG PS at inclusion			<0.0001
Missing	2	0	
0–1 (n, %)	19 (23.2%)	111 (72.5%)	
2–4 (n, %)	63 (76.8%)	42 (27.5%)	
Any comorbidity at inclusion[f]			0.00023
No (n, %)	26 (31.0%)	87 (56.9%)	
Yes (n, %)	58 (69.0%)	66 (43.1%)	
GvHD present at inclusion (only allo-HSCT case recipients and their allogeneic HSCT controls)[b,f]			0.20
Missing	3	2	
No (n, %)	59 (76.6%)	121 (84.6%)	
Yes (n, %)	18 (23.4%)	22 (15.4%)	
Steroid treatment at inclusion			0.41
Missing	1	0	
No (n, %)	10 (12.0%)	26 (17.0%)	
Yes (n, %)	73 (88.0%)	127 (83.0%)	
Time from HSCT to study inclusion, days (median, IQR)	31 (15.0–57.2)	31 (15.0–56.0)	0.89
Year of HSCT (median, IQR)	2021 (2021–2022)	2021 (2021–2022)	0.45
Follow-up, months[g] (median, 95% CI)	20.6 (18.3–25.3)	19.3 (17.1–21.5)	0.13

Shown are numbers of patients per outcome category (n, %) or medians (IQR). Patients missing from the total were not evaluable. p-values are calculated via the X^2 test for categorical variables (or Fisher's exact test if the minimal expectancy requirement is not met) and the Wilcoxon rank sum test for continuous variables. BM: bone marrow, CB: cord blood, CNSD: central nervous system disorder; ECOG PS: Eastern Cooperative Oncology Group performance status, GvHD: graft-*versus*-host disease, HLA: human leucocyte antigen, HSCT: haematopoietic stem cell transplantation, IQR: interquartile range, MDS: myelodysplastic syndrome, MPN: myeloproliferative neoplasms, n: number, PB: peripheral blood, RIC: reduced-intensity conditioning, TBI: total body irradiation. [a]Includes the diagnoses that were given to fewer than 10 patients in total: solid tumours (n = 5), haemoglobinopathies (n = 5), chronic leukaemia (n = 4), plasma cell disorders (n = 3), histiocytic disorders (n = 3), autoimmune diseases (n = 2). [b]The 80 allogeneic HSCT case patients had a total of 145 corresponding controls who also received an allo-HSCT. [c]Including induction failure/relapse/refractory/progression (n = 22), partial remission (n = 8), and other (n = 9). [d]Both *in vivo* and *ex vivo* (n = 1), *ex vivo* only (n = 4), *in vivo* only (n = 75). [e]HSCT or intermediate care (n = 141), intensive care unit (n = 10), peripheral ward (n = 9), HSCT or intermediate care and intensive care unit (n = 3). [f]Details are shown in the Supplementary Material. [g]Calculated via the reverse Kaplan–Meier method; tested via the log-rank test. If focussing the analyses only on the 80 cases after allo-HSCT together with their 145 allo-HSCT controls, patient location at inclusion, ECOG PS at inclusion and presence of any comorbidity at inclusion remained statistically significantly different between both groups (data not shown). When splitting children (n = 81) and adults (n = 156) patient location at inclusion, ECOG PS at inclusion and presence of any comorbidity at inclusion remained statistically significant among adults but only patient location at inclusion and ECOG PS at inclusion among children (data not shown).

Table 1: **Characteristics of patients with (cases) vs without (controls) a CNSD after HSCT at study inclusion.**

did not differ regarding patient baseline characteristics shown in Table 1 (p > 0.05 for all comparisons, data not shown). Likewise, the onset of proven/probable iCNSD vs proven/probable niCNSD vs possible/unclassified CNSD had no statistically significant difference (Fig. 2), also when analysed by the Kaplan–Meier method (Fig. S1). However, when considering patients with different proven/probable iCNSD individually, those with CNS aspergillosis showed the earliest onset (median 14 days after HSCT), followed by patients with

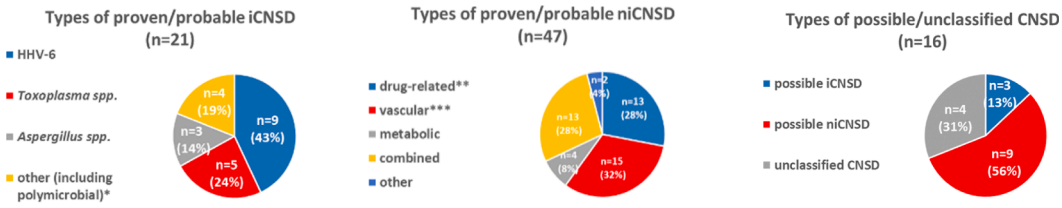

Fig. 1: **Types and spectrum of CNSD. Shown are numbers (%) of patients with proven/probable iCNSD (n = 21, 25%), proven/probable niCNSD (n = 47, 56%), and possible/unclassified CNSD (n = 16, 19%). Details of all individual patients are given in** Table S5**.** *including each one patient with meningoencephalitis by HHV-6 + enterovirus, adenovirus encephalitis, herpes simplex encephalitis + CNS aspergillosis, and *E. faecium* meningitis. **mainly caused by immunosuppressives or anti-infectious agents (specified in Table S5). ***including cerebral bleedings (n = 8, 53.3%), posterior reversible encephalopathy syndrome (PRES, n = 5, 33.3%) and strokes or combined vascular pathologies (n = 2, 13.3%). HHV-6: human herpes virus-6, iCNSD: infectious central nervous system disorder, n: number, niCNSD: non-infectious CNSD.

Parameter	Patients with a CNSD at inclusion (cases, N = 84)	Patients with a proven/probable iCNSD at inclusion (N = 21)	Patients with a proven/probable niCNSD at inclusion (N = 47)	Patients with a possible iCNSD/niCNSD or unclassified CNSD at inclusion (N = 16)	p
CSF analysis[a]					0.016
Done (n, %)	51 (60.7%)	18 (85.7%)	23 (48.9%)	10 (62.5%)	
Not done (n, %)	33 (39.3%)	3 (14.3%)	24 (51.1%)	6 (37.5%)	
CSF WBC (/mm^3)					0.54
Missing (n)	39	3	27	9	
Median, IQR	2 (0.8–11)	2.5 (0.0–5.8)	3 (1.0–38.0)	1 (0.7–6.0)	
CSF protein (mg/L)[b]					0.34
Missing (n)	38	5	26	7	
Median, IQR	405.5 (95.0–762.5)	522 (237.5–1171.8)	399 (230.0–520.0)	412 (7.4–624.0)	
Brain imaging by CT[c] (n, %)					0.031
Missing (n)	35	5	21	9	
Abnormalities	26 (53.1%)	7 (43.8%)	18 (69.2%)	1 (14.3%)	
No abnormalities	23 (46.9%)	9 (56.2%)	8 (30.8%)	6 (85.7%)	
Brain imaging by MRI[c] (n, %)					0.38
Missing (n)	21	0	15	6	
Abnormalities	44 (69.8%)	15 (71.4%)	24 (75.0%)	5 (50.0%)	
No abnormalities	19 (30.2%)	6 (28.6%)	8 (25.0%)	5 (50.0%)	
Brain imaging (MRI vs CT)[c] (n, %)					0.053
Missing (n)	44	5	27	12	
Abnormalities in MRI and CT	21 (52.5%)	7 (43.8%)	14 (70.0%)	0 (0.0%)	
Abnormalities in MRI only	5 (12.5%)	3 (18.8%)	1 (5.0%)	1 (25.0%)	
Abnormalities neither in CT nor in MRI	14 (35.0%)	6 (37.5%)	5 (25.0%)	3 (75.0%)	

Shown are numbers of evaluable patients per outcome category (n, %) or medians (IQR). Patients missing from the total were not evaluable. p-Values are calculated via the X^2 test for categorical variables (or Fisher's exact test if the minimal expectancy requirement was failed) and the Wilcoxon rank sum test for continuous variables. CSF: cerebrospinal fluid, CT: computed tomography, iCNSD: infectious central nervous system disorders, MRI: magnetic resonance imaging, n: number, niCNSD: non-infectious CNSD, WBC: white blood cell count. [a]CSF opening pressure was determined in only one patient. [b]CSF albumin was recorded in 2 patients. [c]Restricted to abnormalities related (or presumably related) to the CNSD. CSF characteristics did also not differ significantly if only allogeneic HSCT recipients were analysed. Presence of brain abnormalities by CT remained significantly different between the 3 groups in this specific cohort (44% vs 74% vs 14%, p = 0.011). Evidence of abnormalities in MRI and CT vs abnormalities in MRI only was also significantly different between the 3 groups if analysing only allogeneic HSCT recipients (44% and 19% vs 77% and 0% vs 0% and 25%, p = 0.015).

Table 2: **Characteristics of CNSD.**

human herpes virus-6 (HHV-6) CNS disease (median 31 days) and neurotoxoplasmosis (median 73 days, p = 0.048, Table S7). In contrast, the difference in median onset times after HSCT between different types of proven/probable niCNSD was not statistically significant (Table S7).

Different clinical symptoms related or presumably related to the CNSD included sensory symptoms (n = 39, 46%), headache (n = 29, 35%), alteration of the level of consciousness (n = 16, 19%), fever (n = 16, 19%), paresis (n = 13, 15%), seizures (n = 12, 14%), psychosis (n = 8, 10%), and others (n = 36, 43%, Table S8).

The onset was acute in 66 (79%) patients and progressive (i.e., non-acute, usually over several days) in 18 (21%). The majority of CNSD (n = 84) were treated with anti-infectious agents (n = 31, 37%), followed by reduction of immunosuppression (n = 29, 35%), neurosurgical intervention (n = 3, 4%), or other treatment modalities (n = 6, 7%, Table S9).

Thirty days after study inclusion (day +30), 54 of 80 evaluable cases (68%) had resolved or improved, and 13 (16%) had ongoing or progressive symptoms. Ten patients (12%) died of the CNSD, and three (4%) died of other causes (Table S10). Hereby, patients with proven/probable niCNSD or possible/unclassified CNSD more frequently resolved or improved CNS symptoms (77% and 80%, respectively) compared to patients with a proven/probable iCNSD (38%). Conversely, the latter had more frequently ongoing CNSD symptoms (29% vs 14% vs 7%) or died because of the CNSD 30 days after study inclusion (24% vs 9% vs 7%, Table S10) (p = 0.036).

By day +30, 22/27 (82%) of children with available data had a resolution or improvement of their CNSD, compared to 32/53 (60%) of adults, though this difference was not statistically significant (p = 0.15, Table S11). Twenty-one out of 29 (72%) children were alive at the last follow-up, compared to 27/55 (49%) of adults, but, again, this difference was not statistically significant (p = 0.068). The causes of death did not significantly differ between these groups, either (Table S12).

Comparing controls to the entire case group, OS was lower (p < 0.0001) in cases—84% (95% CI 76–92%) at one month and 53% (95% CI 42–65%) at 24

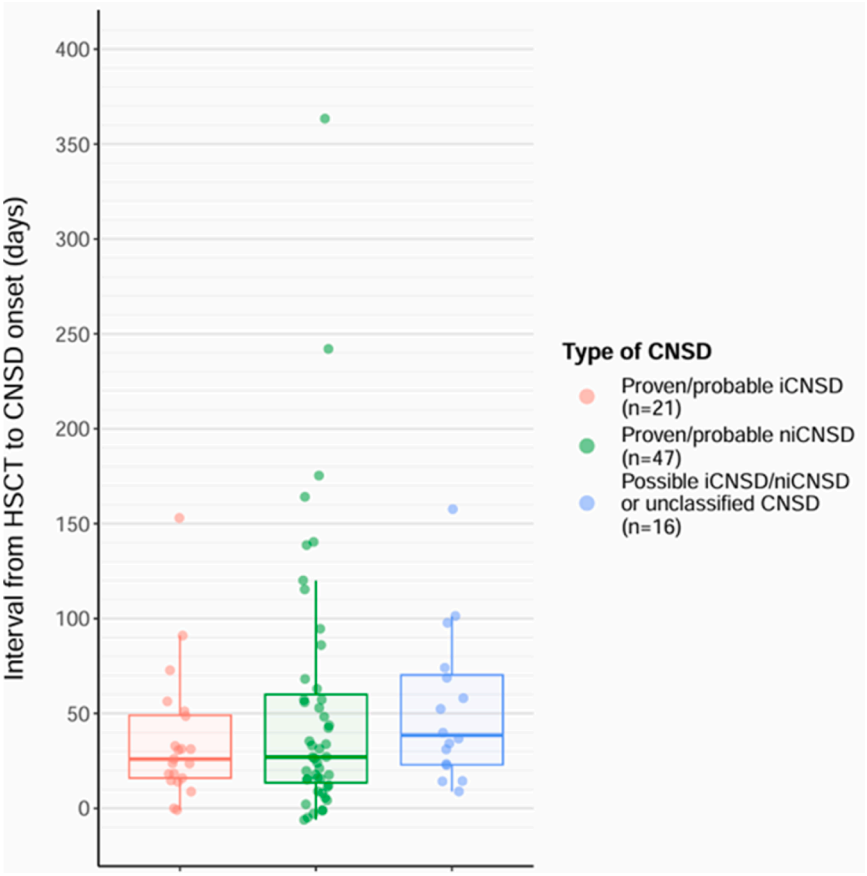

Fig. 2: **Onset times of CNSD (days after HSCT), shown separately for proven/possible iCNSD (n = 21) vs proven/possible niCNSD (n = 47) vs possible iCNSD/niCNSD or unclassified CNSD (n = 16); p = 0.40. The circles represent individual data-points; the box-and-whisker plots summarise the median, quartiles, and truncated range.** A total of 6 cases had a negative time from HSCT to inclusion, e.g., onset between the start of conditioning and HSCT. There was also no significant difference if focussing only on allogeneic HSCT recipients (data not shown). HSCT: haematopoietic stem cell transplantation, iCNSD: infectious central nervous system disorder, n: number, niCNSD: non-infectious CNSD.

months—compared to controls—99% (95% CI 97–100%) and 82% (95% CI 76–89%) at the respective time points (Fig. 3). Hereby, the 24-month OS was higher for controls than for any CNSD subtype: 82% (95% CI 76–89%) vs 32% (95% CI 10–54%) for proven/probable iCNSD patients vs 58% (95% CI 43–73%) for proven/probable niCNSD patients and 66% (95% CI 42–90%) for possible/unclassified CNSD patients ($p < 0.0001$, Fig. 3, Table S13). The same pattern of inferior OS in cases vs controls was observed in the subset of allogeneic HSCT recipients (Fig. 3) as well as the subsets of adults and paediatric patients (Fig. S2). The OS for different patient subgroups (e.g., age categories, HLA matching, use of T cell depletion) is shown in Table S14. Both recipient sex and donor/recipient sex matching had no significant impact on OS (Table S14). Among the 25/153 deceased controls during the study period, the cause of death was most often relapse/progression (17/25 patients, 68%), while cases tended to die of the CNSD itself (15/36 patients, 42%, $p < 0.0001$). Causes of death are shown for the different patient groups in Fig. 4. Among deceased patients, the time to death since inclusion was longer for controls than cases—median 5.6 months (IQR 3.6–7.2 months) vs 1.7 months (IQR 0.5–2.0 months) for proven/probable iCNSD patients, 2.3 months (IQR 1.1–4.3 months) for proven/probable niCNSD patients, and 1.1 months (IQR 0.3–1.4 months) for possible/unclassified CNSD patients ($p = 0.00077$).

A multivariable matched Cox PH analysis found CNSD at inclusion (HR 2.96, 1.13–7.74, $p = 0.027$) to be the only significant predictor of inferior OS when regressed alongside factors such as new-onset CNSD post-inclusion, age, stem cell source and GvHD status at inclusion (Table S15). The same association was found among the subset of 80 allogeneic HSCT case patients and their 145 matched allogeneic controls (HR 3.00, 95% CI 1.15–7.88, $p = 0.025$). CNSD at inclusion

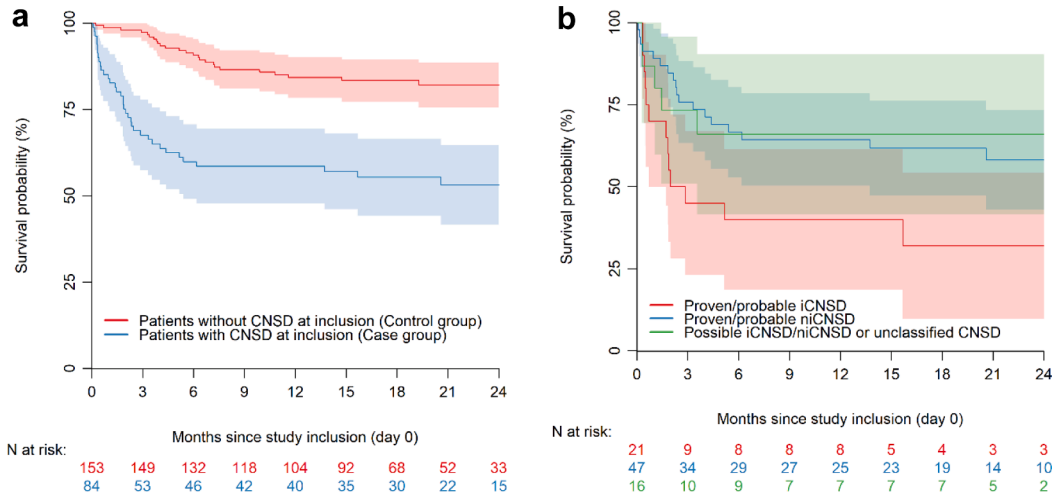

Fig. 3: **(a) Overall survival of patients with a CNSD (n = 84) vs those without at study inclusion (n = 153, p < 0.0001); (b) Overall survival by type of CNSD among patients with a CNSD at inclusion (i.e., case group): proven/probable iCNSD (n = 21), proven/probable niCNSD (n = 47), possible iCNSD/niCNSD or unclassified CNSD (n = 16, p = 0.064). The impact of CNSD on OS in children vs. adults is shown in** Fig. S2**.** CNSD: central nervous system disorder, n: number. The same association between OS and CNSD status at inclusion was found for the subset of allogeneic HSCT recipients (80 cases with 145 matched controls; p < 0.0001 for overall survival, data not shown). For this subset, the 24-month overall survival was 34% (95% CI 11–57%) for proven/probable iCNSD (n = 20), 60% (95% CI 45–76%) for proven/probable niCNSD (n = 44), 66% (95% CI 42–90%) for possible iCNSD/niCNSD or unclassified CNSD (n = 16) and 82% (95% CI 75–89%) for controls (n = 145), p < 0.0001.

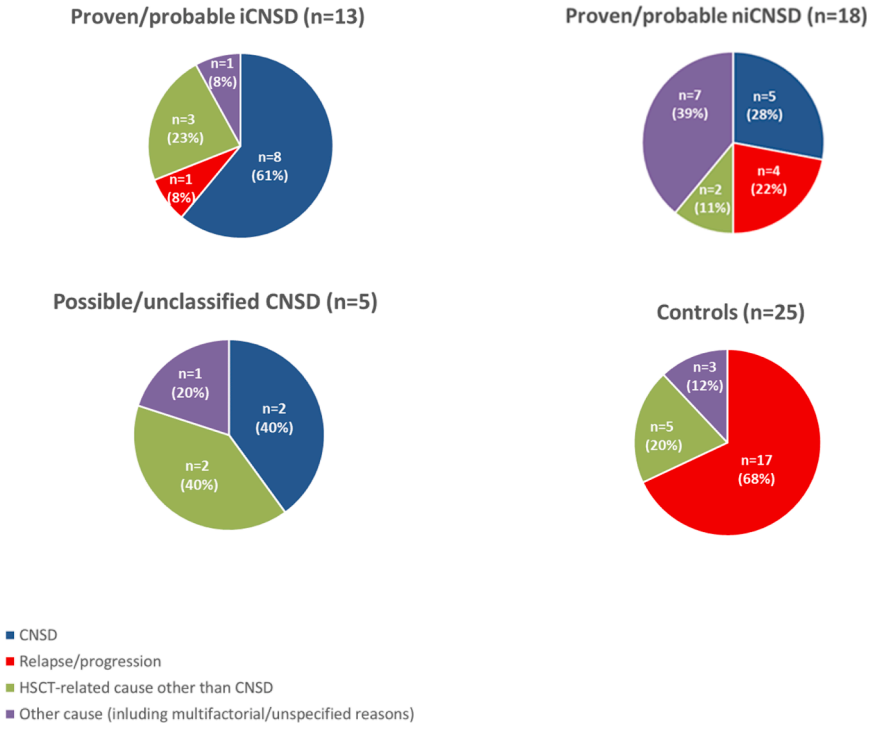

Fig. 4: **Causes of death (at the last follow-up). Shown are numbers and percentages (p < 0.001).** HSCT: haematopoietic stem cell transplantation, iCNSD: infectious central nervous system disorder, n: number, niCNSD: non-infectious CNSD.

also remained the sole significant predictor of inferior OS for the subset of adult patients, HR 2.26 (1.12–4.55), p = 0.023 (analysis not done for the subset of paediatrics due to the small subset size).

The interaction between CNSD at inclusion and several variables including age category, HSCT type, and T-cell depletion in terms of OS was tested. No evidence for interaction effects was found (p > 0.05 for all tests; data not shown).

Nine of 153 controls (6%) developed a new-onset CNSD after study inclusion. New-onset CNSD developed between study inclusion and day +30 (n = 1), between day +30 and day +99 (n = 1) or at day +100 or thereafter of study inclusion (n = 7). Among cases, 10 of 71 evaluable patients (14%) had a new-onset CNSD after study inclusion—eight patients with a proven/probable CNSD and two patients with a possible/unclassified CNSD. All new-onset CNSD in cases were different from the CNSD at inclusion as specified in detail in the Supplementary Material. Hereby, the new-onset CNSD occurred in 9/10 patients up to day +100 and after day +100 in one patient.

The comparison of the cumulative incidence of new-onset CNSD in cases vs controls after study inclusion (Kaplan–Meier plots) is shown in Fig. S3. Fig. S4 shows the cumulative incidence of new-onset CNSD in the total cohort. The 1-year cumulative incidence of new-onset CNSD was calculated at 7% (95% CI 4–11%) for the full set of patients, with the median time-to-onset post-inclusion being 2.5 months (IQR 1.0–4.7 months). It was significantly higher for cases than for controls: 13% (95% CI 5–20%) vs 5% (95% CI 1–8%), p = 0.042 (Fig. S3).

New-onset CNSD for different patient subgroups (e.g., age categories, HLA matching, use of T cell depletion) are shown in Table S14. Both recipient sex and donor/recipient sex matching had no significant impact on new-onset CNSD (Table S14). In a multivariable, cause-specific Cox PH model, the presence of CNSD at inclusion remained a statistically significant parameter for new-onset CNSD—HR 8.88 (95% CI 1.93–40.90, p = 0.0051). This was also the case for the subset of allogeneic HSCT recipients (data not shown). In contrast, the presence of any comorbidity at inclusion was not significant (HR 0.15, 95% CI 0.01–3.62, p = 0.24).

Among cases, the 1-year cumulative incidence of new-onset CNSD after study inclusion was 0% for patients with proven/probable iCNSD, 17% (95% CI 5–28%) for patients with proven/probable niCNSD, and 17% (95% CI 0–38%) for patients with possible/unclassified CNSD (p = 0.16). Additionally, there was no significant difference between adults and children when focussing this analysis on cases—the 1-year cumulative incidence was 17% (95% CI 2–32%) for children vs 11% (95% CI 2–19%) for adults (p = 0.70).

Among cases who died and who had a new-onset CNSD after study inclusion, the causes of death were the CNSD (n = 2), HSCT-related causes other than the CNSD (n = 1), and other/unspecified causes (n = 1). Among controls who died and who had a new-onset post-inclusion CNSD, causes of death were relapse/progression (n = 2) or other/unspecified causes (n = 2). The course of the 19 patients who had new-onset CNSD is shown in Fig. S5.

Cases vs controls had a higher likelihood of having any pre-existing comorbidity prior to HSCT (58/84 patients, 69% vs 66/153 patients, 43%, p = 0.00023, Table 1), including nervous system diseases (20/84 patients, 24% vs 14/153 patients, 9%, p = 0.0039, Table S2).

Among the 80 allogeneic HSCT cases together with their 145 allogeneic HSCT controls, the donor was more frequently mismatched and related in the case than in the control group (26/75 patients, 35% vs 27/138 patients, 20%, p = 0.049), besides the presence of any comorbidity, patient location at inclusion and the ECOG-PS (Table 1). Finally, gastrointestinal, hepatic, and metabolic comorbidities at study inclusion were significantly more frequently recorded in cases than in controls (Table S2).

The percentage of patients with acute or chronic GvHD did not differ statistically between cases and controls (Table 1). Similarly, no statistically significant differences were observed between the groups when comparing the distribution of acute and chronic GvHD grades individually (Table S3).

Cases had statistically significantly higher median serum concentrations for glucose and bilirubin at the study inclusion time point. In contrast, median serum concentrations were significantly lower for total protein, albumin, sodium, potassium, and calcium compared to the controls (Table S4). The median platelet count was also significantly lower at inclusion in cases than in controls. In contrast, no significant differences were observed for other blood values.

Discussion

Prospective studies on CNSD after HSCT, including a control group, are lacking. In this large prospective comprehensive case–control observational study, we analysed 84 patients with a CNSD and compared them to 153 controls lacking a CNSD between HSCT and study inclusion.

Few data have been published on the frequency of CNSD after HSCT. A retrospective study including patients with different high-risk haematological malignancies who underwent allo-HSCT over a 20-year period estimated the incidence of CNS complication at 17% during a median follow-up of 6.8 years.[15] We estimated the frequency of CNSD at 4.6% (95% CI

3.7–5.7%) for allogeneic and 0.3% (95% CI 0.1–0.9%) for autologous HSCT recipients. The higher frequency of new-onset CNSD in controls after study inclusion (6%) than the estimated overall frequency of CNSD based on the number of cases (3%) might be explained by the fact that controls were more closely followed with attention to CNSD than the total number of transplanted patients included in the estimation.

Effective strategies to prevent neurological complications in the current era of transplantation might have contributed to this lower incidence, in addition to the fact that the current prospective study focused on the early phase after HSCT.

Of the 84 cases, 21 patients (25%) had a proven/probable iCNSD, 47 patients (56%) had a proven/probable niCNSD, and 16 (19%) had a possible iCNSD/niCNSD or an unclassified CNSD. Thus, our data confirm previously published analyses showing that niCNSD are more frequent than iCNSD after HSCT.[3] The most frequent proven/probable iCNSD was HHV-6 iCNSD, while chromosomally integrated HHV-6 was not excluded in all these patients. A previous older prospective study, including patients with a CNSD following HSCT between 2000 and 2002, found neuro-aspergillosis prevailing among iCNSD.[3] These data led to the assumption that the broad use of antifungal prophylaxis after HSCT with agents characterised by a better CNS penetration (such as voriconazole and isavuconazole)[5,6] might effectively have reduced the incidence of cerebral invasive fungal disease. Contrasting our findings of a preponderance of HHV-6 iCNSD, others found Epstein–Barr Virus (EBV) to be the most frequent viral CNS infection after HSCT.[16] This discrepancy might be explained by the highly effective and increasing preemptive use of rituximab in patients with EBV viraemia after allo-HSCT,[17,18] besides the guidelines' recommendation for regular EBV PCR screening after high-risk allo-HSCT.[19]

The most frequent proven/probable niCNSD were vascular events (n = 15, 32%)—comprising bleeding in eight patients, posterior reversible encephalopathy syndrome (PRES) in five patients, and strokes or combined vascular pathologies in two patients. This indicates that cerebral bleeding still occurs in high-risk HSCT recipients, despite prophylactic platelet transfusion being recommended in patients after (allo-) HSCT by different societies, including the American Society of Clinical Oncology (ASCO).[20] Novel algorithms to predict CNS vascular diseases, in particular cerebral bleeding, might aim to predict and prevent cerebral vascular events in HSCT recipients in the future.

The second most frequent proven/probable niCNSD (n = 13, 28%) were drug-induced CNSD (e.g., caused by antimicrobials or immunosuppressive agents such as cyclosporine or tacrolimus). Therefore, the development of novel drugs with an optimised toxicity profile, particularly related to CNS complications (such as the use of isavuconazole instead of voriconazole), is warranted. A reduced incidence of CNSD in allo-HSCT recipients with calcineurin-free GvHD prophylaxis has been reported just recently.[21]

The spectrum of CNSD differed significantly between adults and children. Children were more commonly categorised as having a proven/probable niCNSD (66% vs 51% for adults) or unclassified CNSD (28% vs 15%) but less frequently as having a proven/probable iCNSD (7% vs 35%, p = 0.016).

The median CNSD onset time among all cases was 31 days (IQR 15–57 days) without a statistically significant difference between patients with proven/probable iCNSD, proven/probable niCNSD, and possible/unclassified CNSD. In another EBMT-based prospective study recruiting patients after HSCT between 2000 and 2002, CNSD generally occurred later (median 101 days for iCNSD and 50 days for niCNSD).[3] Possible reasons for the earlier onset times may include increased awareness and the broad availability of modern diagnostics (e.g., PCR, neuroimaging), also elucidating subtle neuropathologies in the early phase after transplantation. The current study also found that among patients with proven/probable iCNSD the earliest infection was CNS aspergillosis, followed by HHV-6 (meningo-)encephalitis and neurotoxoplasmosis.

Abnormalities were detected by brain CT and/or MRI in 26 of 40 patients (65%) investigated by both methods. Hereby, CNS abnormalities were detected by MRI and not CT in five of the 26 patients with abnormalities (19%), whereas MRI also detected all abnormalities detected by CT. These observations confirm previous findings[22] and guidelines' recommendations[23] to perform preferentially brain MRI (and not only CT) if a CNS pathology is suspected after HSCT, whenever feasible.

We found that CNSD after HSCT were associated with a large variety of clinical symptoms—including both focal (e.g., seizures, strokes) and non-focal abnormalities (such as consciousness disturbances)—urging a high level of vigilance and timely initiation of adequate diagnostics and treatment in the clinical routine.

Furthermore, at 30 days after inclusion, the CNSD resolved or improved more frequently in children (82%) than in adults (60%), while the latter died more frequently from the CNSD until this time point (17% vs 4%). Superior outcomes of both iCNSD[24] and niCNSD[25] for children compared to adults have already been suggested for non-transplant populations.

OS after study inclusion was statistically significantly worse in cases than in controls and lower in patients with proven/probable iCNSD than in those with proven/probable niCNSD (32% vs 58% at 24 months). A grade 3 or 4 ECOG score was more frequently recorded in cases than controls, though this

wasn't a significant predictor of OS in the multivariable analysis. CNSD at inclusion was the sole predictor of inferior OS upon multivariable analysis. Besides this, CNSD itself was the most frequent cause of death among cases, while for controls this was relapse.

There is limited reliable data on risk factors for CNSD after HSCT, as the majority of published studies are retrospective and did not include a control group of patients without CNSD after HSCT. We found that a pre-existing nervous system disease—comprising vascular and non-vascular pathologies—was associated with the occurrence of CNSD after transplant, besides other factors such as a low platelet count.

Limitations of this study include, among others, the fact that full enrolment was not achieved as initially intended (likely at least in part due to the COVID-19 pandemic). Besides this, neither the case nor the control group was fully homogenous. However, the present study is one of the largest and most sophisticated prospective studies on CNS complications after HSCT and required the participation and challenge of different transplant centres globally. Besides this, to the best of our knowledge, this is the only study including a prospectively evaluated control group with individual CNSD cases together with their two controls matched to the time period after HSCT. Furthermore, different subgroup analyses were performed (e.g., examining interactions between predictor variables and a subgroup analysis focused on allogeneic HSCT recipients only) to check the impact of heterogeneity. Finally, a patient population including children and adults, who received either autologous or allogeneic HSCTs, reflects the real-world diversity of the transplant population. As such, our results and conclusions might be more generalisable than they would be had we selected a more homogeneous case group.

In conclusion, CNSD still represent a clinically relevant complication in patients after HSCT. Hereby, non-infectious causes prevail over CNS infections. A pre-existing nervous system disease prior to HSCT is associated with the development of a CNSD after HSCT. Patients with a CNSD after HSCT have a reduced OS, and the CNSD itself is the cause of death in around 40% of deceased patients. Patients with a proven/probable iCNSD have a worse outcome than those with a proven/probable niCNSD. Novel diagnostics (such as CSF NGS), algorithms, adapted transplant procedures and treatment modalities (e.g., new anti-infectious agents) may help to reduce morbidity and mortality from this complication.

Contributors

MSH: designed the research project, wrote the first manuscript version; PTL, DA, JS, and RDLC: designed the research project; PG: performed the statistical analyses, directly accessed and verified the underlying data in this manuscript; NK: documented and analysed data, directly accessed and verified the underlying data in this manuscript; all other authors: contributed patient data and/or were involved in data analyses and interpretation; all authors: reviewed and approved the final manuscript version.

Data sharing statement

On request selected individual participant data and further documents such as the study protocol, case report files, etc. will be available.

Declaration of interests

K.C. received payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Polish Stem Cell Bank, Gilead Sciences Poland; support for attending meetings/travel from the Polish Stem Cell Bank.

All other authors: no COI related to this work.

Acknowledgements

We thank all HSCT centres and patients and their families for participating in this study.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2026.103792.

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