ORIGINAL ARTICLE

Eastern Journal of Medicine

East J Med 27(3): 437-445, 2022
DOI: 10.5505/ejm.2022.54765

Evaluation of Neurological Imaging After Hematopoietic Stem Cell Transplantation In Adults

Sevil Sadri[1*], Burcu Polat[2], Berrin Balik Aydin[1], Hakan Kocar[1], Aliihsan Gemici[1], Huseyin Saffet Bekoz[1], Omur Gokmen Sevindik[1], Fatma Deniz Sargin[1]

[1]Department of Hematology, Istanbul Medipol University School of Medicine Istanbul, Turkey
[2]Department of Neurology, Istanbul Medipol University School of Medicine Istanbul, Turkey

ABSTRACT

To investigate the risk factors for, and the incidence of, structural abnormalities in brain imaging among hematopoetic stem cell transplant (HSCT) patients and to correlate these findings with physical examinations.
This study retrospectively reviewed all post-HSCT brain imaging taken in the researchers' center between 2014 and 2020.
87 of 627 transplant patients were imaged. 34.5% (n = 30) were female. Age at transplant ranged from 18 to 74 years (median: 45). The most common malignancies were acute myeloid leukemia (AML; n = 21; 24.1%), 51 (58.6%) patients received allogeneic transplantation, and 36 (41.4%) received autologous transplantation. The imaging techniques were dispersed as follows: magnetic resonance imaging (MRI): 83.9% (n = 73), brain computed tomography (CT): 37.9% (n = 33), diffusion MRI: 19.5% (n = 17). 39.1% of the radiological images were normal; 20.7% showed disease recurrence; and 14.9% detected ischemic gliotic lesions. According to the imaging results, there was a statistically significant difference between age values (p = 0.013). Patients with PRES were younger than those with no pathologies in their imaging, while patients with infarcts and ischemic gliotic lesions were older than those with normal imaging (p = 0.001). Patients with disease recurrence were older than those with PRES but younger than those with infarctions (p = 0.001).
Neurological complications are not uncommon in transplant cases. In managing transplantations, it should be remembered that the presence of radiologically positive findings, especially positives for cerebrovascular complications, can significantly reduce survival.

Keywords: Brain imaging, neurological complications, hematopoietic stem cell transplantation, cerebrovascular complications

Introduction

Hematopoietic stem cell transplantation (HSCT) is a curative treatment method, which has been applied to many benign and malignant cases in recent years. However, neurological complications developing after HSCT have been reported to be associated with 11–59% of post-HSCT morbidity and mortality (1-4). Risk for transplant related death maybe reduce with early diagnosis and timely treatment. The variable incidences reported are likely due to different criteria used in retrospective studies to define neurological complications. Early diagnosis and appropriate treatment greatly affect survival. Currently, the neurological complications of HSCT patients are investigated and managed via brain computed tomography (CT), magnetic resonance imaging (MRI), and diffusion MRI. Early post-transplant clinical findings are convulsion, headache, paralysis, and paresthesia (5-6). Systemic infections, microangiopathy, cerebrovascular lesion, hemorrhage, ischemia, and posterior reversible encephalopathy syndrome (PRES) are also seen in radiological clinical findings (7). Cyclosporine-related neurotoxicity has been reported as one of the most common neurological complications (8-9). Neurologic complications after HSCT are frequently life-threating and their diagnosis and management can be highly challenging. Therefore, this study retrospectively examined the neurological symptoms and imaging of patients who underwent autologous or allogeneic stem cell transplantation in the authors' center between 2014 and 2020, including the patients' histories of cranial radiotherapy, preparation regimens, and the relationship between the drugs used in graft versus host disease (GVHD) prophylaxis and neurological complications. In our study we aimed to examine

*Corresponding Author: Sevil Sadrı, Department of Hematology, Istanbul Medipol Universty School of Medicine, Bagcilar, 34214, Istanbul, Turkey
E-mail: sevilsadri@hotmail.com, Phone: +90 (536) 973 03 94
ORCID ID: Sevil Sadri: 0000-0002-6315-9620, **Burcu Polat:** 0000-0002-4104-8508, **Berrin Balik Aydin:** 0000-0001-6826-7818, **Hakan Kocar:** 0000-0001-6869-7682, **Aliihsan Gemici:** 0000-0002-3385-8359, **Huseyin Saffet Bekoz:** 0000-0003-1237-8281, **Omur Gokmen Sevindik:** 0000-0001-9636-4113, **Fatma Deniz Sargin:** 0000-0002-1077-8540
Received: 04.09.2020, **Accepted:** 11.04.2022

the frequency of these post-HSCT neurological complications and investigate the frequency and characteristics of neurological symptoms in these cases and also to investigate their correlation with other parameters.

Materials and Methods

Between January 2014 and September 2020, 627 patients underwent autologous or allogeneic stem cell transplantation and received neurological consultation at the researchers' center. This study retrospectively examined the files of 87 of these patients who had developed neurological complications during or after HSCT. Neurological symptoms presented before transplantation were not considered. The following points were recorded from the patients' files:

1. Demographic characteristics of the cases, including disease type and history of radiotherapy (RT) for the central nervous system (CNS) during diagnosis and follow-up.
2. Administration of:
    a. The high-dose, busulfan-containing, myeloablative regimen used in transplant preparation.
    b. Non-myeloablative regimens.
    c. Myeloablative regimens with total body irradiation (TBI).
    d. Thiotepa-based regimens.
    e. Melphalan-based regimens in autologous patients.
    f. BEAM (carmustine, etoposide, cytarabine, melphalan) regimens.
    g. BeEAM (bendamustine, etoposide, cytarabine, melphalan) regimes. (Those who received these regimens were recorded in seven groups.)
3. Drugs used in GVHD profiles.
4. Electromyography (EMG) and electroencephalography (EEG) findings, which were evaluated in line with neurological consultations.
5. Platelet and neutrophil engraftment days. (Their relationships with neurological imaging were examined.)
6. Neurological symptoms emerging during follow-up.
7. Timing of symptoms.
8. Neurological consultation.
9. Neurological examination findings.
10. Radiological evaluations (CT, MRI, diffusion MRI).
11. Neurological diagnoses received.
12. Positive findings, such as bleeding, infarction, thrombosis, and PRES detected in the neuroradiological examinations.
13. The patient's last recorded living status, if the patient had died.
14. Comorbidities.
15. Frequency of physical examination findings and pathologies detected via imaging. (The relationships between these variables were compared).

This study was conducted with the approval of the ethics committee at the authors' center.

Statistical Analysis: The 2007 version of the Number Cruncher Statistical System (NCSS; Kaysville, Utah, USA) program was used for statistical analysis. While evaluating the study data, in addition to descriptive statistical methods (mean, standard deviation, median, frequency, ratio, minimum and maximum), the distribution of the data was evaluated using the Shapiro–Wilk test. The Kruskal–Wallis test was used to compare three or more groups that did not show a normal distribution of quantitative data, and the Mann–Whitney U test was used to compare two groups that did not show normal distribution. A chi-squared test was employed to determine the relationship between categorical data. Significance was evaluated as $p < 0.05$.

Results

In total, 87 of 627 transplant patients were imaged. 34.5% (n = 30) were female, while 65.5% (n = 57) were male. The most common reasons for transplantation were acute myeloid leukemia (AML; n = 21; 24.1%), acute lymphoblastic leukemia (ALL; n = 19; 21.8%), and multiple myeloma (n = 15; 17.2%). 51 (58.6%) patients underwent allogeneic transplantation, while 36 (41.4%) received autologous transplantation. The disease distribution findings of all cases are summarized in Table 1.

The transplant age ranged from 18 to 74 (median: 45 years; mean; 43.6 ± 15.32). The thrombocyte (platelet) engraftment (day) values ranged from 8 to 162 days (median: 15; mean: 24.58 ± 22.99). The neutrophil engraftment (day) value ranged from 9 to 39 days (median: 15; mean: 16.52 ± 5.8).The platelet value at the time of imaging ranged from 6 to 334 days (median: 47; mean: 83.02 ± 74.88). Imaging was performed on days 2 to 1,513 (median: 49 days; mean: 170.92 ± 294.17) post-HSCT. (Table 2)

Table 1. Descriptive Statistics For Categorical Variables

	n	%
Diagnosis		
Acute Myeloid Leukemia	21	24.1
Acute Lymphoblastic Leukemia	19	21.8
Multiple Myeloma	15	17.2
Non-Hodgkin's Lymphoma	15	17.2
Hodgkin's Lymphoma	6	6.9
Central Nervous System Lymphoma	2	2.3
Thalassemia Major	1	1.1
Testicular Tumor	1	1.1
Myelodysplastic Syndrome	3	3.4
Aplastic Anemia	1	1.1
Medulloblastoma	1	1.1
Primer Myelofibrosis	1	1.1
Adrenoleukodystrophy	1	1.1
Condition Regimen		
Myeloablative	15	17.2
Non-Myeloablative (RIC)	20	23.0
BeEAM	9	10.3
BEAM	9	10.3
Melphalan	14	16.1
Total Body Irradiation	16	18.4
Thiotepa	4	4.6
Symptom		
Headache	28	32.2
Double Vision	11	12.6
Syncope	4	4.6
Convulsions	11	12.6
Confusion	12	13.8
Dizziness	3	3.4
Weakness	9	10.3
Facial Paralysis	7	8.0
Hearing Loss	2	2.3
EMG vs EEG Results		
Not taken	51	58.6
Polyneuropathy	9	10.3
Guillan barre	3	3.4
Normal	3	3.4
Toxic	12	13.8
Seizure	5	5.7
Radiculopathy	4	4.6
Neuroimaging Results		
Normal	34	39.1
PRES	3	3.4
Ischemic Gliotic Lesion	13	14.9
Hemorrhage	9	10.3

Disease Involvement	18	20.7
Infarct	5	5.7
Sinus Vein Thrombosis	1	1.1
Diffuse Leukoencephalopathy	4	4.6
Peripheral Stem cells	81	93.1
Other received bone marrow stem cell	6	6.9
GVHD prophylaxis		
Cyclosporine	45	51.7
mycophenolate mofetil	1	1.1
no medications	36	41.4
Other	5	5.7
Ex	45	51.7
Alive	42	48.3

BEAM Carmustin, Cytarabin, etoposid, melphalan,
BeEAM: bendamustin, Cytarabin, Etoposid, Melphalan
Myeloablative: busulfan, cyclophosphamide

The following symptoms were present during follow-up: headaches (n = 28; 32.2%), confusion (n = 12; 13.8%), seizures (n = 11; 12.6%), weakness (n = 9; 10.3%), facial paralysis (n = 7; 8%), diplopia (n = 11; 12.6%); syncope (n = 4; 4.6%), dizziness (n = 3; 3.4%), and hearing loss (n = 2; 2.3%)(Tablo-3)

The imaging techniques were dispersed as follows: MRI: 83.9% (n = 73), EMG: 41.4% (n = 36) CT: 37.9% (n = 33), diffusion MRI: 19.5% (n = 17), and EEG: 14.9% (n = 13). While 58.6% (n = 51) of the patients did not undergo EMG or EEG, the remaining 41.4% (n = 36) exhibited the following symptoms: PNP: 10.3% (n = 9), toxicity: 13.8% (n = 12), seizures: 5.7% (n = 5), radiculopathy: 4.6% (n = 4), and Guillain-Barré syndrome: 3.4% (n = 3). The remaining 34% (n = 39.1) returned normal results. (Table-1)

39.1% of the radiological images were normal; 20.7% showed disease recurrence; and 14.9% detected ischemic gliotic lesions. (Table-1)

The conditioning regimen was evaluated across seven groups(tablo-1). Most patients received peripheral stem cells (n = 81; 93.1%), while others received bone marrow stem cells (n = 6; 6.9%). 8% of the patients (n = 7) had a history of cranial RT before transplantation (Table-1)

For GVHD prophylaxis, 51.7% (n = 45) received cyclosporine; 1.1% (n = 1) received mycophenolate mofetil; 41.4% (n = 36) received no medications; and 5.7% (n = 5) received other drugs (e.g., antithymocyte globulin [ATG], Rituximab). (Table-1)

51.7% (n = 45) of the patients died, but 48.3% (n = 42) are still alive. Concerning comorbidities, 60.9% (n:53)had none. Physical examination results were normal in 47.1% of the patients (n = 41), while paresthesia and ataxia were found in 4.6% (n = 4) and 2.3% (n = 2), respectively. (Table 4)

The relationships between the neuroimages taken as a result of symptom evaluations are present in Table 3. There were no statistically significant relationships between the symptoms and the neuroimaging results ($p > 0.05$).

Symptomatic patients were physically examined by a neurologist. The results were recorded, and the relationships between the physical examinations and the neuroimaging were evaluated (Table 4). In the outcome variable of individuals with normal physical activity, the incidence of normal (48%), ischemic gliotic lesion (19.5%) and recurence (12.2%) was found to be higher than the other results. There were no statistically significant relationships between the Physical Examination and outcomes.

Table 5 compares the imaging results with thrombocyte engraftment and neutrophil engraftment day and age. Neutrophil engraftment was defined as two of three consecutive days with a neutrophil count of 0.5×10^9/L, while thrombocyte engraftment was defined as the first of three consecutive days with a platelet count of 20×10^9/L without platelet transfusion in the last seven days.

According to the imaging results, there were no statistically significant differences between the platelet engraftment day values or the neutrophil engraftment days.

However, there was a statistically significant difference between age values ($p = 0.07$)

Table 2. Descriptive Statistics For Numerical Variables

	mean±SD	Min-max (Median)
The transplant age	43.6 ± 15.32	18-74 (45)
thrombocyte (platelet) engraftment (day)	24.58 ± 22.99	9-39 (15)
The neutrophil engraftment (day)	16.52 ± 5.8	6-334 (15)
The platelet value at the time of imaging	83.02 ± 74.88	6-334 (47)
Imaging was performed on days	170.92 ± 294.17	2-1513 (49)

Table 3. Relationships between Neuroimaging Results

	normal	PRES	Ischemic gliotic lesion	Bleeding	Reccurence	Infarct	Thrombosis	Leukoencep halopathy	p
Symptoms									
Headache	15 (44,1)	1 (33,3)	5 (38,5)	2 (22,2)	4 (22,2)	0 (0)	1 (100)	0 (0)	0.199
Double_vision	3 (8,8)	0 (0)	1 (7,7)	0 (0)	6 (33,3)	0 (0)	0 (0)	1 (25)	0.193
Syncope	1 (2,9)	0 (0)	1 (7,7)	1 (11,1)	0 (0)	1 (20)	0 (0)	0 (0)	0.312
Convulsion	3 (8,8)	2 (66,7)	1 (7,7)	0 (0)	2 (11,1)	2 (40)	0 (0)	1 (25)	0.060
Confusion	3 (8,8)	0 (0)	2 (15,4)	3 (33,3)	3 (16,7)	0 (0)	0 (0)	1 (25)	0.526
Dizziness	2 (5,9)	0 (0)	1 (7,7)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0.830
Weakness	4 (11,8)	0 (0)	0 (0)	1 (11,1)	2 (11,1)	1 (20)	0 (0)	1 (25)	0.650
Facial_Paralysis	3 (8,8)	0 (0)	1 (7,7)	2 (22,2)	0 (0)	1 (20)	0 (0)	0 (0)	0.404
Hearing_Loss	0 (0)	0 (0)	1 (7,7)	0 (0)	1 (5,6)	0 (0)	0 (0)	0 (0)	0.487

p values were obtained from Fisher-Exact test

In this study, the following results were found at statistically significant levels. Patients with PRES were younger than those with no pathologies in their imaging, while patients with infarcts and ischemic gliotic lesions were older than those with normal imaging ($p = 0.001$). Patients with PRES were also younger ($p = 0.001$) than those with ischemic gliotic lesions, infarcts, disease recurrence, and diffuse leukoencephalopathy. Patients with disease recurrence were older than those with PRES but younger than those with infarctions ($p = 0.001$).

According to symptoms, platelet and neutrophil engraftment day parameters are compared

No statistically significant relationships were found between platelet or neutrophil engraftment and symptoms ($p > 0.05$).

We also compares the relationships between the physical examination findings, determined by the neurologist, and the drugs used for GVHD prophylaxis after transplantation.

There was no statistically significant relationship between the first examination and the drugs ($p> 0.05$). PRES was not seen in women, but it was seen in three (3.4%) male patients. Hemorrhage was also seen more often in males (9.2%). Although disease recurrence happened twice as often in men, no statistically significant relationship was found between gender and outcome ($p > 0.05$). While imaging was found to be mostly normal in AML patients, recurrence was detected in ALL (6.9%) and AML (4.6%) patients. However, no statistically significant relationships were found between symptoms and diagnoses ($p > 0.05$).

Discussion

Although neurological complications are important adverse events in HSCT, their incidence and severity vary widely in the extant literature. In the present study, positive findings were detected in 60.9% of the neuroimages disease recurrence 20.7%, ischemic gliotic lesion

14.9%, hemorrhage 10.3%,, infarct 5.7%, diffuse leukoencephalopathy 4.6%, PRES 3.4%, sinus vein thrombosis 1.1%, Weber et al. (3) report, in their retrospective study, that HSCT-related neurological complications were detected at a 24% prevalence rate over 3.5 years, and the current researchers believe that this difference in percentages occurred because Weber et al. scanned patients for a longer period of time. Dowling et al. (10) report the incidence of

Table 4. Relationships between Physical Examination and Neuroimaging Results

	normal	PRES	Ischemic gliotic lesion	Bleeding	Reccurence	Infarct	Thrombosis	Leukoencephalopathy	p
Physical Examination									
Normal	20 (48.8)	3 (7.3)	8 (19.5)	3 (7.3)	5 (12.2)	0 (0)	1 (2.4)	1 (2.4)	0.015
Paresthesia	1 (25)	0 (0)	0 (0)	0 (0)	2 (50)	1 (25)	0 (0)	0 (0)	0.425
Ataxia	1 (50)	0 (0)	0 (0)	0 (0)	0 (0)	1 (50)	0 (0)	0 (0)	0.424
Anisocoria	1 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0.999
Tremor	0 (0)	0 (0)	0 (0)	0 (0)	1 (100)	0 (0)	0 (0)	0 (0)	0.609
Dilated Pupils	0 (0)	0 (0)	0 (0)	1 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0.253
Facial Nerve Paralysis	2 (28.6)	0 (0)	1 (14.3)	1 (14.3)	3 (42.9)	0 (0)	0 (0)	0 (0)	0.839
Low foot	1 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0.995
N. Abducens Paralysis	1 (25)	0 (0)	0 (0)	0 (0)	2 (50)	0 (0)	0 (0)	1 (25)	0.340
Loss of Muscle Strength	4 (50)	0 (0)	1 (12.5)	0 (0)	3 (37.5)	0 (0)	0 (0)	0 (0)	0.891
Unconsciousness	1 (10)	0 (0)	1 (10)	2 (20)	2 (20)	3 (30)	0 (0)	1 (10)	0.023
Ptosis	1 (50)	0 (0)	1 (50)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0.686
Bilateral Horizontal Nystagmus	0 (0)	0 (0)	0 (0)	1 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0.253
Paraparesis	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (100)	0.092
Other	1 (33.3)	0 (0)	1 (33.3)	1 (33.3)	0 (0)	0 (0)	0 (0)	0 (0)	0.558

p values were obtained from Fisher-Exact test

neurological complications as 12.2% per year and 14.5% at five years.

In the current research, metabolic encephalopathy resulted in EEGs being taken in 12 (13.8%) patients. Metabolic encephalopathy is often multifactorial, caused by multiple organ dysfunctions, sepsis, and drug toxicity, and treatment is directed at the underlying cause. Dowling et al. (10) have found metabolic encephalopathy in 14 (5.3%) patients.

Most of the drugs used in condition regimens for HSCT are often neurologically toxic. Busulfan frequently causes seizures, but antiepileptic prophylaxis is applied to patients who are prescribed it. Ifosfamide can cause visual and auditory hallucinations and encephalopathy, especially in patients with low albumin levels or in those who have previously received cisplatin (11-12) In our study we also compares the relationships between the physical examination findings, determined by the neurologist, and the drugs used for GVHD prophylaxis after transplantation.There was no statistically significant relationship between the first examination and the drugs ($p > 0.05$).

Cerebrovascular disease (CVO) secondary to ischemia or bleeding is a potentially fatal neurological complication. Coplin et al. [13] have found that 36 (2.9%) of 1,245 bone marrow transplant (autologous and allogeneic) patients developed SVO over three years, and 25 (2.0%) died because of this. In the present study, bleeding was detected in nine (10.3%) patients, infarction in five (5.7%), and sinus vein thrombosis in one (1.1%). A subdural hematoma is a common HSCT complication, often associated with underlying long-term thrombocytopenia, and it can occur in both allogeneic and autologous transplantation.

Previous studies have attempted to identify risk factors for neurological complications. Siegal et al. (14) define female gender and TBI as risk factors for neurological symptoms in the first 100 days after transplantation, reporting a one-year incidence of neurological complications of 23%. In a previous study on pediatric patients, high-dose TBI was identified as a risk factor for CNS complications (15).

In the current research, although PRES, bleeding, and disease recurrence were more common in men, none were statistically significant. PRES developing after allogeneic transplantation has

Table 5. Comparison of Parametres Based On The Results of Views

		n	mean ± SD	Min–Max (Median)	p
Platelet	Normal	31	27.23 ± 24.4	8–142 (20)	0.178
	PRES	3	29.33 ± 14.19	14–42 (32)	
	Ischemic Gliotic Lesion	13	29.85 ± 40.98	13–162 (16)	
	Hemorrhage	8	18.13 ± 5.46	10–27 (17.5)	
	Disease Recurrence	16	18.31 ± 6.02	13–35 (17)	
	Infarct	5	18.2 ± 3.03	15–21 (19)	
	Diffuse Leukoencephalopathy	4	32 ± 17.57	16–57 (27.5)	
Neutrophil	Normal	31	16.94 ± 6.28	10–39 (16)	0.352
	PRES	3	18.67 ± 5.51	15–25 (16)	
	Ischemic Gliotic Lesion	13	15.54 ± 6.16	9–31 (13)	
	Hemorrhage	8	15.25 ± 3.15	10–20 (16)	
	Disease Recurrence	16	18 ± 6.54	10–39 (16)	
	Infarct	5	12.8 ± 1.92	11–16 (12)	
	Diffuse Leukoencephalopathy	4	16.25 ± 5.44	12–24 (14.5)	
Age	abNormal	31	41.35 ± 14.58	18–66 (43)	0.007*
	aPRES	3	20.67 ± 1.15	20–22 (20)	
	bIschemic Gliotic Lesion	13	53.31 ± 8.09	41–70 (52)	
	abHemorrhage	8	41.22 ± 13.73	19–58 (43)	
	abDisease Recurrence	16	40.5 ± 16.09	21–74 (34)	
	bInfarct	5	58.4 ± 12.76	43–69 (67)	
	bDiffuse Leukoencephalopathy	4	47.5 ± 21.76	23–72 (47.5)	

P value was obtained from Kruskal–Wallis Test, Within each column, different letters in superscript indicate significant differences ($p<0.05$) according to the All Pairwise

often been associated with cyclosporine toxicity (16-17-18) Wong et al. (16) have found that PRES, caused by tacrolimus, occurred in 1.6% of their sampled patients. However, PRES developed in three (3.4%) patients in the current study, all of whom were taking cyclosporine. The authors' approach to managing PRES has been to lower blood pressure and reduce cyclosporine dosage or switch to another immunosuppressive regimen.

The current research has also found that neurological complications occurred at a significantly higher rate in younger patients. Bihong et al. (19) and Wiznitize et al. (20) have found similar results in parallel with this study.

This research detected disease recurrence in 18 (20.7%) patients. Wiznitize et al. (20) have found it in 27% of their sampled patients, while Weber et al. (3) have reported it as being very low at 9%. The current authors believe in Weber et al. took their images in the early period, as soon as the symptoms developed.

In the neutropenic period, infections may occur due to bacteria, viruses, or fungi because the host's immune system is compromised, and inflammatory responses may not provide classical clinical clues that these infections are present. In this case, the researchers did not find any CNS infections in any patients. They, therefore, believe that the antibiotics, antivirals, and antifungals, which they administered as prophylaxis, as well as their quick follow-ups with patients and the initiation of appropriate treatment during the transport period, prevented CNS infections from occurring.

High-dose chemotherapy and immunosuppressant drugs can cause leukoencephalopathy, which has been found in 6% of pediatric patients (21). This research also found it in four patients (4.6%), but

their symptoms usually improved within a few weeks.

Multiple organ dysfunctions associated with sinusoidal obstruction syndrome (SOS) may present with encephalopathy, fluid retention, and increased bilirubin (22). No neurological symptoms related to SOS were found in this study.

This research found the following results to be statistically significant. Imaging was performed on days 2 to 1,513 (median: 49 days; mean: 170.92 ± 294.17) post-HSCT.

Patients with PRES were younger than those with no pathology in their imaging, while patients with infarcts and ischemic gliotic lesions were older than those with normal imaging ($p = 0.001$; $p < 0.05$). Patients with PRES were also younger than those with ischemic gliotic lesions, infarcts, disease recurrence, and diffuse leukoencephalopathy ($p = 0.001$; $p < 0.05$). The patients with disease recurrence were older than those with PRES but younger than those with infarctions ($p = 0.001$; $p < 0.05$). This study could identify no modifiable risk factors for neurological complications other than age.

Since thrombocytopenia is caused by transfusion, imaging is done at an early stage to rule out hemorrhage. This study detected bleeding in nine (10.3%) patients, but no significant relationship was found between thrombocyte and neutrophil engraftment and imaging. In general, the researchers could find no correlation between imaging findings, neurological examinations, and clinical indications.

Neurological complications are not uncommon in transplant cases. Neuroradiological evaluations should, therefore, be done as early as possible. When managing transplants, it should be remembered that the presence of positive radiological findings, especially positives for cerebrovascular complications, can significantly reduce survival.

This study is limited by the fact that it was a retrospective study and examined only one patient group. All patients who underwent autologous and allogeneic stem cell transplantation for hematological malignancies in a single institution were included. Although this population is likely to represent many large referral centers, the relevance of the results may be limited given the specific subpopulations of the transplant patients. Also, the low number of patients may not be adequate enough to concretely establish risk factors for neurological complications, such as age.

In conclusion neurological complications, especially CNS complications, continue to be an important source of morbidity and mortality, following the increasing prevalence of transplants in the modern age. Such complications are generally common in the early period after transplantation. Strategies to reduce neurological risks can focus on improving GVHD prophylaxis regimens, as well as on providing supportive therapies, early neurological consultations, and early imaging if necessary.

References

1. Openshaw H (2004) Neurological complications of hematopoietic cell transplantation. In: Blume KG, Forman SJ, Appelbaum FR (eds) Thomas' hematopoietic cell transplantation. Blackwell, Malden, pp 811-823.
2. Saiz A, Graus F (2004) Neurological complications of hematopoietic cell transplantation. Semin Neurol 24:427-434.
3. Weber C, Schaper J, Tibuussek D et al. (2008) Diagnostic and therapeutic implications of neurological complications following pediatric haematopoetic stem cell transplantation. Bone Marrow Transplant 41:253-259.
4. Uckan D, Cetin M, Yigitkanli I et al. (2005) Life-threatening neurological complications after bone marrow transplantation in children. Bone Marrow Transplant 35:71-76.
5. Trullemans F, Grignard F, Van Camp B, Schots R. (2001) Clinical findings and magnetic resonance imaging in severe cyclosporine-related neurotoxicity after allogeneic bone marrow transplantation. Euro J Haematol 67:94-99.
6. Coplin WM, Cochran MS, Levine SR, Crawford SW (2001) Stroke after bone marrow transplantation, frequency, etiology, and outcome. Brain 124:1043-1051,
7. Garrick R (2000) Neurological complications. In: Atkinson K (ed) Clinical bone marrow and blood stem cell transplantation. 2nd edn. Cambridge, Cambridge University Press, pp 958-979.
8. Iguchi A, Kobayashi R, Yoshida M, et al. (1999) Neurological complications after stem cell transplantation in childhood. Bone marrow transplant 24:647-652.
9. Antonini G, Ceschin V, Morino S, et al. (1998) Early neurologic complications following allogeneic bone marrow transplant for

leukemia: a prospective study. Neurology 50:1441-1445.

10. Dowling MR, Li S, Dey BR, McAfee SLI, Spitzer TR, Chen YB, Ballen KK (2018) Neurological complications after allogeneic hematopoietic stem cell transplantation: risk factors and impact. Bone Marrow Transplant 53:199-206.
11. Ajithkumar T, Parkinson C, Shamshad F, Murray P (2007) Ifosfamide encephalopathy. Clin Oncol (R Coll Radiol) 19(2):108-114.
12. Howell JE, Szabatura AH, Hatfield SA, Nesbit SA (2008) Characterization of the occurrence of ifosfamide-induced neurotoxicity with concomitant aprepitant. J Oncol Pharm Pract 14(3):157-162.
13. Coplin WM, Cochran MS, Levine SR, Crawford SW. (2001) Stroke after bone marrow transplantation: frequency, etiology, and outcome. Brain 124(Pt 5):1043-1051.
14. Siegal D, Keller A, Xu W, et al. (2007) Central nervous system complications after allogeneic hematopoietic stem cell transplantation: incidence, manifestations, and clinical significance. Biol Blood Marrow Transplant 13:1369-1379.
15. Faraci M, Lanino E, Dini G, et al. (2002) Severe neurologic complications after hematopoietic stem cell transplantation in children. Neurology 59:1895-1904.
16. Maffini E, Festuccia M, Brunello L, Boccadoro M, Giaccone L, Bruno B (2017) Neurologic complications after allogeneic hematopoietic stem cell transplantation. Biol Blood Marrow Transplant 23:388-397.
17. Wong R, Beguelin GZ, de Lima M, et al. (2003) Tacrolimus-associated posterior reversible encephalopathy syndrome after allogeneic hematopoietic stem cell transplantation. Br J Haematol 122:128-134.
18. Hammerstrom AE, Howell J, Gulbis A, Rondon G, Champlin RE, Popat U (2013) Tacrolimus-associated posterior reversible encephalopathy syndrome in hematopoietic allogeneic stem cell transplantation. Am J Hematol 88:301-305.
19. Chen BT, Orlando Ortiz A, Dagis A, Torricelli Ch, Parker P, Openshaw H. (2019) Brain imaging findings in symptomatic patients after allogeneic haematopoetic stem cell transplantation: correlation with clinical outcome. European Society of Radiology 22:2273-2281.
20. Wiznitzer M, Packer RJ, August CS, Burkey ED (1984) Neurological complications of bone marrow transplantation in childhood. Ann Neurol 16:569-567.
21. Nishiguchi T, Mochizuki K, Shakudo M, Takeshita T, Hino M, Inoue Y (2009) CNS complications of hematopoietic stem cell transplantation. AJR2009;192:1003-1011.
22. McDonald GB (2010) Hepatobiliary complications of hematopoietic cell transplantation, 40 years on. Hepatology