Central Nervous System Infections In Recipients of Solid Organ Transplant

Oscar Morado-Aramburo
The University of Texas Health Science Center at Houston
Leeja Joseph
The University of Texas Health Science Center at Houston
Harmanpreet Kaur
The University of Texas Health Science Center at Houston
Rodrigo Hasbun (rodrigo.hasbun@uth.tmc.edu)
The University of Texas Health Science Center at Houston

Research Article

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Abstract

Background

Central nervous system (CNS) infections are severe and life-threatening complications that can occur in solid organ transplant (SOT) recipients. We describe the epidemiology, clinical presentation, diagnosis, disease course, and outcome of CNS infections in SOT.

Methods

We analyzed data of patients who underwent transplantation from September 2012 to February 2023, diagnosed and treated for CNS infections at our institution in Houston, TX. Data were retrospectively collected from medical charts.

Results

Of 1,345 patients who received a SOT, 30 (2.23%) were diagnosed with CNS infection, with a median age of 63 years, 60% were male. Time to CNS infection onset after transplant in 53.3% of the cases was after the first year. There were 15/30 (50%) cases of fungal infection, 8/30(26.7%) of viral infection, 7/30 (23.3%) of bacterial infection. There were no unknown causes. The most common etiologies were *Cryptococcus neoformans* 14/30(46.6%), and *nocardiosis* 3/30 (10%). On presentation, 22 (73.4%) patients had normal mental status, but 21 (70%) reported headaches, and 18 (60%) were febrile. Abnormal neuroimaging was found in 5 cases (16.6%) on computed tomography (CT)-scans and 10 cases (33.3%) on magnetic resonance imaging (MRI) scans. An adverse clinical outcome on discharge was noticed in 33%, and 6.7% died. Fever was associated with an increased risk of adverse clinical outcomes (OR 11; p=0.018).

Conclusion

The incidence of CNS infections in SOT recipients is low but associated with substantial adverse clinical outcomes. The most common causes are fungal, with no unknown etiologies seen in this study.

INTRODUCTION

Central nervous system (CNS) infections have high morbidity and are one of the most severe and life-threatening complications that can occur in solid organ transplant (SOT) recipients. CNS complications happen in up to 40% of SOT patients; most cases are due to diverse etiologies, from infections to cerebrovascular events, cancer, metabolic disorders, and drug toxicity[1]. Infectious causes are less common, under 10%, and arise at any period after the SOT[2].

Immunosuppressive medications commonly used for transplant rejection prevention increase the risk of infections, particularly those caused by opportunistic pathogens. CNS infections can be due to multiple infectious etiologies, including bacteria, viruses, fungi, and parasites[3,4].

In SOT recipients, CNS infections may present with atypical or nonspecific symptoms with a greater diversity of infectious agents than immunocompetent hosts, making diagnosis challenging. Early recognition and prompt treatment are essential to prevent neurological damage and improve outcomes[5,6]. Managing these infections can be complicated by the need to balance the risks of immunosuppression reduction with the potential for graft rejection. Additionally, drug interactions and toxicity may limit the choice of antimicrobial agents[7,8].

CNS infections in SOT recipients data are limited. There is a scant of studies describing the epidemiology, clinical presentation, and outcome. There are no guidelines for the management of these complications at this moment[8,9]. Herein, we determine an outline of the epidemiology, clinical manifestations, and diagnosis and describe the disease course and outcome.

METHODS

Study Design and Study Population

This single-center study was conducted at Memorial Hermann Texas Medical Center (MH-TMC) in Houston, TX. Our study was approved by the University of Texas Health Science Center Institutional Review Board. The present study included a total of 1,345 patients who underwent transplantation from September 2012 to February 2023. We analyzed data from SOT recipients diagnosed and treated for CNS infections at MH-TMC.

Definition

We defined CNS infection as the presence of a positive cerebrospinal fluid (CSF) culture with a pertinent pathogen or a positive reverse-transcription polymerase chain reaction (RT-PCR) assay from the CSF in association with clinical findings of neurological infection (symptomatology or radiographic evidence and/or pleocytosis, elevated protein and/or decreased glucose at CSF analysis)[1,5]. Additionally, CNS infection was considered if clinical findings of neurological infection were present despite the absence of microbiological identification. In addition, an alternative CNS infection definition was brain space-occupying lesions on imaging with a positive blood culture or brain biopsy culture. Furthermore, one case was deemed to have a CNS infection due to clinical findings of neurological infection consistent with hyperammonemia syndrome secondary to *Ureaplasma urealyticum*, which was positive on an RT-PCR assay on a respiratory specimen. Another case with the isolation of *Staphylococcus pasteuri* in the CSF was included, given the presence of a ventriculoperitoneal shunt associated with clinical findings of CNS infection.

Data Collection

All the data were collected and analyzed from electronic medical records retrospectively. We extracted the following data: demographic information, transplant characteristics, including the type of SOT, deceased or living donor, immunosuppressive therapy, and history of transplant rejection or re-transplantation.

Detailed clinic characteristics of CNS infections were noted, including clinical presentation (neurological signs and symptoms, and Glasgow Coma Scale [GCS]), laboratory and microbiological characteristics, radiological findings, diagnosis and management of CNS infections, and clinical outcomes by using the Glasgow Outcome Scale (GOS).

We categorized the GOS into five, and adverse clinical outcomes were from one to four. One was defined as death, two as a vegetative state, three as severe disability (dependent on assistance in daily living activities), four as moderate disability (independent, and can continue the majority of activities in daily living but cannot partake in work and social activities), and five as good recovery. **Statistical Analysis**

A summary of the study population characteristics and the clinical manifestations at presentation of CNS infections was conducted by descriptive analysis. Continuous variables were reported as median and range, while categorical variables were reported as counts and percentages. The adverse clinical outcomes analysis was conducted by Chi-squared test and ANOVA analysis. A p-value < 0.05 was considered statistically significant. Statistical analyses were executed using the IBM SPSS program, version 29.

RESULTS

Study population

Out of the 1,345 transplanted adult patients, our study included 30 patients with a CNS infection, corresponding to an incidence of 2.23% in ten years. Table 1 shows the baseline characteristics. The median age was 63 years old (range, 32–78 years), and 18 patients (60%) were male. CNS infections occurred with preponderance in renal transplant recipients, with 13 of 30 cases (43.3%), followed by heart (8 cases, 26.7%), liver (6 cases, 20%), lungs (2 cases, 6.7%) and simultaneous pancreas-kidney transplant recipients. A large number of patients received basiliximab (86.7%) as induction therapy and immunosuppressive maintenance therapy with steroids (93.3%), mycophenolate mofetil ([MMF] 80%), tacrolimus (90%). Approximately one-third (36.7%) of patients had an episode of rejection.

Table 1
Baseline Demographic Characteristics of 30 patients with CNS infection

Characteristics	N (%)
Age in years, median (range)	63 (32–78)
Male gender	18 (60)
Race	
White	17 (56.7)
Hispanic	8 (26.7)
African American	4 (13.3)
Asian	1 (3.3)
Type of solid organ transplant	
Kidney	13 (43.3)
Heart	8 (26.7)
Liver	6 (20)
Lung	2 (6.7)
Pancreas-kidney	1 (3.3)
Donor Type	
Deceased	28 (93.3)
Living	2 (6.7)
Induction immunosuppression[a]	
Basiliximab	26 (86.7)
ATG	6 (20)
Maintenance immunosuppression[a]	
Prednisone	28 (93.3)
MMF	24 (80)
Tacrolimus	27 (90)
Azathioprine	2 (6.7)
Other[a]	3 (10)
History of transplant rejection[c]	11 (36.7)

Characteristics	N (%)
History of re-transplantation[c]	1 (3.3)

Abbreviations: ATG, Antithymocyte globulin; MMF, Mycophenolate mofetil.

[a]Patients may have received more than one agent for induction and maintenance immunosuppression. 2 renal transplant recipients received basiliximab and ATG for delayed graft function.

[b]Other types of Immunosuppression: 2 on cyclosporine, 1 on sirolimus.

[c]History of transplant rejection and re-transplantation before the CNS infection episode.

Table 2 shows the clinical, laboratory, and microbiological characteristics. Overall, the onset of CNS infection after the transplantation was seen in 53.3% of the study population after the first year. The majority of patients had normal mental status at the time of diagnosis, with 22 (73.4%) having a GCS > 14, in contrast to 4 patients (13.3%) presenting with coma (GCS ≤ 8). A total of 70% of patients reported headaches, 60% were febrile (temperature > 38.0°C or 100.4°F), and 36.7% had nausea or vomiting. Further manifestations observed were photophobia (16.7%), neck stiffness (13.3%), and seizures (3.3%). The median severity of comorbidity based on the Charlson index was 3 (range, 0–9), categorized as moderate or severe. Brain imaging was done in 27 cases (26 had a computerized tomography scan [CT-scan], and 23 had a magnetic resonance imaging [MRI]). Abnormal findings in the brain CT-scan were found in 16.6% of patients and 33.3% on MRI. Brain space-occupying lesions were observed only in 3 patients with bacterial and fungal infection (1 with *nocardiosis* and 2 with *Cryptococcus neoformans*).

Table 2
Clinical, Laboratory, and Microbiological Characteristics of 30 patients with CNS infection

Characteristics	N (%)
Time to onset since transplant	
≤ 3 months	3 (10)
3–12 months	11 (36.7)
≥ 12 months	16 (53.3)
Glasgow Coma Scale on presentation	
GCS > 14	22 (73.4)
GCS 9–14[a]	4 (13.3)
GCS ≤ 8[b]	4 (13.3)
Neurological signs and symptoms	
Headache	21 (70)
Fever	18 (60)
Nausea/vomiting	11 (36.7)
Photophobia	5 (16.7)
Neck stiffness	4 (13.3)
Seizures	1 (3.3)
Charlson comorbidity index (median, range)	3 (0–9)
Abnormal findings on brain CT-scan[c]	5 (16.6)
Abnormal findings on brain MRI[d]	10 (33.3)
CSF analysis (median, range) (n = 26)[e]	
Leukocytes (per mm^3)	46 (0-1380)
RBC (per mm^3)	27 (0-24750)
Glucose (mg/dL)	60.5 (10–134)
Protein (mg/dL)	99 (27–452)
Peripheral leukocytes (thousand/µl, median, range)	7.2 (1-23.4)
Type of infection	
Fungal infection	15 (50)

Characteristics	N (%)
Cryptococcus neoformans	14
Histoplasma capsulatum	1
Viral infection	8 (26.7)
HSV-1 meningoencephalitis	2
VZV meningoencephalitis	2
EBV encephalitis	2
COVID-19 encephalitis	1
KSHV/HHV-8 encephalitis	1
Bacterial infection	7 (23.3)
Nocardiosis[f]	3
Neurosyphilis	1
MRSA	1
Staphylococcus pasteuri	1
Ureaplasma urealyticum	1
Extra cranial involvement	16 (53.3)
Time to initiation of therapy (days, median, range)	2 (0–19)
Relapse of disease	8 (26.7)
GOS at discharge	
Adverse clinical outcomes	10 (33.3)
Death	2 (6.7)
Persistent vegetative state	1 (3.3)
Severe disability	3 (10)
Moderate disability	4 (13.3)
Good recovery	20 (66.7)
GOS at 1y follow-up (n = 19)[g]	
Adverse clinical outcomes	3 (15.8)
Death	0 (0)
Persistent vegetative state	0 (0)

Characteristics	N (%)
Severe disability	1 (5.3)
Moderate disability	2 (10.5)
Good recovery	16 (84.2)

Abbreviations: COVID-19, Coronavirus disease 2019; CSF, cerebrospinal fluid; CT-scan, computed tomography scan; EBV, Epstein–Barr virus; GCS, Glasgow Coma Scale; GOS, Glasgow outcome scale; HSV-1, Herpes simplex virus-1; KSHV/HHV-8, Kaposi's sarcoma herpesvirus/ Human herpesvirus-8; MRI, magnetic resonance imaging; MRSA, Methicillin-resistant Staphylococcus aureus; RBC: red blood cell; VZV, Varicella zoster virus.

[a] *Indicative of altered mental status.*

[b] *Indicative of coma.*

[c] *Abnormal findings on brain CT-scan.*

• Patients with C. neoformans: vasogenic edema in the right frontal region, left frontal, left insular, right temporal, and left basal ganglion metastatic lesions. Multiple foci of supra and infratentorial parenchymal abnormality with gelatinous pseudocyst.

• Patients with nocardiosis: vasogenic edema within the right parietal and right frontal lobes. A focal lesion in the left cerebellum associated with diffuse vasogenic edema concerning for abscess.

• Patient with Staphylococcus pasteuri: stable positioning of left frontal approach ventriculostomy catheter, terminating at the left lateral ventricle.

[d] *Abnormal findings on brain MRI.*

• Patients with C. neoformans: acute hydrocephalus with slight ventricular system size increase. T1 hyperintensity in the right frontal region. Multifocal infarcts. Nodular leptomeningeal enhancement in the frontal and parietal convexities. Leptomeningeal enhancement, development of areas of infarct involving the midbrain, the parahippocampal gyri, and the right anterior superior cerebellum. The leptomeningeal enhancement over the cerebellar folia and anterior pons.

• Patients with nocardiosis: lesions with restricted diffusion in the right occipital lobe, prominent surrounding vasogenic edema, and 10.4 mm mass in the inferior right frontal lobe. Multifocal subcentimeter supratentorial intraparenchymal lesions with central restricted diffusion, peripherally enhancing, and minimal to mild edema. Multiple intraparenchymal abscesses and mild associated mass effect overlying the left side of the 4th ventricle.

• Patient with HSV-1: subacute infarct in the right cerebellum near the middle cerebellar peduncle.

[e] *CSF results available from different patients in the study population.*

[f] *Nocardia abscessus, nocardia farcinica, and nocardia species.*

[g] *GOS at 1 year of follow-up of patients' data availability.*

Laboratory and radiological characteristics of CNS infection are detailed in Table 2. CSF white blood cell count (WBC) median was 46/mm3 (range, 0–1380/mm3), CSF glucose median was 60.5 mg/dL (range, 10–134 mg/dL), CSF protein median was 99 mg/dL (range, 27–452 mg/dL), and peripheral WBC median

was 7.2 thousand/ml (range, 1-23.4 thousand/ml). A CSF protein ≥ 100 mg/dL and CSF glucose < 40 mg/dL were found in 13 patients (43.3%) and 8 patients (26.6%), respectively.

Microbiological Findings

Of the 26 CSF samples available from different patients in the study population (n = 30), 16 samples (53.3%) had a positive culture, 8 samples (26.6%) had a positive RT-PCR, 1 sample was positive for CSF-Venereal Disease Research Laboratory test (VDRL), and 1 sample was positive for a cryptococcus antigen. Out of the 16 samples with positive culture, 1 was positive for *Staphylococcus pasteuri*, which was associated with a ventriculoperitoneal shunt. Of 4 of the 30 cases that did not have CSF, 2 cases with *nocardiosis* were diagnosed based on brain imaging (CT-scan and MRI) of findings suggestive of abscess with positive blood culture, 1 with a positive brain biopsy culture with *Nocardia* species, and 1 with a positive RT-PCR *with Ureaplasma urealyticum* from a bronchoalveolar lavage specimen in association with clinical findings of encephalopathy due to CNS infection consistent with hyperammonemia syndrome secondary to this pathogen.

Fungal infections predominated, causing 50% (15/30), viral infections accounted for 27% (8/30), and bacterial infections caused 23.3% (7/30) of all CNS infections. The microorganisms more frequent were *C. neoformans* (14/30 [46.6%]), Nocardiosis (10%), Herpes simplex virus-1 (HSV-1), Varicella zoster virus (VZV), and Epstein–Barr virus (EBV) with 6.6% each one of them, respectively, Table 2. There were no CNS infection cases with unknown microbiology etiology.

Clinical Outcomes

An adverse clinical outcome upon discharge was seen in 33.3% of the study population (Table 2). Four (13.3%) had a moderate disability, 3 (10%) had a severe disability, 1 (3.3%) had a vegetative state, and 2 (6.7%) died. A favorable outcome was seen in 20 patients (66.7%) with a good recovery. An adverse clinical outcome at 1-year follow-up (19 of 30) was seen in 15.8% of the patients. Furthermore, a good outcome was seen in most patients 16 (84.2%).

Bivariate analysis, seen in Table 3, identified fever (odds ratio [OR], 11; 95% confidence interval [CI], 1.16–103.9; p = 0.018) as a variable associated with an increased risk of an adverse clinical outcome. No statistically significant differences were found in gender, type of SOT, the presence of headaches, seizures, extracranial involvement, CSF pleocytosis, brain CT-scan, or MRI findings.

Table 3
Bivariate Analysis of Baseline Variables and Adverse Clinical Outcomes of the 30 patients with a CNS infection

	At discharge			
Variables	N	Adverse Outcomes[a], No. (%)	Odds Ratio (95% CI)	*P* Value[b]
Male gender	18	6 (33.3)	1 (0.21–4.70)	1
Non-renal organ transplant recipient	16	14 (82.3)	0.23 (0.04–1.18)	0.070
Fever	18	9 (50)	11 (1.16–103.9)	0.018
Headache	21	5 (23.8)	0.25 (0.04–1.30)	0.091
Seizures	1	1 (100)	0.31 (0.18–0.53)	0.150
Extra cranial involvement	16	6 (37.5)	1.5 (0.32–6.99)	0.605
Lack of CSF pleocytosis[c]	7	2 (28.6)	0.55 (0.08–3.58)	0.529
Abnormal findings on brain CT-scan	5	3 (60)	3.75 (0.49–28.38)	0.184
Abnormal findings on brain MRI	10	5 (50)	2.25 (0.40-12.43)	0.349

Abbreviations: CT-scan, computed tomography scan; CSF, cerebrospinal fluid; MRI, magnetic resonance imaging.

[a] Adverse clinical outcomes were defined as GOS of 1 to 4: 1 (death), 2 (persistent vegetative state), 3 (severe disability), or 4 (moderate disability).

[b] P values are from the test comparing patients with and without adverse outcomes.

[c] CSF pleocytosis is defined as 6 or more leukocytes.

The ANOVA analysis shown in Table 4 did not identify any baseline variables to be statistically significant associated with having an adverse clinical outcome, including age, GCS on presentation, Charlson comorbidity index, CSF analysis (leukocytes, protein, and glucose), and peripheral leukocytes.

Table 4
ANOVA Analysis of Baseline Variables and Adverse Clinical Outcomes of the 30 patients with a CNS infection

At discharge				
Variables	N	Adverse Outcomes[a], No. (%)	Median (range)	*P* Value[b]
Age	30	10 (33.3)	65.5 (55–78)	0.161
GCS on presentation	30	10 (33.3)	15 (6–15)	0.519
Charlson comorbidity index[c]	30	10 (33.3)	3 (0–6)	0.788
CSF leukocytes (per mm^3)	26[d]	10 (38.5)	20 (1-100)	0.181
CSF protein (mg/dL)	26[d]	10 (38.5)	100 (27–169)	0.674
CSF glucose (mg/dL)	26[d]	10 (38.5)	68.5 (10–134)	0.175
Peripheral leukocytes (cells/mm^3)	30	10 (33.3)	7 (2.7–14.6)	0.953

Abbreviations: CSF, cerebrospinal fluid; GCS, Glasgow Coma Scale.

[a] *Adverse clinical outcomes were defined as GOS of 1 to 4: 1 (death), 2 (persistent vegetative state), 3 (severe disability), or 4 (moderate disability).*

[b] *P values are from the test comparing patients with and without adverse outcomes.*

[c] *Severity of comorbidity was categorized as moderate or severe if the Charlson comorbidity index is ≥ 3.*

[d] *26 CSF results available from different patients of the 30 patients in the study population.*

DISCUSSION

In this cohort, the CNS infections incidence was comparable to what has been published, ranging from 1–24%, but varying depending on the type of organ transplanted and the study period[1,2,10]. The incidence found was 2.23% in ten years. There is a lack of available data despite the significance of the problem; additionally, the literature reported has been mainly focusing only on renal transplant recipients in contrast to our cohort, which includes various types of SOT recipients[3,11]. Overall, it is consistent with what the recent Swiss national study focusing on CNS infections after renal recipients showed, which concluded it is a relatively rare complication in this population[5].

We found a similar range of pathogens as other SOT recipients cohorts[3,5,8,12]. Moreover, our SOT recipients cohort had an increased risk of developing a fungal CNS infection. Nonetheless, the

predominance of viral infections has been previously highlighted in CNS infection after SOT[1,3,13,14]. Our study demonstrates unique characteristics of CNS infections; *C. neoformans* caused almost half of the cases in the cohort. This differs from the general population epidemiology in CNS infections[15]. However, our findings are comparable to what has been reported, being C. neoformans the third-most frequent invasive fungal infection in a large SOT recipients cohort, and to the French cohort, which was undoubtedly the foremost cause of CNS infection (with 41 cases, 20% of all)[5,17,18]. This was expected, given that C. neoformans has a tropism to the CNS in immunocompromised hosts[19,20,21]. The viral pathogens were the etiology in one-quarter of the population study, being VZV, EBV, and HSV-1 encephalitis the most frequent pathogens, comparable to what the Swiss cohort found[1]. The study held in the Netherlands incorporated only bacterial CNS infections[8]. In the Croatian study, there were mainly bacterial and viral etiologies[3]. Our cohort identified cases with a broad diversity of pathogens. The host characteristics and epidemiologic risk factors were variable. Additionally, with the net state of immunosuppression, these are the most significant factors determining such variety.

In our study, the majority had an onset of CNS infection manifestations after 1-year post-transplant. Similar to what was found in the literature, in a recent study, patients presented CNS infections either within the first 5 years after the transplantation or after immunosuppression was increased[3]. On the contrary, in another study done in the Netherlands, all episodes (with bacterial meningitis) were identified in the late period post-transplant (more than 6 months)[8].

Similar to prior studies, there were few clinical manifestations of CNS infection with the corresponding classic signs and symptoms of bacterial meningitis. The classic triad with fever, altered consciousness (GCS < 15), and neck stiffness was seen only in 1 patient[8]. Additionally, in contrast to the Swiss cohort, where only 38% of patients presented with fever at admission, in our cohort, 60% presented with fever[1]. Our study highlights the distinctive challenge of diagnosing CNS infection after SOT because of the blunted and atypical manifestations[1]. SOT recipients with ambiguous and slight neurological symptoms should be included in clinicians' differential diagnoses for infection[8].

Overall, neuroradiological findings are diverse and unspecific, although changes in white matter are commonly observed[22]. Brain CT scans, in recent studies, have found to be less sensitive and showed no evidence of abnormalities as compared to MRI[3,11,23]. In our study, the MRI found abnormalities in 5 patients that the CT did not detect. Therefore, as the Croatian cohort, our results advise MRI for diagnosing CNS infections in SOT patients[3]. Three brain space-occupying lesions occurred in disseminated *nocardiosis* and 2 cases with cryptococcosis similar to the Swiss study. However, all their cases were due to *Nocardia farcinica*, contrary to our cohort, which was due to various species (*Nocardia abscessus, farcinica, and species*)[1].

The mortality found in our study was lower (6.7%) compared to other cohorts, which went from 15.4–33%[1,3,8]. The French cohort reported an increased and premature mortality of 50–70% at 1 year

secondary to Staphylococci, Enterobacteria, or filamentous fungi. Contrary to our cohort, which outcomes were better with inferior mortality rates and more satisfactory functional recovery[1].

This study has a few limitations that should be considered. We identified a few cases with a CNS infection. The collected data was retrospectively obtained by reviewing medical records. Given the heterogeneity and low number of patients identified, it was not feasible to determine risk factors for developing CNS infections in SOT recipients. Nevertheless, this study provided helpful data on CNS infections in the SOT population since it included almost all types of SOT recipients. Further analyses should be conducted to build clear guidelines for managing CNS infections in SOT recipients.

In conclusion, the incidence of CNS infections is low but is associated with a significant proportion of adverse clinical outcomes. Furthermore, prevail as a considerable cause of mortality in SOT patients, especially fungal infections. Additionally, the detection of CNS infection may be retarded, given the unique challenge, despite the improved diagnostics tests. Therefore, an interdisciplinary approach with a better understanding and a high level of attention may improve outcomes.

Declarations

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Author contributions. R. H. designed the project. O. M., L. J., H. K. collected the data. O. M. and R. H. analyzed and interpreted the data and wrote the manuscript. All the authors revised and approved the final version of the manuscript.

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