Central Nervous System Infections in Heart Transplant Recipients

Diederik van de Beek, MD, PhD; Robin Patel, MD; Richard C. Daly, MD; Christopher G. A. McGregor, MB, FRCS, MD; Eelco F. M. Wijdicks, MD, PhD

Objective: To study central nervous system infections after heart transplantations.

Design: Retrospective cohort study.

Setting: Cardiac Transplant Program at Mayo Clinic, Rochester, Minnesota.


Results: Central nervous system infections developed in 8 patients (3%), all of whom presented within the first 4 years after transplantation. The most common presentations were acute or subacute confusion or headache (88%), often without the classic symptoms of fever and neck stiffness. Direct cerebrospinal fluid examination was unrevealing in most cases, though cerebrospinal fluid protein levels were elevated in all patients with infections. Diagnoses included cryptococcal meningitis (n=3), progressive multifocal leukoencephalopathy (n=2), varicella-zoster virus encephalitis (n=2), and Aspergillus fumigatus infection (n=1). Three of 8 patients died (38%) and 2 (25%) survived with mild sequelae. Central nervous system infection was a significant predictor of mortality (hazard ratio, 4.39; 95% confidence interval, 1.72-11.18; P=.002).

Conclusions: Central nervous system infections are rare but devastating complications of heart transplantations. Recognition of these infections is difficult owing to a paucity of clinical manifestations. We report here, for the first time, varicella-zoster virus central nervous system infection in heart transplantations.

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Heart transplantation is a therapeutic option for end-stage heart failure. Approximately 24,000 patients have undergone heart transplantation in the United States throughout the last 10 years. During the last 2 decades, improvements in surgical techniques and immunosuppressive regimens have resulted in improved survival of heart transplant recipients. Previous reports have emphasized the importance of infections of the central nervous system (CNS) after heart transplantation. However, current transplantation practices have likely affected the occurrence and characteristics of CNS infections. Herein we provide a detailed description of CNS infectious diseases occurring in 315 heart transplant recipients, emphasizing changes over time and challenges in clinical recognition and management.
Three patients developed CNS infections during their hospital stay.

All patients developed their first symptoms and signs within 4 years of transplantation, half within 1 year after transplantation. The most common presentation of CNS infection was a confusion state or headache (88%). Most patients presented with a temperature of 38°C or less. Neurologic examination showed neck stiffness in only 1 patient; 3 had a moderate decrease of consciousness. Focal neurologic abnormalities (vision loss and ataxia) were present in 2 patients. Cerebrospinal fluid (CSF) examination was performed in 7 patients and showed the causative organism in 5 of them (71%) (Table 3). Cerebrospinal fluid white cell counts were normal in the majority (71%); 1 additional patient had marginal pleocytosis (8 cells/mm³). Cerebrospinal fluid-blood glucose ratios were normal in all patients, but CSF protein levels were uniformly elevated (>4.5 g/dL [100 mg/dL] [to convert to g/L, multiply by 10.0]).

Cryptococcal meningitis was diagnosed in 3 patients. All of these patients presented with headache and a normal level of consciousness. The duration between symptom onset and presentation was short (0-2 days) and the time between symptom onset and diagnosis was 2, 7, and 14 days. Neurologic examination results were normal, with the exception that patient 1 had slight papilledema. Computed tomography results were normal in all 3 patients. Cerebrospinal fluid opening pressures were measured; 2 patients had elevated pressures. Initial CSF white cell counts were normal to low. However, repeated lumbar punctures showed substantial pleocytosis in 2 patients. Cerebrospinal fluid fungal cultures were positive for Cryptococcus neoformans in all 3 patients; CSF cryptococcal antigen titers were found in 2 patients (1:64, positive in undiluted CSF only). Serum cryptococcal antigen titers were found in all 3 patients (1:8, 1:16, 1:256). All were treated with a combination of amphotericin B deoxycholate and 5-flucytosine, followed by suppressive fluconazole for approximately 6 months. None showed clinical deterioration following initiation of therapy and all had favorable outcomes. These patients with cryptococcal meningitis died 3, 12, and 18 years after heart transplantation owing to leukemia, cardiac arrest, and cerebral infarction, respectively.

Progressive multifocal leukoencephalopathy (PML) was diagnosed in 2 patients; they presented with progressive neurologic deterioration 15 and 36 months after transplant. Patient 4 presented with progressive bilateral visual loss. Magnetic resonance imaging (MRI) showed asymmetric patchy areas of hyperintensity in the occipital-temporal-parietal regions (Figure 1). Lumbar punctures revealed borderline elevated CSF protein levels but had otherwise normal results. Polymerase chain reaction results for JC virus were negative. A reversible posterior leukoencephalopathy syndrome was suspected and cyclosporine therapy was discontinued. After further neurologic deterioration, diagnostic brain biopsy was performed showing positive in situ hybridization for JC virus. Therapy with cytarabine was initiated, but the patient deteriorated further and died 13 months after diagnosis (37 months after transplantation).

Table 1. Baseline Characteristics of 315 Heart Transplant Recipients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (interquartile range), y</td>
<td>52 (38-59)</td>
</tr>
<tr>
<td>Male, No. (%)</td>
<td>229 (73)</td>
</tr>
<tr>
<td>White race, No. (%)</td>
<td>293 (93)</td>
</tr>
<tr>
<td>Patients aged 0-17 y, No. (%)</td>
<td>25 (8)</td>
</tr>
<tr>
<td>History, No. (%)</td>
<td></td>
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<tr>
<td>Hypertension</td>
<td>85 (27)</td>
</tr>
<tr>
<td>Smoking</td>
<td>104 (33)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>29 (9)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>144 (46)</td>
</tr>
<tr>
<td>Stroke/transient ischemic attack</td>
<td>36 (12)</td>
</tr>
<tr>
<td>Baseline measurements</td>
<td></td>
</tr>
<tr>
<td>Mean serum creatinine level (SD), µmol/L</td>
<td>1.3 (0.6)</td>
</tr>
<tr>
<td>Mean body mass index (SD)ª</td>
<td>25.1 (4.9)</td>
</tr>
<tr>
<td>Etiology of heart failure, No. (%)</td>
<td></td>
</tr>
<tr>
<td>Idiopathic</td>
<td>108 (34)</td>
</tr>
<tr>
<td>Ischemic</td>
<td>92 (29)</td>
</tr>
<tr>
<td>Congenital</td>
<td>36 (11)</td>
</tr>
<tr>
<td>Amyloidosis</td>
<td>33 (11)</td>
</tr>
<tr>
<td>Miscellaneousb</td>
<td>46 (15)</td>
</tr>
</tbody>
</table>

ªCalculated as weight in kilograms divided by height in meters squared.

b Hypertrophic cardiomyopathy (n=9), radiation cardiomyopathy (n=9), valvular cardiomyopathy (n=9), restrictive cardiomyopathy (n=5), intractable ventricular tachycardia (n=2), failed heart transplant (n=2), postpartum cardiomyopathy (n=2), cardiomyopathy after chemotherapy (n=3), cardiac hemochromatosis (n=1), cardiomyopathy with Becker muscular disorder (n=1), family history of sudden death (n=1), endocardial fibroelastosis (n=1).
Patient 1 presented with subacute encephalopathy. Cerebrospinal fluid polymerase chain reaction results were negative for JC virus and MRI was not performed because of the patient’s shrapnel. A brain biopsy not guided by neuroimaging showed gliosis, but in situ hybridization for JC virus was negative. The patient progressively deteriorated and died 11 months after transplantation.

Thirty-six (11%) patients in the total cohort had varicella-zoster virus (VZV) infection; all but 1 had skin lesions (herpes zoster infection, shingles). Two patients presented with papular skin lesions and a moderate decrease of consciousness (patients 7 and 8). Both patients had VZV-positive pretransplant serologies. Patient 7 developed a rash on her lip and labia, followed by headache, vomiting, chills, and a decrease of consciousness. Patient 8 was admitted to the hospital with severe Pseudomonas aeruginosa pneumonia and developed a rash on his scalp 1 day prior to onset of decrease of consciousness. Both patients received empirical treatment with acyclovir on the clinical suspicion of VZV encephalitis. Cerebrospinal fluid polymerase chain reaction results for VZV were positive in both cases. Patient 7 subsequently developed a mild numbness of her left arm and leg (MRI was not performed). Magnetic resonance imaging in patient 8 performed on the day of admission showed white matter changes (Figure 2). Both patients recovered and were living at the time of this manuscript’s preparation. Patient 8, however, has been dependent in daily activities since this episode. Twenty-one of 35 patients (7%)...
had herpes simplex virus 1 or 2 infections; however, none of these patients developed herpes simplex virus encephalitis.

One patient had cerebellar hemorrhage due to *Aspergillus fumigatus* infection (patient 6). She was hospitalized after autologous bone marrow transplant and suffered from *A. fumigatus* pneumonia. She died of multiorgan failure 4 days after cerebellar hemorrhage; autopsy showed intravascular cerebral *A. fumigatus* infection.

![Figure 1. A, Axial view of fluid-attenuated inversion recovery magnetic resonance imaging shows asymmetric patchy areas of hyperintensity consistent with the diagnosis of progressive multifocal encephalopathy (patient 4). B, Axial computed tomography (patient 6) shows right cerebellar hemorrhage; autopsy confirmed *Aspergillus fumigatus* infection.](image)

![Figure 2. A, Fluid-attenuated inversion recovery magnetic resonance imaging (MRI) in patient 8 shows white matter changes. There was no associated mass effect, enhancement, or restricted diffusion consistent with leukoaraiosis. There was no follow-up MRI study in this patient. B, Diffusion-weighted axial MRI showing normal diffusion. Diffusion-weighted MRI can be helpful in distinguishing varicella-zoster virus-associated vasculitis and preexisting white matter changes.](image)
Effective antimicrobial prophylactic strategies have led to a decline in the incidence of several opportunistic infections in heart transplant recipients. Two large cohort studies have described a combined total of 40 patients with CNS infections after heart transplantation from 1968 to 1987 (Table 4). Twelve patients (30%) were infected with *Listeria monocytogenes* or *Toxoplasmosis gondii*. Patients in the Cardiac Transplant Program at the Mayo Clinic receive lifelong prophylactic treatment with trimethoprim-sulfamethoxazole. In case of an allergy to trimethoprim-sulfamethoxazole, the *T gondii*–seropositive donor and –seronegative recipient receive pyrimethamine daily for 3 months. All patients are counseled before and after transplantation about risks of foodborne toxoplasmosis and listeriosis. They are also advised to not change feline litter boxes. Patients seronegative for VZV received the varicella vaccine prior to transplantation. All of our transplant candidates received pretransplant conjugate pneumococcal vaccine polyvalent and posttransplant prophylaxis with either acyclovir (6 weeks) or valganciclovir (3 months).

In the context of these strategies, changes in the hosts at risk, and improvement of diagnostic strategies, we report that the spectrum of CNS infections in heart transplant recipients has evolved to newer complications, such as PML and VZV encephalitis. Additional strategies, such as vaccination (ie, pretransplant administration of the zoster vaccine live), may influence the rate of CNS infections in this important population in the future.

Cryptococcal meningitis was the most common CNS infection. Although the relative frequency of cryptococcal meningitis increased across the time periods studied, the absolute risk on this infection decreased (Table 3).

Progressive multifocal leukoencephalopathy is an opportunistic infection of JC virus in CNS white matter that leads to neurologic deficits associated with demyelination. In a retrospective study of non-AIDS PML-associated disease at the Mayo Clinic, 7% of patients (n = 58) were transplant recipients (including 2 of our patients). Three patients with PML after heart transplantation have been described in the literature. When combining our cases with these, symptoms have universally developed after the first year of transplantation. Progressive multifocal leukoencephalopathy typically presents with subacute neurologic deficits, altered mental status, and visual symptoms, as in our patients. Magnetic resonance imaging shows asymmetric, well-demarcated, non-enhancing lesions, which are hyperintense in T2-weighted and fluid-attenuated inversion recovery MRI, with preferential location in the subcortical white matter. The sensitivity of polymerase chain reaction analysis of CSF is approximately 75%. In patients with a high clinical suspicion of PML and negative CSF polymerase chain reaction results, a brain biopsy is warranted.

There is no specific treatment for PML. Decrease of any potential sources of immunosuppression is recommended; however, this poses a dilemma after heart transplantation. The use of cytarabine is controversial. A clinical trial in AIDS patients with PML showed no beneficial effect, but in an open-label study including 16 PML patients without AIDS, cytarabine was associated with stabilization of symptoms at 1 year. Cytarabine is associated with significant bone marrow toxicity.

Varicella-zoster virus encephalitis has not been previously reported in heart transplant recipients, to our knowledge, but has been described in patients after bone marrow transplantation or in patients with HIV infection. No patients with VZV encephalitis were reported in a case series of 630 liver transplant recipients in the Mayo Clinic from 1985 to 1995 (E.F.M.W., personal communication, May 7, 2007). Although immunosuppressive protocols differ between transplant populations (eg, heart and liver), this does not necessarily mean that specific protocols predispose patients for VZV encephalitis. There are few recent systematic studies on CNS infections in different transplant populations. Whether VZV encephalitis is emerging in other transplant populations should be a subject of further research.

Cerebral vasculitis is a feared complication of VZV encephalitis. Magnetic resonance imaging of the brain in patients with VZV vasculitis may reveal ischemic or hemorrhagic infarcts, often both, of cortical and subcortical gray and white matter. However, VZV can also result in deep white matter ischemic or demyelinating changes and mimic the appearance of leukoaraiosis in early stages. Varicella-zoster virus lesions will progress relatively quickly, coalesce, and usually enhance.

The herpes zoster incidence in our cohort of 315 patients is similar or somewhat lower than rates in previous reports (11%) but is greater than that in the general popul-
Most herpes zoster infections are uncomplicated and are treated with high-dose oral acyclovir. Intravenous treatment with acyclovir is recommended in disseminated disease or in cases with suboptimal response to oral treatment. Because the reported mortality rate of VZV encephalitis is high, we suggest that heart transplant recipients with dermatomal zoster infections be treated with oral valacyclovir, leading to high CSF concentrations, or with intravenous acyclovir, rather than oral acyclovir or famciclovir, even when the infection occurs relatively late after the transplant. In addition, a decrease of consciousness or focal neurologic abnormalities in heart transplant recipients with skin lesions should lead to prompt empirical intravenous acyclovir and quick diagnostic tests.

The overall incidence of herpes simplex virus type 1 or 2 infection in this cohort was 7%, but none of these patients developed a concurrent herpes simplex virus CNS infection. Herpes simplex virus encephalitis after heart transplantation has not been reported in the literature. Recently, reports of heart transplant recipients with encephalitis caused by human herpes virus 6 and the West Nile virus have been published.

Heart transplant recipients are at risk of systemic and CNS aspergillosis. Our patient with CNS aspergillosis was described previously in 2001. A retrospective study of 22 organ transplant patients with CNS aspergillosis showed that the most common neurologic symptoms are decrease of consciousness and focal motor deficits. Aspergillosis in that study was fungal vasculitis with ischemic or hemorrhagic infarction. Awareness of this devastating disease is needed. Possible clues to this diagnosis are sinusitis or lung infections and systemic aspergillosis. The prognosis is poor, though a recent retrospective study showed that voriconazole is a promising treatment option.

Our study emphasizes a shift in infectious causes of CNS infections during the last 2 decades. Central nervous system infections often present with symptoms of subacute confusion or headache, without classic symptoms and signs of fever and neck stiffness. Cerebrospinal fluid examination can be unrevealing, though CSF protein levels are often elevated. Nevertheless, appropriate management and rapid diagnosis can be achieved by taking a careful history and with physical examination, neuroimaging, and diagnostic microbiological techniques. Awareness of CNS infectious diseases is essential. Because the mortality and morbidity rates are high, aggressive diagnosis and intervention are warranted in heart transplant recipients with suspected CNS infection. Molecular diagnostic testing of CSF for VZV and JC virus as well as serum and CSF cryptococcal antigen testing are particularly useful in appropriate cases. Whether vaccination with zoster vaccine live would diminish the incidence of post-transplant VZV infection requires further study.

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Correspondence: Elco F. M. Wijdicks, MD, PhD, Department of Neurology, Mayo Clinic College of Medicine, Rochester, MN 55905 (wijde@mayo.edu).

Author Contributions: Study concept and design: van de Beek, Patel, Daly, and Wijdicks. Acquisition of data: van de Beek, McGregor, and Wijdicks. Analysis and interpretation of data: van de Beek, Patel, and Daly. Drafting of the manuscript: van de Beek, Patel, and Wijdicks. Critical revision of the manuscript for important intellectual content: van de Beek, Patel, Daly, McGregor, and Wijdicks. Statistical analysis: van de Beek. Obtained funding: van de Beek and Patel. Administrative, technical, and material support: Patel and McGregor. Study supervision: Patel, Daly, McGregor, and Wijdicks.

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