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.

Arch Neurol. 2007;64(12):1715-1720

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EART 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.\(^1\) During the last 2 decades, improvements in surgical techniques and immunosuppressive regimens have resulted in improved survival of heart transplant recipients.\(^2\) Previous reports have emphasized the importance of infections of the central nervous system (CNS) after heart transplantation.\(^2,3\) 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.

CME available online at www.archneurol.com

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RESULTS

Baseline characteristics at time of transplantation are provided in Table 1. The most common causes of heart failure were idiopathic dilated myopathy and ischemic heart failure, in 200 of 315 patients (63%). A considerable number of patients had amyloidosis (11%). Follow-up was complete for

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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 sex, 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>
</tr>
<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>Mean serum creatinine level (SD), μmol/L</td>
<td>1.3 (0.6)</td>
</tr>
<tr>
<td>Mean body mass index (SD)</td>
<td>25.1 (4.9)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Etiology of heart failure, No. (%)</th>
<th></th>
</tr>
</thead>
<tbody>
<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>Miscellaneous</td>
<td>46 (15)</td>
</tr>
</tbody>
</table>

a Calculated 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).

306 of 315 patients (97%); 9 patients were lost to follow-up at 1 (n=4), 2 (n=1), 3 (n=1), and 6 (n=3) years after transplantation. During the study period, 95 patients died (30%). Median clinical follow-up was 6 years (interquartile range, 2-10). Stepwise Cox regression identified 4 baseline predictors of mortality: elevated serum creatinine levels (hazard ratio [HR], 2.16; 95% confidence interval [CI], 1.57-2.96; P < .001), amyloid etiology (HR, 2.92; 95% CI, 1.64-5.19; P = .03), history of hypertension (HR, 2.04; 95% CI, 1.29-3.24; P = .002), and female sex (HR, 2.09; 95% CI, 1.51-2.83; P < .001). To evaluate the association between CNS infection and mortality, we included CNS infections in the Cox model as time-dependent predictors together with the baseline predictors. In this multivariate model, CNS infection was a strong predictor for mortality (HR, 4.39; 95% CI, 1.72-11.18; P = .002).

There were 8 patients with CNS infections (median age, 58 years) (Table 2). There was mismatched serology between donor and recipient in 2 patients: patient 6 had negative serology for cytomegalovirus, while her donor was positive for cytomegalovirus; patient 1 was negative for the Epstein-Barr virus and his donor was positive prior to transplant. There were no mismatches with respect to toxoplasmosis serology.

Immunosuppressive regimens consisted of combinations of cyclosporine (n=7), prednisone (n=7), azathioprine (n=6), mycophenolate mofetil (n=1), and sirolimus (n=1). One patient with amyloidosis (patient 6) underwent subsequent autologous bone marrow transplantation and was treated with cyclophosphamide and granulocyte-macrophage colony-stimulating factor.

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 confusional 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 [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 deoxycylolate 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).
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.

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.
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*.2,3 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). 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,4,5 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 live6), 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).7 Three patients with PML after heart transplantation have been described in the literature.8,10 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.7 Magnetic resonance imaging shows asymmetric, well-demarcated, nonenhancing lesions, which are hyperintense in T2-weighted and fluid-attenuated inversion recovery MRI, with preferential location in the subcortical white matter.7 The sensitivity of polymerase chain reaction analysis of CSF is approximately 75%.7 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,11 but in an open-label study including 16 PML patients without AIDS, cytarabine was associated with stabilization of symptoms at 1 year.12 Cytarabine is associated with significant bone marrow toxicity.11,12

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.5,13,14 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.13 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.13 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 popu-
aspergillosis.19 The prognosis is poor, though a recent ret-
sisis are sinusitis or lung infections and systemic
aspergillosis in that study was fungal vasculitis with is-
in our patient, the main neuropathologic finding of CNS
plant recipients with dermatomal zoster infections be treated
with oral valacyclovir, leading to high CSF concentra-
tions,6 or with intravenous acyclovir, rather than oral acy-
clovir or foscarnet, even when the infection occurs rela-
tively 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.
Recenty, reports of heart transplant recipients with en-
cephalitis caused by human herpes virus 6 and the West Nile
virus have been published.16,17

Heart transplant recipients are at risk of systemic and
CNS aspergillosis. Our patient with CNS aspergillosis was
described previously in 2001.18 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.19 As
in our patient, the main neuropathologic finding of CNS
aspergillosis in that study was fungal vasculitis with is-
chemic or hemorrhagic infarction. Awareness of this dev-
astating disease is needed. Possible clues to this diagno-
sis are sinusitis or lung infections and systemic
aspergillosis.19 The prognosis is poor, though a recent re-
trospective study showed that voriconazole is a promis-
ing treatment option.20

Our study emphasizes a shift in infectious causes of CNS
infections during the last 2 decades. Central nervous sys-
tem infections often present with symptoms of subacute
confusion or headache, without classic symptoms and signs
of fever and neck stiffness. Cerebrospinal fluid examination
then be unrevealing, though CSF protein levels are of-
ten elevated. Nevertheless, appropriate management and
rapid diagnosis can be achieved by taking a careful his-
tory and with physical examination, neuroimaging, and
diagnostic microbiological techniques. Awareness of CNS
infectious diseases is essential. Because the mortality and
morbidty rates are high, aggressive diagnosis and inter-
vention 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 crypt-
tococcal antigen testing are particularly useful in appro-
riate cases. Whether vaccination with zoster vaccine live
would diminish the incidence of posttransplant VZV in-
fecction requires further study.

Accepted for Publication: May 7, 2007.
Published Online: October 8, 2007 (doi:10.1001/archneur.
.64.12.noc70065).
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van de Beek, McGregor, and Wijdicks. Analysis and interpre-
tation 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 con-
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Statistical analysis: van de Beek. Obtained funding: van de
Beek and Patel. Administrative, technical, and material sup-
port: Patel and McGregor. Study supervision: Patel, Daly,
McGregor, and Wijdicks.

Financial Disclosure: None reported.

Funding/Support: Dr van de Beek is supported by the Meerwaldt Foundation, the Netherlands Organization for
Health Research and Development (ZonMw), and grant
019.2006.1.310.001 from NWO-Rubicon.

Additional Contributions: Norbert G. Campeau, MD,
helped with Figure 2.

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