Neuropathology of Heart Transplantation

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ABSTRACT: The neuropathology of 18 cardiac transplant recipients was reviewed with the clinical findings. Pathological changes were noted in the central nervous system (CNS) in 94% of the patients, the most frequent being cerebral vascular in origin (72%). Eight patients (44%) had multiple cerebral infarcts and morphologically, a large number of these antedated the transplantation. In addition 4 patients had acute focal ischemic changes which occurred after transplantation. Intracranial hemorrhage was noted in 5 patients (28%), including one case of fatal intracerebral hemorrhage following an acute hypertensive episode after the transplantation. While systemic infection was common (10 patients), there were only 5 cases of intracranial infection; including 3 cases of cytomegalovirus infection, one of candidiasis and one of aspergillosis. Post-transplant seizures, occurring in a third of the patients, were related to a variety of causative factors such as sepsis, intracranial hemorrhage, cerebral ischemia, metabolic encephalopathy and cyclosporin neurotoxicity. Of note in this series was the absence of CNS lymphoma or other systemic lymphoproliferative disorder.

RESUME: Neuropathologie dans la transplantation cardiaque Nous avons revu la neuropathologie ainsi que les observations cliniques chez 18 cas de transplantation cardiaque. Des changements anatomopathologiques ont été notés au niveau du système nerveux central chez 94% des patients, le plus fréquent étant d’origine cérébro-vasculaire (72%). Huit patients (44%) avaient des infarctus cérébraux multiples, dont un grand nombre précédait chronologiquement la transplantation, selon leur aspect morphologique. De plus, 4 patients avaient des changements ischémiques focaux qui étaient survenus après la transplantation. Une hémorragie intracrânienne a été observée chez 5 patients (28%), incluant un cas d’hémorragie intracrânienne fatale à la suite d’un épisode aigu d’hypertension après la transplantation. Bien que l’infection systémique était fréquente (10 patients), il n’y avait que 5 cas d’infection intracrânienne, dont 3 cas d’infection à cytomegalovirus, un de candidose et un d’aspergillose. Les convulsions post-transplantation, survenues chez le tiers des patients, étaient reliées à des causes diverses telles que la septicémie, l’hémorragie intracrânienne, l’ischémie cérébrale, l’encéphalopathie métabolique et la neurotoxicité de la cyclosporine. Il est à noter que nous n’avons pas relevé de cas de lymphome du SNC ou d’autre affection lymphoproliferative systémique dans cette série.


Since the first human cardiac transplant performed by C.N. Barnard on December 3, 1967, cardiac transplantation has become an accepted method for treating some cases of intractable cardiac failure. A reliable method for monitoring the onset of graft rejection became available with the introduction of endomyocardial biopsy. The advent of cyclosporin in the early 1980’s has further improved the control of rejection. Because of the nature of the surgical procedure and the prognostic significance of graft rejection, most attention has been centered primarily on the changes in the heart and only secondarily on the changes in the other organs. Despite the high incidence of neurological complications in cardiac transplant recipients, there are only a handful of autopsy studies on the pathological changes in the central nervous system (CNS). This paper will review our experience of the neuropathology of cardiac transplant at the University of Western Ontario in Canada and attempt to correlate the autopsy findings with the clinical history. As the neuropathology of patients with post-cardiac transplant seizures has never been studied previously, we will also take a closer look into this subject.

PATIENTS AND METHODS

From 1981 to 1986, there were 125 cardiac transplants performed at the University Hospital, London, Ontario in Canada. Of these patients, 25 were known to have died. Amongst these 25 patients, 18 had a full autopsy with complete neuropathological examination. Out of the 18, 15 had orthotopic cardiac transplants and 3 had heart-lung transplants. Twelve were males and 6 were females. The various diseases leading to the transplantation included congenital heart diseases (2 patients), primary pulmonary hypertension (1 patient), ischemic cardiomyopathy (6 patients), post infective cardiomyopathy (4 patients) and idio-
Table 1: Neuropathological Findings in Heart Transplantation

<table>
<thead>
<tr>
<th>Case</th>
<th>Sex/ Age</th>
<th>Neurologic Pre-transplant Manifestations</th>
<th>Post-transplant Manifestations</th>
<th>Survival Time</th>
<th>General Autopsy Findings</th>
<th>Neuropathological Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M/39 yr</td>
<td>L. TIA</td>
<td>Generalized seizures</td>
<td>50d</td>
<td>Disseminated CMV Infection - liver, lungs, kidneys &amp; skeletal muscle involvement; Multiple infarcts - liver</td>
<td>Cerebral CMV; acute diffuse ischemic encephalopathy frontal &amp; temporal (ACA, MCA &amp; PCA), caudate, hippocampus &amp; cerebellum; Alzheimer type II astrocytosis; CPM; old infarcts - R frontal, parietal, L occipital &amp; pitiutary</td>
</tr>
<tr>
<td>2</td>
<td>M/31 yr</td>
<td>—</td>
<td>Behavioural changes</td>
<td>47d</td>
<td>Acute rejection; pulmonary CMV &amp; Klebsiella abscesses</td>
<td>Acute focal ischemia-hippocampus, substantia nigra; microglial nodules —</td>
</tr>
<tr>
<td>3</td>
<td>M/51 yr</td>
<td>Episodic confusion &amp; disorientation</td>
<td>—</td>
<td>2 hrs</td>
<td>Acute pulmonary embolism; Right heart failure</td>
<td>Acute subdural hemorrhage; acute pitiutary infarcts; acute focal ischemia - L frontal with thrombo emboli in blood vessels</td>
</tr>
<tr>
<td>4</td>
<td>F/20 yr</td>
<td>—</td>
<td>—</td>
<td>2d</td>
<td>Acute pulmonary embolism</td>
<td>Acute subarachnoid hemorrhage old infarcts - L internal capsule, L parietal &amp; hippocampus</td>
</tr>
<tr>
<td>5</td>
<td>M/25 yr</td>
<td>—</td>
<td>Generalized seizures</td>
<td>8d</td>
<td>E. coli pneumonia; cardiac necrosis</td>
<td>Cerebral &amp; leptomeningial aspergillosis; Old infarcts - R frontal</td>
</tr>
<tr>
<td>6</td>
<td>M/24 yr</td>
<td>—</td>
<td>—</td>
<td>&lt;1 hr</td>
<td>Pulmonary aspergillosis; CCF</td>
<td>Cerebral &amp; leptomeningial aspergillosis; Old infarcts - R frontal</td>
</tr>
<tr>
<td>7</td>
<td>M/39 yr</td>
<td>L hemiparesis &amp; cerebellar dysfunction</td>
<td>Deficits persisted; ? Thalamic pain syndrome</td>
<td>800d</td>
<td>Acute rejection; streptococcal pneumonia</td>
<td>Old infarcts - R basal ganglia &amp; L cerebellum; glissis-R thalamus; sideralcinosis - basal ganglia</td>
</tr>
<tr>
<td>8</td>
<td>M/25 yr</td>
<td>—</td>
<td>Generalized seizure</td>
<td>31d</td>
<td>Acute rejection; broncho-pneumonia pulmonary embolism; massive centrilobular necrosis</td>
<td>Acute diffuse ischemic encephalopathy-hippocampus, cerebellum, pontine nuclei &amp; anterior horn cells; Alzheimer type II astrocytosis; Purkinje cell loss</td>
</tr>
<tr>
<td>9</td>
<td>F/36 yr</td>
<td>Numbness &amp; tingling of limbs</td>
<td>—</td>
<td>2d</td>
<td>Adult respiratory distress syndrome</td>
<td>Siderocalcinosis-basal ganglia; neurogenic atrophy-skeletal muscle</td>
</tr>
<tr>
<td>10</td>
<td>F/43 yr</td>
<td>TIA</td>
<td>Severe hypertension with coma</td>
<td>3d</td>
<td>Acute pulmonary edema; L ventricle hypertrophy</td>
<td>Acute massive hemorrhage - basal ganglia &amp; thalam; acute pitiutary infarct; siderocalcinosis-basal ganglia</td>
</tr>
<tr>
<td>11</td>
<td>M/39 yr</td>
<td>TIA-R homonymous hemianopsia</td>
<td>Memory deficit; poor concentration</td>
<td>967d</td>
<td>Candida septicemia; bronchiolitis obliterator; myocardial infarct</td>
<td>Old infarcts - L occipital &amp; R parietal</td>
</tr>
<tr>
<td>12</td>
<td>M/21 yr</td>
<td>Episodic dizziness &amp; cardiogenic shock</td>
<td>Dysphasia, dysarthria &amp; confusion</td>
<td>42d</td>
<td>Acute legionella pneumonia; APN; candididiasis - lungs; myocardial infarct; hepatic congestion &amp; fibrosis</td>
<td>Old infarcts - R frontal, L parietal, basis pontis; acute focal ischemia - frontal &amp; parietal cortex; Alzheimer type II astrocytosis</td>
</tr>
<tr>
<td>13</td>
<td>M/51 yr</td>
<td>—</td>
<td>—</td>
<td>5d</td>
<td>Acute pulmonary embolism; CCF</td>
<td>Focal leuкоencephalopathy, multiple - cerebral hemispheres pons &amp; cerebellum; old pitiutary infarct</td>
</tr>
<tr>
<td>14</td>
<td>F/15 yr</td>
<td>—</td>
<td>—</td>
<td>55d</td>
<td>Acute rejection</td>
<td>Acute diffuse ischemic encephalopathy-frontoparietal (watershed zones of ACA &amp; MCA), occipital (PCA) and putamen</td>
</tr>
<tr>
<td>15</td>
<td>F/51 yr</td>
<td>Syncopal attack</td>
<td>—</td>
<td>7d</td>
<td>Myocardial necrosis &amp; hemorrhage; pulmonary edema</td>
<td>Old infarcts - L parietal</td>
</tr>
<tr>
<td>16</td>
<td>F/24 yr</td>
<td>Syncopal attack</td>
<td>Generalized seizures</td>
<td>359d</td>
<td>Acute rejection; pulmonary embolism</td>
<td>Acute diffuse ischemic encephalopathy-frontal, occipital, parietal &amp; temporal (ACA, MCA &amp; PCA), hippocampus &amp; cerebellum</td>
</tr>
<tr>
<td>17</td>
<td>M/46 yr</td>
<td>Episodic confusion</td>
<td>Confusion &amp; behavioural changes; generalized seizures</td>
<td>35d</td>
<td>Candida septicemia</td>
<td>Cerebral candidiasis; hemorrhage - L occipital &amp; spinal cord; subarachnoid hemorrhage; Alzheimer type II astrocytosis</td>
</tr>
<tr>
<td>18</td>
<td>M/32 yr</td>
<td>L TIA</td>
<td>Generalized seizures with postical L leg weakness</td>
<td>31d</td>
<td>Ruptured thoracic aorta; pulmonary CMV</td>
<td>Acute focal ischemia - R parietal; subdural hematoma - R motor area; old infarcts - R frontal &amp; parietal; microglial nodules</td>
</tr>
</tbody>
</table>

TIA = Transient Ischemic Attacks  
CPM = Central Pontine Myelinolysis  
CCF = Congestive Cardiac Failure  
APN = Acute Papillary Necrosis  
ACA = Anterior Cerebral Artery Territory  
MCA = Middle Cerebral Artery Territory  
PCA = Posterior Cerebral Artery Territory
pathic cardiomyopathy (5 patients). The ages of patients at the
time of death varied from 15 to 51 years with a mean age of 34
years. Post-transplant survival time ranged from less than an
hour to 967 days, the average being 136 days.

Briefly, cardiac transplantation was performed under
hypothermia and by placing patients on cardiopulmonary
bypass. Perfusion pressure was maintained between 60 to 80
mm Hg. during the cross-clamp period. The average cross-
clamp time was 72 minutes (range 58-126 minutes). The aver­
age bypass time was 93 minutes (range 63-332 minutes). Most
the patients required inotropic support initially when coming off
the bypass and this was usually tapered and discontinued within
the first 48 hours postoperatively. The mainstay of immuno­
suppressive therapy for the control of graft rejection was
Cyclosporin A. The patients were initially treated with
Antithymocyte Globulin (ATG) for the least five days at a vari­
able dosage to keep the absolute neutrophil count to 2 x 10^9/L.
Eighty mg of IV methylprednisolone twice daily was also
given. The ATG was then discontinued and Cyclosporin A was
given prior to surgery with a loading dose of 10 mg/kg and then
adjusted to maintain the blood levels at about 200 ng/ml. The
methylprednisolone was changed to prednisone when the
patient was able to take oral medication and tapered as before.
The Cyclosporin A was maintained at about 200 ng/ml for the
first year and then the dose was decreased to keep the blood
level at 100 ng/ml. Endomyocardial biopsy was performed on a
weekly basis initially and then every three to six months.
Rejection was treated with boluses of 1 gram of methylpred­
nisolone for 3 days and if necessary with the addition of ALG
or azathioprine.

In all 18 cases, the brain and spinal cord were studied macro­
scopically after fixation in 20% formalin for at least 7 days.
After fixation, the brains were cut into coronal slices after tran­
section of the midbrain. In most cases, standard blocks were
taken from frontal, temporal and occipital cortex with adjacent
white matter, basal ganglia, thalami, hippocampi, cerebellum,
brain stem and spinal cord as well as areas which were abnor­
mal on macroscopic examination. For case 8 there were
insufficient blocks taken from the cerebral hemispheres before
the brain was discarded. No sections were available for micro­
scopic examination of the spinal cord in cases 13 and 14. All
paraffin sections were stained with haematoxylin and eosin and
with special stains when indicated. Histological sections and the
clinical charts were carefully reviewed to correlate the neu­
ropathological findings with the clinical data.

RESULTS

Clinical neurological manifestations were noted in 13
patients (72%). Preoperative neurological events were docu­
mented in 11 patients and postoperative events in 11. At autops­
y, CNS lesions were found in all but one patient (94%).
Cerebrovascular lesions, excluding acute diffuse ischemic
encephalopathy secondary to terminal circulatory collapse, were
found in 13 patients (72%). Intracranial infections were noted in
5 patients (28%). The neuropathological findings are summa­
rized in Table 1.

Cerebral infarcts were found in 8 patients (44%). These
infarcts were mostly multiple and usually involved the cortex
and deep grey matter. Based on the clinical information avail­
able and the neuropathological assessment, all patients had
some infarcts that antedated the transplantation. These old cer­
bral infarcts were found in patients with massive myocardial
infarcts (cases 1 & 7), congenital heart diseases (cases 11 & 18),
idiodpathic cardiomyopathy (cases 5, 6 & 13) and one post-infect­
tive cardiomyopathy (case 12). The causes of cerebral infarcts in
these patients were related to embolism from cardiac sources or
cerebral hypoperfusion secondary to cardiac dysfunction.
Three patients had transient ischemic attacks (cases 1, 11 & 18)
before transplantation in which the cerebral infaracts were locat­
ed on pathological examination in appropriate regions to
account for the symptoms of the attacks. Another two patients
had symptoms such as syncope (cases 15) and episodic dizzi­
ness (cases 12) that were related to cardiac arrhythmia. One
patient (case 7) with left hemiparesis and cerebellar dysfunction
had infarcts of the right basa! ganglia, internal capsule and left
cerebellum visualized on the computerized tomography (CT)
before transplantation. Two patients had no neurological mani­
festation documented before transplantation. Only three (cases
7, 11 & 12) of the eight with cerebral infaracts had persistence or
progression of neurological deficits after transplantation.
The mean survival time for this group was 219 days as compared to
136 days in all the eighteen patients studied. Focal neuronal
ischemic changes as opposed to diffuse ischemic encephalopa­
thy due to terminal cardiovascular collapse, were noted in four
patients after transplantation. Pituitary infarcts were seen in 4
patients. In two of them, the infarcts were acute and related to
the hypoperfusion that occurred terminally.

Acute diffuse ischemic encephalopathy resulting from termi­
nal circulatory collapse was noted in 4 patients. In 2 of these
patients (cases 1 and 16), the distribution of acute neuronal
damage was diffuse rather than restricted to the watershed zones
of major cerebral arterial territories. There were insufficient
samples from the cerebral cortex in one patient (case 8) for us to
comment on the changes in the watershed zones. There were,
however, severe diffuse ischemic changes in this case involving
the hippocampus, cerebellum, pontine nuclei of basis pontis and
anterior horn cells of the spinal cord. All four patients had mod­
erate but prolonged hypotension. Acute ischemic neuronal
changes involving the watershed zones of anterior and middle
cerebral arteries were seen in one patient (case 14) who had
acute severe graft rejection and died following a sudden cardiac
arrest. The involvement of the hippocampus in these 4 patients
was variable; 2 patients (cases 8 and 16) with ischemic changes
in pyramid cells in h1 to h5, one (case 1) with changes mainly
in h1 and one (case 14) with normal hippocampus. Generalized
seizures were also noted in the 3 patients with ischemic neu­
ronal changes in the hippocampus.

Intracranial hemorrhage was seen in 5 patients (28%). In the
most severe case (case 10), the patient had an episode of acute
hypertension postoperatively which did not respond to treat­
m. This was followed by aphasia, right hemiparesis and rapid
progression to coma and death. A CT of the head done
before death documented a large hematoma in the basal ganglia
and thalami. The neuropathological examination confirmed the
CT finding of basal ganglionic and thalamic hemorrhage.
Subarachnoid hemorrhage was encountered in 2 patients. The
first patient (case 5) was diagnosed clinically as a metabolic
encephalopathy with generalized seizures. At autopsy, extensive
Recent subarachnoid hemorrhage was found on the convexities of both hemispheres. Another patient (case 17) developed focal seizures which became generalized. Diffuse old subarachnoid hemorrhage and intracerebral hematoma were found in association with systemic and cerebral candidiasis. Subdural hemorrhage was the finding in another two patients. The first patient (case 4) died of pulmonary embolism two days post-transplantation and a recent subdural hemorrhage was noted in the posterior cranial fossa. A subdural hematoma was noted over the right motor cortex in another patient (case 18) with generalized seizures and postictal weakness of the left leg.

Intracranial infection was present in 5 out of the 10 patients with systemic infection. Three patients had systemic cytomegalovirus infection (CMV). In the first (case 1), intranuclear viral inclusions were seen in the cortical neurons, brain, skeletal muscles and peripheral nerves (Figures 1 & 2). In the second and third patients (cases 2 and 18) only microglial nodules were seen in the brain. Cerebral mycosis was encountered in two patients. One patient (case 17) began to have seizures nine days post-operatively and despite adequate treatment with phenytoin and phenobarbital the seizures persisted. Two days prior to the onset of seizures he was noted by the nursing staff to have personality and behavioural changes. A CT scan revealed only old cortical infarcts. Cerebrospinal fluid (CSF) examination revealed xanthochromia with normal sugar and protein. The CSF cultures were negative for bacteria and viruses. The India ink test was negative but CSF fungal culture was not obtained. The seizures were thought to be metabolic in origin though the patient had pulmonary candidiasis. At neuropathological examination, in addition to the intracranial hemorrhage noted above, there were multiple microglial nodules and microabscesses in the brain parenchyma. Pseudohyphae and yeast bodies were identified by periodic acid Schiff (PAS) and Gomori methenamine silver (GMS) stains as consistent with those of Candida species (Figure 3). Systemic candidiasis was found at the general autopsy. In a second patient (case 6) pulmonary and cerebral aspergillosis was identified microscopically with PAS and GMS stains from autopsy material (Figure 4). This patient must have acquired the infection before transplantation as he survived less than one hour post-operatively. The patient was presumed to be immunosuppressed as he was treat-
ed with methylprednisolone for drug induced thrombocytopenia sometime before the transplantation.

Alzheimer type II astrocytosis was seen in 4 patients with severe jaundice (cases 1, 8, 17 and 18). Clinically, they exhibited a varying degree of confusion and the electroencephalogram (EEG) changes were consistent with diffuse encephalopathy. All of them were associated with systemic infection, including two with intracranial infection (cases 1 and 17). At autopsy, a variety of pathological changes were noted in the liver which included massive centrilobular necrosis (case 8), severe congestion and fibrosis (case 12), multiple abscesses (case 17), infarcts and CMV inclusions (case 1). Central pontine myelinolysis was also noted in one (case 1) without disturbance of serum sodium levels. Siderocalcinosis of the small vessels of the globus pallidus and hippocampi, a relatively nonspecific finding in older persons, was noted in 4 cases. We also documented a patient (case 13) with multiple foci of demyelination and necroses with prominent axonal swellings in the centrum semiovale, internal capsule, basis pontis and cerebellum resembling cases of disseminated necrotizing leukoencephalopathy described in cancer patients treated with chemotherapy and CNS irradiation.

Post-transplant seizures were recorded clinically in 6 patients. These seizures occurred during the first 2 weeks after the transplants or just prior to the terminal event. Clinically, five out of the six cases were diagnosed as metabolic disorders. Systemic infection was present in 5 cases (cases 1, 5, 8, 17 and 18) including the patients with cerebral CMV infection (cases 1 and 18) and cerebral candidiasis (case 17). Cerebrovascular lesions such as old cerebral infarcts (cases 1, 5, 18) and intracranial hemorrhages (cases 5, 17, 18) were noted in 4 patients. In another 3 patients (cases 1, 8, 16) there was a history of acute circulatory failure either preceding or during the course of generalized seizures. At neuropathological examination, there was evidence of acute diffuse ischemic encephalopathy with hippocampal involvement. A patient (case 18) with generalized seizures and postictal left leg paresis also had multiple old infarcts of the right frontal and parietal cortex as well as a subdural hematoma over the right motor cortex discovered at autopsy. Finally, a 24-year-old female (case 16) who had a serum magnesium level of 0.64 mmol/L (normal 0.77 ± 0.6 mmol/L) developed generalized seizures one week after transplantation. She was successfully treated with magnesium sulphate and remained seizure-free about a year before she succumbed to graft rejection. During the terminal phase of her illness she developed another attack of generalized seizures.

No cerebral lymphoma or systemic lymphoproliferative disease was noted in these patients.

DISCUSSION

As in previous series which showed that 60-80% of the heart transplant patients had CNS lesions, neuropathological findings are very frequent in our patients. Careful neuropathological examination correlates well with the clinical findings and is useful in establishing the temporal sequences of clinical events. Generally, the pathological changes in the CNS are the complications of the original cardiac disorders, the heart surgery, the cardiopulmonary bypass, circulatory disturbances, graft rejection, immunosuppression, metabolic encephalopathy and impaired hemostasis.

Cerebral infarction, a frequent cerebrovascular complication could be the result of events happening before, during or after transplantation. Cerebral embolism from mural thrombi or valvular vegetations and circulatory insufficiency from impaired myocardial function or cardiac arrhythmia are important causes for cerebral infarcts prior to transplant. Cerebral infarcts could also be related to events that occurred during the operation such as embolization of air or prosthetic material to the cerebral circulation and low perfusion while the patient is on the cardiopulmonary bypass. Hypotensive episodes during and after the surgery contribute to the severe hemodynamic changes and the impairment of autoregulation of cerebral blood flow leading ultimately to cerebral ischemia. Acute and chronic rejection of the graft could cause myocardial damage, thus giving rise to cerebral circulatory insufficiency or embolism.

In our study, in addition to acute focal neuronal ischemia which occurred after transplantation, most of the cerebral infarcts antedated the transplantation. However, most of these infarcts were either asymptomatic or associated with transient or episodic symptoms, the exception being the one patient with the left hemiparesis and cerebellar dysfunction. Another two patients however, did develop progressive neurological deficits after the transplantation. Otherwise patients with pretransplant cerebral infarcts did not appear to fare worse in terms of survival time or neurological deficits than those without infarcts.

The distribution of neuronal damage in our cases of acute diffuse ischemic encephalopathy also deserves comment. According to Adams et al, the neuropathological consequences of global ischemia appear to depend on the rapidity and degree to which cerebral blood flow is reduced. Our findings are essentially similar in that the accentuation of watershed lesions was seen in one patient with a precipitous drop of cerebral blood flow, whereas a more diffuse pattern of neuronal damage without watershed accentuation was noted in two patients with more gradual and sustained reduction of cerebral blood flow. The hippocampal involvement, however, instead of being minimal, as previously reported was rather variable. There were 2 patients with severe and extensive neuronal damage in the hippocampus; one with moderate neuronal damage and the other with no damage. Although we have no ready explanation for the hippocampal changes, we noted that the 3 patients with neuronal damage had general seizures terminally. An interesting speculation would be that the seizures could aggravate ischemia and induce excitotoxic neuronal damage in the hippocampus.

Intracranial hemorrhage, though a less frequent finding than infarction is certainly more ominous and was responsible for the demise of one patient and contributed to the fatal outcome of another two. Post-transplant hypertension, an important precipitating factor for intracerebral hemorrhage, is one of the known adverse effect of Cyclosporin A. Other hemorrhagic complications relate to disturbed hemostasis from systemic heparinization, inadequate replacement of clotting factors and platelets following blood loss and altered platelet function that occurs during the bypass. As well, systemic sepsis with disseminated intravascular coagulopathy will also predispose to intracranial hemorrhage.

The occurrence of opportunistic infections in cardiac transplant patients is due to their depressed immune status. Although systemic infections were common in our patients,
only 5 had CNS involvement. These included cerebral CMV infection and mycoses secondary to systemic infection. The incidence of CMV infection in heart transplant patients could be as high as 45% and such infection may be acquired from the donated heart or a result of viral reactivation or reinfection. Cerebral candidiasis is probably the most common postmortem cerebral mycosis and yet it is rarely appreciated clinically. Because this mycosis usually produces intracerebral microabcesses, noncaseating granulomas and microglial nodules without diffuse leptomeningitis, CSF examination may not identify the infection. Evidence of CNS abnormalities from clinical examination or CT, especially in the immunocompromised patient with candidiasis of other organs such as lungs, gastrointestinal tract, kidney, etc. may be the only indication of cerebral involvement. Aspergillosis is the other common mycosis involving the brain in the immunocompromised. Because of the propensity of the fungus to invade larger cerebral vessels causing vascular damage and thrombosis, hemorrhagic infarction is a common presentation. As such, focal neurological deficits are more frequent clinical findings and fungal meningitis remains unsuspected. Thus even though both cerebral mycoses are associated with high morbidity and mortality, they are very difficult to diagnose clinically. Therefore, a high index of suspicion is warranted for the diagnosis of these intracranial infections, especially in immunocompromised patients who developed progressive neurological or neuropsychiatric symptoms.

The high incidence of post-transplantation seizures is attributed to a variety of causative factors such as intracranial infection, intracranial hemorrhage, cerebral infarcts, cyclosporin neurotoxicity, metabolic and ischemic encephalopathy. As mentioned, neurological manifestations in an immunosuppressed patient are a valuable clue for the diagnosis of intracranial infection. Seizures have been reported at the onset or during the course of a variety of cerebrovascular diseases. In a series of 104 consecutive autopsy-proven cases of cerebral infarct and hemorrhage, seizures were documented in 12% of the patients as compared to 2.7% in controls. Most of these seizures were associated with old cortical infarcts which were considered embolic in origin. A significant number of these patients had generalised seizures. In our series, 3 patients with seizures were found to have old cortical infarcts. However, seizures were also noted in 3 patients with acute diffuse ischemic encephalopathy. Though these seizures could have occurred in the setting of metabolic encephalopathy, sepsis, and cerebral infarction, nevertheless the association between acute cerebral ischemia and seizures has been well established. Most intracranial hemorrhages and cerebral infarcts could be excluded by a careful neurological examination followed by a CT. Serum electrolyte abnormalities and diffuse encephalopathic changes in the EEG would suggest metabolic encephalopathy. Seizures, tremors and depression have also been reported as a major side effect of Cyclosporin A. As in one of our patients, this neurotoxicity of Cyclosporin A is associated with hypomagnesemia and therefore could be reversed by magnesium replacement.

Hypodensities of the white matter in the absence of cerebral edema have been documented in the CT of patients after renal and liver transplantation. Because these white matter changes disappeared in the CT after the cessation of cyclosporin therapy, many feel that such radiographic abnormalities could be relatively specific to cyclosporin neurotoxicity. The neuropathological findings described are severe reactive astrocytosis in the white matter with no evidence of fungi, viral inclusions, recent or old hemorrhages. In one of our cases, there was no CT documentation of these lesions but the white matter lesions seen histologically resemble those found in disseminated necrotizing leukoencephalopathy, an entity that has been reported in cancer patients treated with chemotherapy and CNS irradiation. Similar lesions were also found in the basis pontis of patients with human immunodeficiency virus (HIV) infection and other forms of immunosuppression. Though no definite pathogenesis is known, a common denominator for such white matter pathologies appears to be immunosuppression, whether it occurs in post-transplant patients on cyclosporin, cancer patients on chemotherapy and radiotherapy or patients with HIV infection. Linking this leukoencephalopathy to immunosuppression would certainly make infection by opportunistic organisms such as CMV a possibility. The lack of clinical and pathological evidence of infection in our patient, however, does not rule out such a possibility.

In comparing our series with that of Schober and Herman in 1973, a difference is noted in the relative frequency of intracranial infections and cerebrovascular lesions. In their 31 cases, there were 18 cases with CNS lesions and out of these 12 had CNS infection. These 12 cases included 5 instances with cerebral mycoses, 2 with CMV infection, 1 with toxoplasmosis and 10 with disseminated microglial nodules in the brain consistent with herpes encephalitis. Cerebrovascular lesions were only documented in 5 cases and cerebral lymphoma in one. Hotson and Pedley in 1976, in a clinical survey of the neurological complications of cardiac transplantation, studied 83 patients (including the 31 autopsy cases of 1973) and found neurological disorders in 50% of the patients. Again, intracranial infection was responsible for one-third of the CNS disorders. Cerebrovascular disease constituted only 9% of the neurological complications. These studies were done at the time when azathioprine and high doses of steroid were used as immunosuppressants. The findings were in distinct contrast to ours in which cerebrovascular lesions (72%) were more frequent than intracranial infection (28%). Montero and Martinez analyzed the neuropathological findings in 23 cardiac transplant patients from 1981 to 1985 and found cerebrovascular lesions in 60% and intracranial infections in 20%. Subsequently, Martinez and Puglia, having expanded the same series to include 50 patients, again noted that vascular lesions were the most frequent CNS complications in heart transplantation. In their series as in ours, Cyclosporin A and lower doses of steroid were used to control graft rejection. It has been suggested that Cyclosporin A provides powerful immunosuppression and allows lower doses of steroids to be used; thus decreasing the morbid effects of steroids. Though the incidence of infection in patients on Cyclosporin A as compared to those on high dose steroid and azathioprine is not significantly reduced, the morbidity and mortality are marked reduced. This steroid sparing effect of Cyclosporin A is perhaps even more apparent in autopsy studies which reflect the mortality of a disease. Apart from this, there is also a conspicuous absence of cerebral herpes infection in the patients of Montero and Martinez as well as ours in comparison to the transplant patients in the pre-cyclosporin era. While causes for the decrease of herpes involvement of the CNS are uncertain, this may also contribute...
to the lower incidence of CNS infections. The pattern of other CNS infections such as cerebral mycoses, however, remains roughly the same. The high frequency of cerebrovascular diseases is mainly the result of the large number of patients with cerebral infarcts which antedated the transplantation. Hypotension and cardiac arrest during the surgical and after-procedure may also lead to neuronal ischemic changes. Post-transplantation hypertension resulting from the use of Cyclosporin A, is another important cause of cerebrovascular disorders.20

The increased risk of lymphoid neoplasm has always been a concern in transplant recipients.47-50 Although various reports have shown the occurrence of lymphoma in patients treated with Cyclosporin A, this is considered to be due to severe immunosuppression rather than to the effect of Cyclosporin A per se.51 It is interesting to note that while no lymphoproliferative disorder was found in our patients, cerebral lymphoma had been noted in series before the cyclosporin era.5.6

This study highlights the frequency of neuropathological changes and their contributions to the morbidity and mortality of cardiac transplant recipients. We have also noted the decline in incidence of CNS infections since the introduction of cyclosporins. Our study suggests that the pathogenesis of post-transplant seizures could be multifactorial and many of the neurological complications in cardiac transplant patients could account for their occurrences. In addition to metabolic disorders and cyclosporin neurotoxicity, the role of infections and cerebrovascular diseases in post-transplant seizures is examined.

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REFERENCES


