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.

RÉSUMÉ: 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 aigus qui étaient survenus après la transplantation. Une hémorragie intracrânienne a été observée chez 5 patients (28%), incluant un cas d'hemorragie intracérébrale 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 cytomégalovirus, 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 lymphoproliférative systémique dans cette série.

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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.[1] A reliable method for monitoring the onset of graft rejection became available with the introduction of endomyocardial biopsy.[2,3] The advent of cyclosporin in the early 1980's has further improved the control of rejection.[4] 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).[5-7] 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-

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Table 1: Neuropathological Findings in Heart Transplantation

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

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

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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 average 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 immunosuppressive 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 variable dosage to keep the absolute neutrophil count to 2×10^9/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 methylprednisolone for 3 days and if necessary with the addition of ALG or azathioprine.

In all 18 cases, the brain and spinal cord were studied macroscopically after fixation in 20% formalin for at least 7 days. After fixation, the brains were cut into coronal slices after transection 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 abnormal 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 microscopic 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 neuropathological findings with the clinical data.

Results

Clinical neurological manifestations were noted in 13 patients (72%). Preoperative neurological events were documented in 11 patients and postoperative events in 11. At autopsy, 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 summarized 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 available and the neuropathological assessment, all patients had some infarcts that antedated the transplantation. These old cerebral infarcts were found in patients with massive myocardial infarcts (cases 1 & 7), congenital heart diseases (cases 11 & 18), idiopathic cardiomyopathy (cases 5, 6 & 13) and one post-infective 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 infarcts were located 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 dizziness (cases 12) that were related to cardiac arrhythmia. One patient (case 7) with left hemiparesis and cerebellar dysfunction had infarcts of the right basal ganglia, internal capsule and left cerebellum visualized on the computerized tomography (CT) before transplantation. Two patients had no neurological manifestation documented before transplantation. Only three (cases 7, 11 & 12) of the eight with cerebral infarcts 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 encephalopathy 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 terminal 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 moderate 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 neuronal 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 treatment. 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

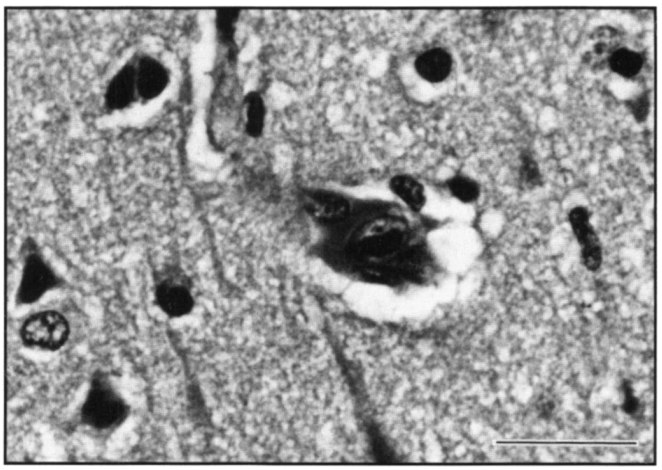

Figure 1 — Cytomegalovirus inclusion body within nucleus of a neuron in the cortex (hematoxylin-eosin stain; Bar = 30 μm).

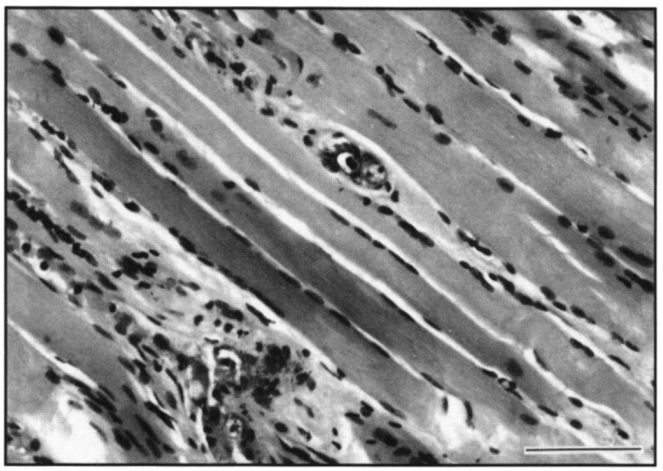

Figure 2 — Cytomegalovirus inclusion bodies within nuclei of skeletal muscle (Hematoxylin-eosin stain; Bar = 40 μm).

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-

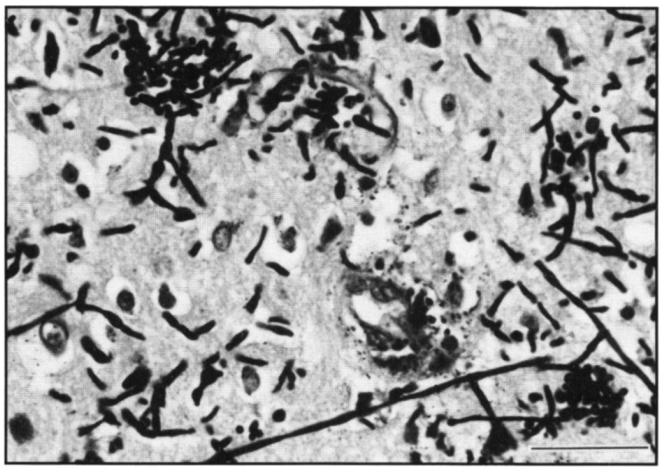

Figure 3 — Pseudohyphae and yeast forms in cerebral candidiasis. Note the lack of inflammatory response (Periodic Acid-Schiff stain; Bar = 40 μm).

Figure 4 — Fungal hyphae of Aspergillus species with acute angle branchings in lateral ventricle. There is a polymorphonuclear infiltrate and the choroid plexus is seen at the top right corner (Gomori methenamine silver stain; Bar = 100 μm).

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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.[8] 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.[9]

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,[6,7] 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.[10,11] 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.[12,13] 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.[14] 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.[14,15] 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.[16,17]

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.[4,18-20] 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.[20] 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.[5-7,22,23] 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.[24] Cerebral candidiasis is probably the most common postmortem cerebral mycosis and yet it is rarely appreciated clinically.[25] Because this mycosis usually produces intracerebral microabscesses, 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.[26] Because of the propensity of the fungus to invade larger cerebral vessels causing vascular damage and thrombosis, hemorrhagic infarction is a common presentation.[26] 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.[27-32] 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.[27] Most of these seizures were associated with old cortical infarcts which were considered embolic in origin.[27,28] 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.[30,31] 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.[33,34] As in one of our patients, this neurotoxicity of Cyclosporin A is associated with hypomagnesemia and therefore could be reversed by magnesium replacement.[33]

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.[34-37] The neuropathological findings described are severe reactive astrocytosis in the white matter with no evidence of fungi, viral inclusions, recent or old haemorrhages.[36] 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.[9,38,39] Similar lesions were also found in the basis pontis of patients with human immunodeficiency virus (HIV) infection and other forms of immunosuppression.[40-42] Though no definite pathogenesis is known, a common denominator for such white matter pathology 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.[43] 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.[6] 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,[6]) and found neurological disorders in 50% of the patients.[5] 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%.[7] 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.[44] 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.[4,18,19,45,46] 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.[5-7] 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 cyclosporin. 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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