Current Concepts of Cerebrovascular Disease and Stroke

Spectrum of Neurologic Events Following Cardiac Transplantation

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Cardiac transplantation is increasingly an alternative treatment for selected patients with intractable heart failure. Since its introduction in 1967, advances in postoperative care, particularly in the use of immunosuppressive regimens, have improved survival to 85% at 1 year and 65% at 5 years. Although graft rejection and infection remain major causes of mortality, neurologic complications occur in 50-60% of patients and contribute significantly to morbidity and quality of survival. Knowledge of the spectrum of neurologic complications combined with an intensive diagnostic and therapeutic approach is needed to reduce the neurologic morbidity.

Cerebrovascular Events

In autopsy series, ischemic-anoxic neuronal changes, laminar necrosis, and remote and recent infarcts have been found in up to 50% of patients. Ischemic-anoxic changes, invariably associated with encephalopathy and seizures in the early postoperative period, have been correlated with cardiopulmonary bypass mean pressures of less than 50 mm Hg and postoperative hypoperfusion or circulatory collapse. Remote cerebral infarcts are present in 20% of cases in autopsy series and in 13-15% in clinical series. Although intraoperative or postoperative hypotension may cause worsening of preexisting neurologic deficits, the majority of remote infarcts in autopsy series have not been associated with new neurologic manifestations. Recent infarcts, which have been identified in approximately 13% of autopsy patients, are often accompanied by early postoperative encephalopathy, seizures, and focal neurologic deficits. Perioperative infarcts have been attributed to cardioembolism in the setting of acute cardiac rejection, intraoperative aortic thrombosis, fat embolization, and cerebrovascular atherosclerosis.

Petechial subarachnoid hemorrhages and subdural hemorrhages have been rarely reported and may reflect consumption of platelets and coagulation factors and the use of anticoagulation during extra-corporeal circulation. Hemorrhagic infarction raises the suspicion of cerebral embolism or the presence of an angiodestructive opportunistic infection such as Aspergillus. Intracerebral hemorrhage is rare and has been attributed to uncontrolled hypertension or coagulopathy. However, in our institution, lobar intracerebral hemorrhage in the absence of an underlying vascular anomaly, chronic hypertension, or coagulopathy occurred in 5% of early transplants. These patients were young, had smaller body surface areas, and were transplanted for cardiomyopathy. All had relatively lower preoperative mean arterial pressure and greater postoperative improvement in mean arterial pressure and cardiac index. The mechanism of hemorrhage is probably relative cerebral hyperperfusion from abrupt increases in blood pressure and cerebral blood flow in the presence of a disordered cerebral autoregulatory response. All of these patients had a prodromal period of vascular headache that preceded the hemorrhage. Similar but less dramatic relative hemodynamic changes occurred in an additional group of patients with vascular headache alone within the first week postoperatively. In these patients the headaches, often accompanied by nausea, vomiting, flushed facies, and bounding pulses, responded, sometimes exquisitely so, to β-adrenergic blocking agents.

Encephalopathies and Neurobehavioral Syndromes

In the immediate postoperative period, encephalopathy and psychosis with disorientation and confusion are usually related to a global hypoxic-ischemic insult. Encephalopathies have also been associated with multiple metabolic abnormalities, renal and hepatic dysfunction, multiple organ failure, sepsis, and as part of a terminal illness. In patients with preoperative biventricular dysfunction and hepatic congestion, impaired metabolism and renal excretion of anesthetics and nitroprusside also need to be considered.

Cyclosporine has been associated with a leukoencephalopathy in noncardiac transplant patients. The leukoencephalopathy presents with seizures, focal neurologic deficits, areas of increased signal in the white matter on magnetic resonance image (MRI) scanning, and elevated blood cyclosporine levels. The syndrome is presumably due to cyclo-
Sporine toxicity, as cerebrospinal fluid cyclosporine levels represent 4–7% of whole blood cyclosporine levels, and the syndrome is reversible with temporary discontinuation of cyclosporine.  

A careful search for infection should be instituted when encephalopathy or neurobehavioral syndromes persist despite correction of metabolic abnormalities since these may be due to cerebral opportunistic organisms that are otherwise unsuspected.

Seizures

Seizures occur in approximately 15% of patients after cardiac transplantation. In the immediate postoperative period, recurrent focal seizures or multifocal seizures are usually the result of focal cerebral infarction or anoxic-ischemic encephalopathy. In association with an early postoperative vascular headache and a relative hyperdynamic state, seizures may also be a manifestation of relative cerebral hyperperfusion. Severe metabolic disturbances may also cause seizures, particularly hypomagnesemia related to cyclosporine use. Elevated levels of cyclosporine in the absence of hypomagnesemia have also been associated with seizures. The patients respond to lowering the cyclosporine dose.

Seizures in the early postoperative period are usually isolated events that occur in brief clusters. Since they lead to epilepsy infrequently, long-term antiepileptic drug therapy is seldom indicated. Outside of the early postoperative period, however, focal or generalized seizures may be the presenting manifestation of an intracranial opportunistic infection that requires intensive evaluation with computed tomographic (CT) or MRI scanning and spinal fluid analysis.

Parenteral benzodiazepines are least likely to induce the hepatic enzyme system responsible for metabolizing cyclosporine and corticosteroids and are the preferred initial treatment. If maintenance therapy is warranted, valproic acid should be used for generalized seizures in the absence of hepatic dysfunction. Focal seizures and secondarily generalized seizures require an alternative choice. However, carbamazepine, phenytion, and phenobarbital all stimulate hepatic enzyme systems and result in decreased levels of cyclosporine and corticosteroids with decreased immunosuppressive effect. Hirsutism and gingival hyperplasia are enhanced with the concomitant administration of cyclosporine and phenytion. When anticonvulsants are required, cyclosporine concentrations need to be monitored and adjusted carefully, and steroids may need to be increased approximately 25–30% to maintain immunosuppression.

Peripheral Nerve Injuries

Peripheral nervous system injuries after cardiac transplantation are similar in incidence and distribution to those complicating open heart surgery in approximately 13% of cases. The most common injury is a lower trunk brachial plexopathy attributed to stretching during chest wall retraction or compression by a hematoma incurred at the time of jugular vein cannulation for line placement. Recurrent laryngeal nerve injury is uncommon and is also presumed to be due to traction. Phrenic nerve injuries with diaphragmatic paralysis or prolonged postoperative hiccups are more likely cold-induced from packing the heart in ice at the time of transplantation. Saphenous nerve injuries can be incurred during femoral arterial cannulation for cardiopulmonary bypass or cardiac-assist device placement. Neuropathies of the peroneal nerve localized to the fibular head and the ulnar nerve localized to the elbow are related to compression either from intraoperative positioning or from prolonged periods of bed rest in obtunded or cachectic patients.

Central Nervous System Infections

Infectious complications have been reduced from 14% to 5% with newer immunosuppressive regimens that combine cyclosporine, azathioprine, and corticosteroids. However, the mortality of patients with intracranial infections remains high and is due as often to the disseminated nature of their disease as to the consequences of intracranial involvement. Survival is dependent on prompt diagnosis and institution of appropriate therapy, and, therefore, knowledge of the spectrum of pathogens and a high index of suspicion because of the subtleties of presentation are critical.

Immunosuppressive therapy designed to prevent allograft rejection, by definition, results in a defect in cell-mediated immunity, rendering the individual susceptible to certain fungi (Aspergillus, Mucor, Candida, Cryptococcus, Histoplasma, and Coccidioides), protozoans (Toxoplasma, Strongyloides), bacteria (Listeria, Nocardia, Mycobacterium), and viruses (herpesviruses, hepatitis, papovaviruses). Exogenous immunosuppression is also modulated by the concomitant immunosuppressive effects of chronic viral infection (cytomegalovirus, Epstein-Barr virus), certain metabolic derangements, and nutritional status. In the immediate posttransplant period, immunosuppression may reactivate a smoldering or subclinical infection, or infection can be transmitted via an infected allograft or through the various portals common to any surgical patient.

The first month is not a high-risk period for central nervous system (CNS) infections, but patients who have established chronic viral infections at this point will be at higher risk in the subsequent months. The risk of infection is at its peak between 1 and 6 months posttransplantation, and after 6 months at least half of the infections are associated with increased immunosuppressive therapy for acute recurrent or chronic rejection. The clinical course is most often subacute or chronic, although Listeria and Aspergillus may evolve acutely over days. The signs and symptoms, which are often subtle, include combinations of headache, fever, meningismus, encephalopathy, and focal neu-
rologic deficits. Given the propensity of certain organisms to seed the CNS, an intensive search for CNS involvement should be undertaken in neurologically symptomatic or in asymptomatic individuals with pulmonary or cutaneous involvement by *Aspergillus*, *Nocardia*, or *Cryptococcus*, and in the presence of *Listeria* bacteremia.

*Aspergillus* accounts for nearly 25% of all intracranial infections and occurs after the first posttransplant month. The intracranial infection is due to hematogenous spread from a pulmonary source and produces areas of focal meningoencephalitis or circumscribed solitary or multiple brain abscesses. The clinical presentation may be acute with focal neurologic deficits, encephalopathy, and seizures or a subacute encephalopathy. The organism is angiinvasive, and the presence of hemorrhage is highly suggestive of *Aspergillus*. CT scanning shows low density lesions, often involving deep structures, that may be either minimally ring enhancing or nonenhancing. The spinal fluid may be normal, and aspiration is required for diagnosis. Early detection and intensive antifungal therapy can successfully contain the cerebral infection, but the mortality rate remains high in the presence of disseminated disease.

Toxoplasmosis accounts for approximately 12% of intracranial infections and is associated with concomitant viral infections, particularly cytomegalovirus. As with *Aspergillus*, a meningoencephalitis or focal brain abscess is the most common type of involvement, with headache and fever being mild or absent. Serologic testing can be helpful in distinguishing between reactivation of latent infection and recent acquisition from an infected donor heart. Seroconversion after transplantation of a seropositive donor heart is an indication for prophylactic treatment since these patients are at high risk for fulminant disseminated infection. Ring enhancement on CT scanning is often seen, and MRI can be helpful in detecting small areas of hemorrhage in the abscesses. Rising antibody titers and regression of lesions with appropriate therapy may be diagnostic, but brain aspirates are often required for definitive diagnosis.

*Cryptococcus* and *Listeria* each account for 10% of intracranial infections. *Cryptococcus* typically presents as a chronic meningitis, although CT or MRI scanning may show small areas of focal meningoencephalitis. Headaches and fever are commonly present, but meningeal irritation is often absent. Cerebrospinal fluid findings demonstrate a lymphocytic pleocytosis (usually less than 400 white blood cells per cubic millimeter) and hypoglycorrhachia. In the uncommon acute presentations a polymorphonuclear pleocytosis may be more suggestive of a bacterial infection. Cryptococcal antigen determination in cerebrospinal fluid is the most sensitive technique for diagnosis and serves as a guide to therapy, with titers of less than 1:250 associated with a good clinical outcome.

*Listeria* presents as an acute or subacute meningitis, usually of less than 10 days' duration, and is rarely seen within the first posttransplant month. The most common presentation includes fever and headache with variable meningeal irritation, although a rhombencephalic form has been described that involves multiple cranial neuropathies and progressive obtundation. Cerebrospinal fluid findings are typical of a bacterial meningitis, with increased opening pressure, polymorphonuclear pleocytosis, and elevated protein. Gram stains may be negative, or the organism may appear as a coccobacillary form mistaken for *Streptococcus pneumoniae*. *Listeria* has a propensity for seeding the CNS, and diagnostic lumbar puncture should be performed in any patient with a documented *Listeria* bacteremia.

Diffuse viral encephalitis is produced by all four human herpes group viruses (cytomegalovirus, herpes simplex, herpes zoster, and Epstein-Barr), which may also produce a myelopathy. Cytomegalovirus infection is often associated with concomitant infections with other opportunists and is usually part of a disseminated infection in which chorioretinitis can be an important clue. Herpes simplex also occurs with disseminated viremia and is more easily cultured from mucosal vesicles or urine than from cerebrospinal fluid. Herpes zoster infection usually occurs after dissemination from a localized dermatologic infection and may involve the spinal roots and cord at that level. Regression of disseminated herpes zoster has been reported with reduced immunosuppressive therapy. Epstein-Barr virus infection impairs modulation of B-lymphocytes and is felt to be an important determinant in the development of monoclonal B-cell primary CNS lymphomas. The human papovavirus, JC virus, produces progressive multifocal leukoencephalopathy (PML), which has been reported in long-term survivors of organ transplants. The clinical presentation is a slowly progressive multifocal neurologic disease with encephalopathy and delirium. Brain biopsy is required for accurate diagnosis. PML will be seen more commonly as survival rates from cardiac transplantation continue to improve.

Rhinocerebral involvement with *Mucor* accounts for 4% of intracranial infections and tends to occur in diabetics. The infection originates in the paranasal sinuses, is angiinvasive, and spreads contiguously to involve orbital structures and cranial nerves and ultimately invades the brain. Visualization of a black eschar on palatal or nasal mucosa or blackish purulent drainage is characteristic. Biopsy and debridement as well as correction of hyperglycemia and acidosis, coupled with appropriate antifungal therapy, can contain the disease prior to CNS involvement.

The most common causes of focal meningoencephalitis/abscess are *Nocardia* and *Candida* species. *Nocardia* has a clinical presentation similar to that of *Aspergillus*, invariably in the presence of a
pulmonary infection but with a more chronic progression of symptoms. Bacterial cerebritis and abscess formation with gram-negative organisms are much less common.

*Candida* seeding of the central nervous system usually takes the form of a subacute or chronic meningitis or of multiple cerebral abscesses that are a preterminal sign of disseminated disease. *Candida* can sometimes be cultured from the cerebrospinal fluid, but, as with the other infections, brain aspiration is usually required for prompt diagnosis.

**Complications of Immunosuppressive Agents**

Chronic corticosteroid administration can contribute to osteoporosis and excessive weight gain, producing low back pain and vertebral compression fractures that occur most commonly in the thoracic and lumbar vertebrae. A steroid-induced myopathy may produce proximal lower extremity weakness but is less common since the use of cyclosporine, which allows for lower doses of corticosteroids. Mood alterations consisting of euphoria, dysphoria, and mild agitation are common with steroid administration and may occur at any stage of treatment. While the most efficacious treatment of steroid-induced mental symptoms is drug withdrawal, this is sometimes not possible, and patients often respond well to phenothiazines or butyrophenones. Less frequent complications include epidural lipomatosis, which may require spinal cord decompression, and pseudotumor cerebri.

Cyclosporine has been implicated in a number of direct neurotoxic effects, of which encephalopathy and seizures have already been discussed. A wide variety of additional neurologic symptoms have been associated with the use of cyclosporine, most commonly a 10-Hz postural tremor of the extremities that is aggravated by action and occurs in up to 20% of patients. This is rarely disabling and responds to lowering of the cyclosporine level. Other symptoms include burning acral dysesthesias, cerebellar ataxia, paraparesis with sphincter dysfunction, and a myelopathy with cerebellar features, areflexia, and long tract signs. Isolated cases of a multiorgan thrombotic microangiopathy, visual hallucinations, and mixed axonal and demyelinating neuropathy have been attributed to cyclosporine as well.

**Neoplasms**

Primary CNS lymphoma occurs in approximately 2% of all transplant patients. The tumors are commonly multicentric and involve subependymal white matter, deep perivascular spaces, and leptomeninges. Encephalopathy and neurobehavioral changes are the most common clinical presentation, and the clinical and radiographic appearance may be indistinguishable from an intracranial opportunistic infection. The lesions may be undetectable on a nonenhanced CT scan but typically enhance with contrast administration and are present as areas of increased signal on T2-weighted MRIs. Cerebrospinal fluid cytology is rarely positive, and diagnosis requires stereotactic biopsy to differentiate tumor from infection.

The exact mechanism of the malignant transformation of B-cells is unknown. A chronic Epstein-Barr virus infection has been implicated, with proliferation of B-lymphocytes in the absence of the body’s normal immunoregulatory system, which suppresses the polyclonal B-cell proliferation. CNS lymphoma may regress with reduction of immunosuppressive therapy or can be treated with radiotherapy.

**References**


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