

# Neurologic Complications of Orthotopic Liver Transplantation

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**O** rthotopic liver transplantation (OLT) has been successful in treating patients with chronic hepatic disorders ranging from cirrhosis to hepatocellular carcinoma. Patient outcome has improved substantially because of better preservation of donor livers and surgical advances such as venovenous bypass, refinements in biliary reconstruction, and improvement in current immunosuppressive regimens.<sup>1</sup> Despite these advances, neurologic complications are an important cause of morbidity and mortality in patients receiving OLT and are a challenge for both the transplant surgeon and the neurologist.

Neurologic complications have been estimated to develop in more than 30% of patients who receive OLT.<sup>2</sup> Moreover, 75% of such patients develop neurologic complications within the first month after the procedure.<sup>1,2</sup> **Table 1** lists the major neurologic complications of OLT. Anoxia, septic encephalopathy, brain hemorrhage, and seizures are the most frequent complications encountered. Patients who have neurologic symptoms or signs prior to transplantation (eg, chronic hepatic encephalopathy) are at a greater risk for neurologic complications after surgery. Patients who have involvement of the nervous system after transplantation have a higher mortality,<sup>2</sup> and more than 70% of patients who die of complications of OLT have nervous system pathology.<sup>3</sup> This article reviews the major neurologic complications of OLT. Encephalopathy, seizures, infection, cerebrovascular complications, immunosuppressive agent-associated complications, and neoplasm development are discussed.

## ENCEPHALOPATHY

Encephalopathy is the most frequent neurologic complication of OLT. Up to 84% of patients exhibit some degree of encephalopathy during their postoperative course.<sup>1</sup> The encephalopathy occurs typically but not exclusively in the early postoperative period (ie, within 1 month of surgery).<sup>4</sup> Some studies suggest that the risk of encephalopathy after OLT is related to the presence of preoperative hepatic encephalopathy;<sup>5</sup> however, this theory has not been systematically confirmed.<sup>1</sup>

In most patients with postoperative encephalopathy,

the etiology is difficult to identify (**Table 2**). According to one study, etiologies were found to be multifactorial or undetermined in 64% of encephalopathic patients.<sup>6</sup> However, subsequent pathologies at autopsy identified subarachnoid hemorrhage, meningitis, infarction, polyclonal B-cell lymphoma, spinal cord necrosis, and cytomegalovirus infection.<sup>6</sup> Patients who undergo OLT are also at risk for central pontine myelinolysis, particularly in the early postoperative period.<sup>7</sup>

## SEIZURES

Seizures are the second most common neurologic complication reported in OLT patients. Seizures have been reported to occur in 25% to 46% of patients who have undergone OLT.<sup>1,8,9</sup> Most seizures in liver transplant patients are tonic-clonic in type; a high percentage (up to 28%) of these patients subsequently suffer an episode of status epilepticus.<sup>8</sup> Approximately 50% of the patients who develop seizures experience their first ictal event within 1 week after transplantation; more than two thirds of these patients experience seizures within 1 month after transplantation.<sup>8,9</sup>

The etiology of seizures in an OLT patient is usually related to a central nervous system (CNS) lesion (eg, stroke, central pontine myelinolysis, CNS infection)<sup>8</sup> and is often preceded by clinical encephalopathy. Seizures may also be a result of other complicating factors and have been associated with an uncommon syndrome with cerebellar involvement<sup>9</sup> in which patients have exhibited dysarthria, ataxia, and extremity weakness after their initial seizure. Although the patients improved with supportive treatment, both were left with residual neurologic deficits.<sup>9</sup> In general, seizures are an indication to search for central CNS abnormalities, particularly if associated with an encephalopathic clinical picture, which may be hemorrhagic and/or infectious in nature.

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**Table 1.** Neurologic Complications in Orthotopic Liver Transplant Patients

Complication	Frequency, %
Encephalopathy	> 80
Seizure	25–46
Infection	10
Cerebrovascular complications	< 10
Immunosuppressive agent–associated complications	< 10
Neoplasm development	< 5

### INFECTION

Infection involving the nervous system, which is most likely caused by the effects of immunosuppression, occurs in approximately 10% of patients who have undergone OLT. Infections can either occur in the context of cerebral hemorrhage or systemically with subsequent neurologic involvement (**Table 3**).<sup>10,11</sup> Frequently, both clinical scenarios are present.<sup>11</sup>

In cases of hemorrhage, *Enterococcus* and *Candida* species are often detected in the CNS vessels and blood as well as systemically. In addition, *Aspergillus* may be associated with sepsis and nonhemorrhagic involvement of the CNS.<sup>10,11</sup> In autopsy studies of patients who have died after OLT, *Aspergillus* was the most frequently encountered pathogen within the CNS,<sup>1</sup> and 20% of patients who die of OLT complications have evidence of infection within the CNS.<sup>3</sup> Primary viral infection of the CNS is infrequent.<sup>11</sup> However, viral infections from cytomegalovirus, hepatitis B, or hepatitis C may uncommonly cause fulminant systemic failure with secondary involvement of the CNS.<sup>11</sup> In situ hybridization studies have revealed significantly higher levels of cytomegalovirus DNA in brain specimens of patients who have undergone OLT compared with age-matched, nonimmunocompromised control patients.<sup>6</sup> However, formalized detailed studies have not been performed to confirm these observations.

### CEREBROVASCULAR COMPLICATIONS

With the improvements in surgical technique over the past decade, cerebrovascular complications are much less frequent today than during the early development of OLT. Nevertheless, anoxia and hemorrhage still occur in approximately 7% of all patients who undergo OLT.<sup>2</sup> Approximately 50% of the patients who die as a result of OLT complications have some degree of cerebrovascular compromise.<sup>3</sup> More than two thirds of OLT patients who develop anoxia subse-

**Table 2.** Causes of Postoperative Encephalopathy in Orthotopic Liver Transplant Patients

Subarachnoid hemorrhage
Central pontine myelinolysis
Infection
Meningitis
Lymphoma
Spinal cord necrosis
Viral infection

quently die, and OLT patients who experience CNS hemorrhage have a 40% mortality rate.<sup>12</sup>

Anoxic-ischemic events occur early in the postoperative course. Anoxic events tend to occur approximately 10 days after transplantation and are often preceded by transient or varying degrees of hypotension.

Hemorrhage and infarcts can occur throughout the postoperative period. Infarcts tend to occur earlier (ie, within 1 week), whereas hemorrhage occurs within 1 month.<sup>13</sup> Hemorrhage into the CNS typically occurs in the frontal and parietal lobes and less commonly in the subcortical regions.<sup>14</sup> As noted previously, hemorrhage is often associated with bacteremia and/or fungemia. In an autopsy series, Martinez et al<sup>1</sup> found that 24% of patients had evidence of cerebral hemorrhage, whereas 9% had evidence of infarcts; coexistent fungal or bacterial infection was noted in most patients. Clinical histories of these patients also revealed substantial systemic and/or metabolic complications, which masked focal neurologic signs in 50% of the patients.<sup>1</sup> Other studies have confirmed these data.<sup>3</sup>

### IMMUNOSUPPRESSIVE AGENT–ASSOCIATED COMPLICATIONS

Immunosuppressive agents have revolutionized clinical transplantation medicine, allowing the avoidance of immune system attack on the orthotopic graft. However, the development and use of medications such as cyclosporine, FK506, and OKT3 also introduced the side effects of the drugs as well as chronic immunosuppression (**Table 4**).<sup>15</sup>

#### Cyclosporine

In the first study of the direct effects of an immune suppression drug, de Groen et al<sup>16</sup> reported a syndrome of confusion, cortical blindness, quadriplegia associated with seizure, and coma in patients treated with cyclosporine after OLT. Although cyclosporine had been previously associated with headaches and

**Table 3.** Etiologic Pathogens in Orthotopic Liver Transplant Patients

<b>Typically associated with hemorrhage</b>
<i>Enterococcus</i>
<i>Candida</i>
<b>Typically not associated with hemorrhage</b>
<i>Aspergillus</i>
Cytomegalovirus
Hepatitis B
Hepatitis C

tremulousness, this report was the first of a more serious neurologic complication.<sup>2</sup> The symptoms of this syndrome were associated with high trough cyclosporine levels and decreased serum cholesterol levels. However, other reports have not confirmed this finding, and whether the low cholesterol level was etiologic or a risk factor for the syndrome is unclear.<sup>2,10</sup>

Additional follow-up studies have further defined the syndrome of cyclosporine-induced neurologic toxicity.<sup>3,10</sup> Patients exhibit tremulousness and restlessness, and approximately 50% of patients demonstrate an acute confusional state with psychosis, 20% of patients experience seizures, and less than 10% of patients demonstrate speech apraxia, action myoclonus, and cortical blindness.<sup>3,10</sup> In more than 75% of patients, the toxicity was associated with intravenous therapy; minimal changes were noted on magnetic resonance imaging (MRI), and no associations were found with trough levels of cyclosporine.<sup>10</sup> All patients recovered after cyclosporine was discontinued and subsequently administered at a lower dose.<sup>2,10,15</sup> Such complications usually occur within the first month of cyclosporine treatment. In contrast, a case has been reported of chronic cyclosporine neurotoxicity in a patient presenting with a brachial monoparesis and complex visual syndrome in addition to seizures and confusion after 2 years of cyclosporine therapy.<sup>17</sup> The patient partially improved with discontinuation of the medication, although persistent white matter changes were evident on T<sub>2</sub>-weighted MRI images.<sup>17</sup>

#### FK506

The immunosuppressive agent FK506 is associated with more frequent and more severe neurologic complications compared with cyclosporine, particularly in the early postoperative period after OLT.<sup>11</sup> In a prospective study of OLT patients, Mueller et al<sup>11</sup> revealed

**Table 4.** Neurologic Complications of Immunosuppressive Agents

<b>Cyclosporine</b>	<b>FK506</b>
Tremulousness	Headache
Headache	Tremor
Confusion/psychosis	Delirium
Coma	Coma
Seizures	Seizures
Speech apraxia	<b>OKT3</b>
Action myoclonus	Aseptic meningitis
Cortical blindness	Meningoencephalitis
Brachial monoparesis	Optic disk swelling
Visual hallucinations	Abducens palsy
	Capillary leak syndrome

twice the incidence of neurotoxicity in patients treated with FK506 compared with patients treated with cyclosporine. Follow-up revealed a more frequent occurrence of late neurotoxicity in the patients treated with FK506 compared with the patients treated with cyclosporine. In addition, if late neurologic complications developed, the mortality rate was significantly higher in patients treated with FK506 compared with patients treated with cyclosporine. However, the patients treated with FK506 also had severe metabolic abnormalities, which suggest that other factors may be involved in addition to the direct toxicity of FK506 to the nervous system.<sup>11</sup> Burkhalter et al<sup>18</sup> found similar results. These researchers ascribed the minor neurologic complications (tremor, headaches) to direct effects of the drug, but suggested that the major complications were multifactorial in origin and could not be ascribed to the FK506 alone.<sup>18</sup> However, an anecdotal report suggested that FK506 could cause a vasculitis in susceptible patients, which could account for some of the more severe complications noted in earlier studies.<sup>19</sup> The extent to which FK506 is directly responsible for neurologic complications is currently unknown.

#### OKT3

OKT3 is a murine monoclonal immunoglobulin G used to treat acute cellular rejection of allografted organs. Patients who have received the antibody can develop a subacute aseptic meningitis with or without an associated meningoencephalitis.<sup>20</sup> Some smaller studies have suggested that this disorder may occur in up to one third of patients treated with OKT3.<sup>20</sup> According to Strominger et al,<sup>21</sup> acute optic disk swelling and an

abducens nerve palsy may be associated with the aseptic meningitis. OKT3 has also been implicated in a capillary leak syndrome that results in an encephalopathy and seizures caused by focal breakdown of the blood-brain barrier.<sup>22</sup> In general, fever and transient cognitive dysfunction should prompt an evaluation for aseptic meningitis in patients treated with OKT3.

#### NEOPLASM DEVELOPMENT

Patients who are chronically immunosuppressed are at risk of developing primary CNS lymphoma. Typically a B-cell tumor, CNS lymphoma develops in approximately 2% of all transplant recipients who are immunosuppressed with either cyclosporine or FK506. These tumors can involve multiple areas of the brain, spinal cord, and/or meninges, and may present as an encephalopathy.<sup>23</sup> On MRI, the lesion is often thought to represent a sign of infection in an immunocompromised patient.<sup>23</sup> Primary CNS lymphoma is typically diagnosed with stereotactic biopsy and treated with radiation and chemotherapy.<sup>23</sup> Care must be taken to preserve both the immune system and the orthotopic graft in patients with immunocompromise caused by transplantation.

#### SUMMARY

OLT has prolonged and improved the lives of many patients with hepatic disease. However, neurologic complications do occur, and the astute clinician must recognize symptoms early to ensure the best possible outcome for patients. A thorough neurologic examination with appropriate diagnostic imaging and laboratory evaluation can detect most of the causes of neurologic involvement in patients who have undergone OLT. HP

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