CHAPTER 36

Neurological problems in liver transplantation

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Introduction

Neurological problems are reported in 13–47% of patients after orthotopic liver transplantation (LT) [1, 2], with a significantly lower incidence in living donor liver transplantation versus patients who receive a cadaveric graft [3]. Most neurological complications occur early after surgery and increase morbidity, mortality, and hospital stays [4–6].

In 1999, a Task Force was set up under the auspices of the European Federation of Neurological Societies (EFNS) to devise guidelines to prevent and manage neurological problems in LT [4]. We considered six key topics in clinical practice: immunosuppression neurotoxicity, seizures, central pontine myelinolysis (CPM), neuromuscular disorders, cerebrovascular disorders, and central nervous system (CNS) infections. Attention focused on problems emerging in the first 6 months after surgery.

The present article is an update and revision of the previous guidelines.

Search strategy

Each member of the Task Force was assigned one of the six selected topics and systematically reviewed the relevant literature through the MEDLINE database of the National Library of Medicine from January 2005 to June 2009, the Cochrane Library, existing guidelines (National Clinical Clearinghouse, Scottish Intercollegiate Guidelines Network, National Institute of Clinical Excellence) and textbooks.

Data collection and analysis of evidence was performed independently by each participant according to the above assignment.

On the basis of the single reports, A.S. produced a first draft of the updated guidelines, which was then submitted several times for the approval of all the members until any discrepancies on each topic were solved and a consensus was reached.

Grading of recommendations

The literature is analysed giving the class of evidence (I–IV) according to EFNS guidelines [7].

The recommendation section includes statements classified in levels A–C derived from Classes I–III of evidence according to EFNS guidelines when feasible. For those clinical areas exhibiting Class IV scientific evidence, recommendations were based on the agreement obtained and indicated in the text as Good Practice Points (GPP).

Results

Immunosuppression neurotoxicity

The most widely used immunosuppressants in LT are the calcineurin inhibitors ciclosporin (CS) and
tacrolimus (FK506). Mycophenolate mofetil, sirolimus (or rapamycin), and its derivate everolimus have recently been introduced. Corticosteroids, OKT3, and antithymocyte globulin complete the immunosuppressive regimen. Neurotoxicity is mainly associated with CS and FK506, amounting to 10–30% for CS and up to 32% for FK506 [4, 6]. Sirolimus, everolimus, and mycophenolate mofetil lack the neurotoxicity of calcineurin inhibitors [4, 8, 9]. Neurotoxicity often occurs early after surgery, not always related to high drug plasma levels. Manifestations vary and mainly affect the CNS. They are usually distinguished in minor (tremor, headache, insomnia, paraesthesiae) and major (encephalopathy, akinetic mutism, seizures, speech disorders, polyneuropathy, myopathy).

Several predisposing factors have been advocated for the neurotoxicity of calcineurin inhibitors: hypcholesterolaemia, hypomagnesaemia, hypertension, and hepatic encephalopathy [4, 10] (Class III). New oral formulations of CS (Neoral) [11] and delayed starting and low-dosage regimens [12] seem to attenuate the severity of neurotoxicity, whereas it may be exacerbated by concomitant treatments (e.g. metoclopramide) [13, 14] (Classes III and IV). Magnetic resonance imaging (MRI) may disclose non-enhancing high-resolution T2 images mainly involving the posterior white matter. However, CS- and FK506-related pontine abnormalities, similar to CPM, have also been reported, sometimes associated with an insidious speech disorder that may rapidly evolve into mutism and locked-in syndrome [4]. Given its sensitivity in revealing cerebral white matter abnormalities, MRI supports the diagnosis of neurotoxicity [15–17] (Classes II and IV).

To treat neurotoxicity, a reduction of dose and switching from CS to FK506 and vice versa have been suggested [18, 19] (Class IV).

The recent use of novel drug combinations (calcineurin inhibitors plus mycophenolate mofetil or sirolimus) allows lower dosages of CS and FK506 [20] without weakening the immunosuppression efficacy (Class IV). The same occurs with the implementation of so-called CS- and FK506-sparing regimens by switching to mycophenolate mofetil or sirolimus [4, 21] (Class IV).

In most cases, these approaches lead to a resolution of symptoms [22, 23] (Class IV) and a reversal of neuroimaging abnormalities [15, 16, 24, 25] (Class IV). However, some patients with irreversible deficits are occasionally seen [26, 27] (Class IV), especially if the immunosuppressive regimen is not changed promptly.

Minor side effects are usually transient and self-limiting. Headache, tremor, paraesthesia, and insomnia are successfully managed with symptomatic conventional treatment [1] (Class IV). However, a change in the immunosuppressive regimen has occasionally been necessary in refractory headache [28–30] (Class IV). Recently, a favourable prophylactic effect of riboflavin on post-transplant headache has been reported [31] (Class IV).

OKT3 neurotoxicity usually presents with headache, rarely with transient aseptic meningitis, and exceptionally with a diffuse encephalopathy. The use of lower doses or pre-treatment with steroids, antihistaminic drugs, or indomethacin may decrease the severity of symptoms [32] (Class IV). Acute side effects of corticosteroids include behavioural and mood disorders, while chronic use may lead to myopathy, both reversible with adjustment of therapy [33] (Class IV).

**Recommendations**

**CS and tacrolimus neurotoxicity**: prevention requires minimum efficacious doses, oral administration as soon as possible, strict monitoring of plasma levels (including metabolites), electrolyte imbalance (e.g. hypomagnesaemia), hypertension check and correction, and attention to pharmacological interactions (Level C). Brain MRI is the choice diagnostic tool (Level B) and should be performed as soon as severe neurotoxicity is suspected (GPP). In case of major side effects, prompt switching to a non-calcineurin inhibitor (e.g. sirolimus) is indicated (GPP). Secondary options include conversion from CS to tacrolimus and vice versa (GPP). Minor complications require switching only in case of intractable and invalidating symptoms. Generally, their treatment should follow the guidelines for these disorders, administering drugs lacking both hepatotoxicity and interference with immunosuppressants (e.g. gabapentin for paraesthesiae, riboflavin for migraine prophylaxis) (GPP).

**OKT3 neurotoxicity**: prevention consists of administering minimal dosages and premedication with corticosteroids (GPP). Aseptic meningitis does not need treatment because it is usually self-limiting. Encephalopathy requires antiedema agents and very rarely OKT3 withdrawal (GPP).

**Corticosteroid neurotoxicity**: severe acute behavioural disorders may be treated by a temporary reduction and/or withdrawal of intravenous steroid administration. Brief regimens of low-dose neuroleptics may be considered (GPP).
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Seizures

Seizures occur in 0–40% of LT recipients [4, 6, 34], with a tendency to lower numbers in the more recent reports. Most are generalized tonic-clonic seizures. Convulsive or non-convulsive status epilepticus is rare. Seizures occur most often early after surgery, due to drugs, acute metabolic derangement, hypoxic–ischaemic injury, cerebral lesions, sudden withdrawal of narcotic agents, or inadvertent discontinuation or changes in anticonvulsant drugs in patients with epilepsy. Immunosuppressant toxicity is the main aetiology [4].

Preventive measures mainly focus on the control of metabolic parameters and correct drug management. The diagnostic approach includes a wide spectrum of tests to cover all possible causes [35, 36] (Class IV). Cerebral MRI is the investigation of choice to search for seizure aetiology in the general population [37] (Class II) and also seems applicable in LT patients, as MRI can detect immunosuppressant-related brain damage, CNS infection, metabolic lesions, stroke, or CNS tumours.

No randomized controlled trials are available on the use of antiepileptic drugs in liver-transplanted patients. Treatment can be problematic because of both the interference between most antiepileptics and immunosuppressants, and the frequent need for intravenous therapy. Switching between tacrolimus and CS has been described to be effective for seizure control in immunosuppressant-induced cases [38] (Class IV). Among intravenous anticonvulsants, phenytoin was preferred in the past [35] (Class IV).

Considering the pharmacokinetic properties of levetiracetam (no protein-binding, no dependence upon liver cytochrome P450, renal excretion, no known active metabolites, no drug–drug interactions) and initial clinical experiences [39], this new antiepileptic drug can be recommended as a first-line therapy for seizure control in LT patients, although data from controlled studies are lacking (Class IV). Among oral antiepileptics, gabapentin, pregabalin, phenobarbital and phenytoin may reduce CS, tacrolimus and corticosteroid blood levels, with a delayed effect of up to 10 days. Prognostic studies report a favourable outcome for both survival and absence of seizure recurrence after a short period of therapy (1–3 months) if seizures are induced by metabolic derangements or calcineurin inhibitors [34, 35, 41] (Classes III and IV). Seizures due to cerebrovascular events, sepsis or organ rejection have a poor prognosis [34].

Recommendations

Seizure prevention requires close monitoring of metabolic parameters and immunosuppressant levels, and caution in managing discontinuation or adjustment of epileptogenic drugs (GPP). The diagnostic approach should routinely include laboratory tests, EEG, and neuroimaging. Cerebrospinal fluid (CSF) examination is indicated when CNS infection is suspected (GPP). Brain MRI is the current standard of reference (Level B). When MRI is not available or is contraindicated, computed tomography (CT) can be applied (Level C).

The first-line intravenous antiepileptic drug is levetiracetam at a dose of 500 mg twice daily (up to 1000 mg twice daily) (Class IV). Alternatively, phenytoin could be used dosed to target a level between 10 and 20 μg/ml (GPP). When oral administration is possible, gabapentin, pregabalin, or levetiracetam should be considered (GPP). Status epilepticus management must be managed according to guidelines for the general population (GPP). In most cases, antiepileptic therapy can be suspended after 3 months (Level C).

Central pontine myelinolysis (CPM)

CPM is usually seen in alcoholic and malnourished patients, attributed to a rapid correction of hyponatraemia. CPM has been reported in 1–8% of LT recipients [4]. The high incidence in LT is likely to be favoured by the usual hyponatraemic state of patients with cirrhosis and by the large replacement of fluids during the operation, leading to a sharp increase in plasma levels of sodium. CPM occurs early after surgery. The clinical picture can vary considerably from paucisymptomatic pictures to misleading presentations or severe signs characterized by dysarthria, paraparesis, or quadriparesis [4]. A high mortality rate has been reported [42, 43].

Hyponatraemia and an abrupt rise in serum sodium (>18 mM/l per 24–48 h) are significantly related to CPM in LT recipients [42, 43] (Class IV). Other risk factors may be the plasma osmolality increase after surgery, the duration of the operation, and high CS levels [43] (Class IV).
There is no definite therapy for CPM. Sporadic suggestions include the use of steroids or plasmapheresis [44] alone or in combination with intravenous immunoglobulins [45] (Class IV). Re-inducing hyponatraemia when undergoing LT, a perioperative hourly correction rate at or below 0.5 mM/l per hour should be maintained. The correction rate should not exceed 8 mM/l per day (GPP). MRI should be performed early and repeated if negative (GPP).

Neuromuscular disorders

Neuromuscular disorders present with focal or generalized weakness [4]. Focal weakness includes mononeuropathies, with an incidence of 2–13%, and brachial plexopathy (1–5.8%). Axonal involvement is common. Invasive procedures, perioperative positioning and rarely compressive masses (e.g. haematoma) are the main causes. Generalized weakness occurs in 1.5–10% of patients and consists of axonal or demyelinating polyneuropathy and necrotizing myopathy, mainly related to immunosuppression neurotoxicity and critical illness. Guillain–Barré syndrome and chronic inflammatory demyelinating polyneuropathy are also reported [4].

No systematic studies have analysed the risk factors for neuromuscular complications in LT. Diabetes and alcoholism do not seem to increase the risk of perioperative mononeuritis [51] (Class III). High doses of corticosteroids and the use of non-depolarizing neuromuscular blocking agents are reported to favour quadriplegia after LT [51, 52] (Class III). Diagnosis is mainly based on conventional electrophysiological study, muscular enzyme assessment and CSF examination. Nerve or muscle biopsy should also be considered. The prognosis is usually good [52–54] (Class IV), but some patients need mechanical supports to walk.

The prevention of perioperative neuropathy is focused on careful perioperative nursing [55] (Class IV). Mini-
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CNS infections
CNS infections in LT recipients are favoured by immunosuppression, the incidence being estimated to reach 5% [69, 70], with a high mortality [49, 71]. It seems reasonable to differentiate CNS infections after LT into those clinically relevant within 1 month after organ transplantation and those infections with the highest risk of occurring 1–6 months after LT.

Infections leading to CNS disease within 1 month are usually caused by the fact that the pathogenic agent was already present before transplantation, was acquired through the transplanted organ, occurred as a complication of surgery, or represents an intensive care complication (e.g., invasive catheter-associated infection, etc.) [71, 72]. Beside staphylococci, LT recipients have an immediate post-surgery risk of infection with enteric organisms, i.e., Gram-negative bacteria, enterococci or Candida.

The highest risk of developing a post-transplant CNS infection is seen 1–6 months after LT. In this period of time, parasites, fungi, and viruses of the family of herpesviridae (herpes simplex virus type 1 and type 2, human herpes virus 6, cytomegalovirus, varicella zoster virus) act as opportunistic pathogenic agents [72, 73]. Opportunistic infections presenting beyond 6 months after LT are frequently seen in patients with a chronic rejection reaction, namely in those patients needing high-dose

Cerebrovascular disorders
Acute cerebrovascular disorders occur in 2–6.5% of LT recipients, mostly with cerebral haemorrhage, usually within 2 months after surgery [4, 63, 64]. Focal deficits may be obscured by diffuse encephalopathy. Several risk factors are recognized, those directly associated with hepatic failure such as coagulation disturbances, and those secondary to immunosuppressive therapy such as hypercholesterolaemia, diabetes, and hypertension [65–68]. Perioperative events, such as cerebral hypoperfusion and massive transfusion, may also favour cerebrovascular injury. Causes of cerebral bleeding include Aspergillus angioapathy and mycotic aneurysms. Older age and systemic infection may be possible risk factors of in-hospital intracranial haemorrhage [64].

Adjustment of cerebrovascular risk factors before, during, and after LT is the main preventive measure [65, 67] (Class IV).

Diagnosis and treatment are similar to those adopted in the general population. Attention is paid to the search for infection as a cause of acute cerebrovascular disorders, in order to institute prompt systemic antibiotic/antifungal therapy once infection occurs, especially in elderly patients [64, 65] (Class III–IV). Effective measures should be taken to prevent post-transplant infection, such as improvement of patient’s systemic condition, bacteriological surveillance, and infection control measures.

Recommendations
Prevention includes correction of coagulopathies before surgery (e.g., administration of platelets and blood products, but with caution due to the risk of consumptive coagulopathy), avoiding perioperative cerebral hypoperfusion, and control of cerebrovascular risk factors after LT (especially hypertension) (GPP). According to general guidelines, CT scanning is the preferred diagnostic test in the early phases of acute cerebrovascular disorders, especially to detect haemorrhage (Level C). Despite its greater sensitivity, MRI is often not tolerated or is not applicable immediately after LT, but should be considered to characterize vascular lesions or to rule out other aetiologies (GPP).

A search for bacteriaemia or fungaemia to detect infection should be routinely applied (GPP). The general treatment of cerebrovascular disorders in LT should not differ from that applied in the general population (GPP). Concomitant antifungal treatment should be given in the presence of angiopathy related to CNS infections (Level C).
immunosuppression, particularly if they need additional immunosuppressive therapeutics.

Beside infections with members of the herpesviridae family (cytomegalovirus, Epstein–Barr virus), hepatitis B or C virus infections may already be seen affecting the central and peripheral nervous systems. In addition, such patients may develop the Epstein–Barr virus–associated B-cell lymphoproliferative disease [72]. Clinical patterns include meningitis, encephalitis, abscesses, a combination of all three, or even septic embolism.

Neuroimaging, spinal tap after excluding increased intracranial pressure, and a search for signs of systemic infection are the core of diagnosis. Brain biopsy can be performed in individual cases [69, 74] (Class IV). CSF polymerase chain reaction is crucial in detecting viral infections [75] (Class I). Prevention focuses on eradicating infection in donor, recipient, or both, and optimizing intensive care management, mainly avoiding nosocomial contamination, during both surgery and post-surgery intensive care management [69, 72, 76, 77] (Class III). No prospective data are available suggesting the need for specific prophylactic antimicrobial strategies for CNS infection in transplanted patients. Treatment is based on guidelines for immunocompromised patients [71, 72, 75, 78–82] and LT centres’ experience [69, 72, 83] (Class III). Antimicrobial agents can interfere with drugs used in liver-transplanted patients (e.g. voriconazole with tacrolimus and sirolimus, phenytoin and carbamazepine; amphotericin B with CS) [84].

**Recommendations**

An early in-depth diagnostic approach is advocated, including brain CT/MRI, lumbar puncture and possibly brain biopsy, and the search for extracerebral sources of infection (GPP). CSF polymerase chain reaction is essential for viral infections (Level A). Prompt administration of therapy on suspicion of the diagnosis without definitive proof is needed to control infection (GPP). An exhaustive search for latent infection in donor and recipient is required, including close monitoring for intestinal strongyloidiasis in patients who have lived for long periods in tropical or subtropical countries (Level C). Exposure to hospital contamination must be avoided (Level C). Specific drug protocols to prevent brain infections are not required (GPP).

Treatment of neurolisteriosis consists of prolonged administration of ampicillin intravenously; the second choice includes trimethoprim-sulfamethoxazole (Level C). For brain nocardiosis, prolonged administration of trimethoprim-sulfamethoxazole is suggested (Level C).

For brain aspergillosis, the first choice drug is voriconazole: initially, 6 mg/kg intravenously every 12 h in two doses, then 4 mg/kg intravenously every 12 h, switching to oral dosing (the same dosage) as tolerated and clinically justified; the maintenance regimen consists of 200–300 mg orally every 12 h. The duration of intravenous therapy should be between 6 and 27 days, followed by oral administration for 4–24 weeks (Level A). In cases of intolerance, contraindications, or therapy failure, use liposomal amphotericin B (1–5 mg/kg per day) or caspofungin 50 mg/day (with a loading dose of 70 mg on day 1) or itraconazole (except after voriconazole) (Level B). Surgical resection may be considered. Rhinocerebral mucormycosis needs maximally dosed liposomal amphotericin B (5–10 mg/kg per day).

First-line treatment for cryptococcal meningitis is a combination of (liposomal) amphotericin B plus 5-flucytosine. Schedule treatment includes: induction with amphotericin B (0.7 mg/kg per day) and flucytosine (150 mg/kg per day) for 2 weeks, followed by consolidation with flucytosine for 8–10 weeks (400–800 mg/day), followed by 6–12 months at lower doses of flucytosine (200 mg/day) (Level A). Treatment for herpesvirus-6 and cytomegalovirus encephalitis is ganciclovir and foscarnet, either alone or in combination (Level C). For progressive multifocal leukoencephalopathy, cidofovir is an option (GPP).

**Conflicts of interest**

We declare that we have no conflict of interest in connection with this paper.

**References**

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