

## EFNS guidelines on management of neurological problems in liver transplantation

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Neurological impairment after orthotopic liver transplantation (OLT) is common and represents a major source of morbidity and mortality. The diagnosis and management of neurological problems occurring after OLT are difficult and evidence-based guidelines for this task are currently lacking. A Task Force was set up under the auspices of the European Federation of Neurological Societies to devise guidelines to prevent and manage neurological problems in OLT. We selected six major neurological problems and approached them combining an evidence-based scientific literature analysis with a search of consensus by means of a Delphi process. Search results were translated into a series of recommendations constituting a basis for better care of patients with neurological complications after OLT.

### Background and objectives

Neurological problems are reported in 13–47% of patients after orthotopic liver transplantation (OLT) [1]. Most neurological complications occur early after surgery and increase the risk of mortality [2,3]. The spectrum of clinical presentations is wide and the etiology heterogeneous. Management is empirical and currently based mainly on practical experience, without evidence derived from scientific literature. Our study aimed to devise a uniform management protocol across different centers involved in the neurological care of liver-transplanted patients. We considered some topics highly relevant in clinical practice: immunosuppression neurotoxicity, seizures, central pontine myelinolysis, cerebrovascular disorders, neuromuscular disorders and cerebral infections. Our guidelines mainly address the prevention, diagnosis and management of problems emerging in the first 6 months after surgery.

### Search strategy

Assessment of reliable scientific literature and search of consensus by means of a Delphi process [4] were

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applied. Literature on selected topics was systematically reviewed (by MG and AS) through the MEDLINE database of the National Library of Medicine from 1969, Cochrane Library, existing guidelines (National Clinical Clearinghouse, Scottish Intercollegiate Guidelines Network, National Institute of Clinical Excellence) and textbooks. On the basis of literature analysis and the suggestions of panel members, a large number of statements were identified and submitted to the participants, who had to rank their agreement using a scoring system of 0 to 9 points, where 0–3 was disagreement, 4–6 uncertain, 7–9 agreement. Agreement had to be obtained with a maximum of three rounds. An 80% agreement level among members was set as acceptable. The material obtained by the Delphi process was integrated and summarized in graded recommendations. The literature was surveyed continuously up to December 2004 to update the recommendations which were approved by all members.

### Grading of recommendations

The literature analysis is presented giving the class of evidence (I–IV), according to the European Federation of Neurological Societies (EFNS) guidelines [5].

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 by the Delphi process and indicated in the text as good practice points (GPP).

## Results

### Immunosuppression neurotoxicity

The most commonly used immunosuppressants in OLT are the calcineurin inhibitors cyclosporin (CS) and tacrolimus (FK506). Mycophenolate mofetil and sirolimus 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 [6] and up to 32% for FK506 [7]. Sirolimus and mycophenolate mofetil lack the neurotoxicity of calcineurin inhibitors [8–10]. Neurotoxicity often occurs early after surgery, not always related to high plasma levels. Manifestations are various, mainly affecting the central nervous system, and are usually distinguished as minor (tremor, headache, insomnia, paresthesiae) and major (encephalopathy, akinetic mutism, seizures, speech disorders, polyneuropathy, myopathy).

#### *Literature analysis*

Several predisposing factors have been advocated: hypocholesterolemia [11], hypomagnesemia [12], hypertension [13] [class IV], and hepatic encephalopathy [2,6] [class III]. New oral formulations of CS (Neoral) [14] as well as delayed-starting and low-dosage regimens [15] seem to attenuate the severity of neurotoxicity, whereas it could be exacerbated by concomitant treatments (i.e. metoclopramide) [16,17] [class III, IV]. Magnetic resonance imaging (MRI) may reveal non-enhancing high-resolution T2 images mainly involving posterior white matter. However, CS- and FK506-related pontine abnormalities, similar to central pontine myelinolysis (CPM), have also been reported [18–21], sometimes associated with an insidious speech disorder which may rapidly evolve into mutism and locked-in syndrome [class IV]. Given its sensitivity in revealing cerebral white matter abnormalities, MRI supports the diagnosis of neurotoxicity [22,23] [class II, IV].

To treat neurotoxicity, a reduction of doses and conversion from CS to FK506 and vice versa have been suggested [24,25] [class IV]. The recent use of novel combinations of drugs (calcineurin inhibitors plus mycophenolate mofetil or sirolimus) allows lower dosages of CS and FK506 [26] without weakening the immunosuppression efficacy [class IV]. The same occurs with the implementation of the so-called CS- and FK506-sparing regimens by switching to mycophenolate mofetil [27] or sirolimus [8] [class IV].

In most cases, these approaches lead to a resolution of symptoms and reversal of neuroimaging abnormalities [21–23] [class IV]. However, some patients with

irreversible deficits are occasionally seen, especially if the immunosuppressive regimen is not changed promptly [28] [class IV].

Minor side effects are usually transient and self-limiting. Headache, tremor, paresthesiae, 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 [29] [class IV].

OKT3 neurotoxicity usually presents with headache, rarely with a transient aseptic meningitis and exceptionally with a diffuse encephalopathy [30]. The use of lower doses or pretreatment with steroids, antihistaminic drugs or indomethacin may decrease the severity of symptoms [31] [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 [32] [class IV].

### Recommendations

#### *CS and FK506 neurotoxicity*

Prevention requires minimum efficacious doses, oral administration as soon as possible, strict monitoring of plasma levels (including metabolites), electrolyte imbalance (i.e. hypomagnesemia) and 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 cyclosporine 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 paresthesiae, 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 (e.g. haloperidol, olanzapin, quetiapin, risperidon) may be considered [GPP].

## Seizures

Seizure incidence is about 5% [6,33,34]. Most are generalized tonic-clonic, but a focal onset may have escaped observation. Convulsive or non-convulsive status epilepticus is rare. Seizures occur early after surgery. Causes are drugs, acute metabolic derangement, hypoxic-ischemic injury, cerebral lesions, sudden withdrawal of narcotic agents, inadvertent discontinuation or changes in anticonvulsant drugs in epileptics. Immunosuppressant toxicity is the main etiology [3,33].

### *Literature analysis*

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 [33,35] [class IV]. Cerebral MRI is suggested as the investigation of choice to search for seizure etiology in the general population [36] [class II]. This also seems to be applicable in liver-transplanted patients, as MRI can help detect immunosuppressant-related brain damage. No randomized controlled trials are available on the use of antiepileptic drugs in liver-transplanted patients. Treatment can be problematic both because of the interference between most antiepileptics and immunosuppressants and the usual need for intravenous therapy. Among intravenous anticonvulsants, phenytoin is preferred [33,37] [class IV]. Among oral antiepileptics, gabapentin [35] and levetiracetam [38] are of interest both for their efficacy and lack of hepatic induction [class IV]. Prognostic studies report a favorable outcome both for survival and absence of seizure recurrence after a short period of therapy (3 months) in most cases [33,34] [class III, IV].

## Recommendations

Seizure prevention requires close monitoring of metabolic parameters (in particular, electrolytes) and immunosuppressant levels, and caution in managing discontinuation or adjustment of epileptogenic drugs [GPP]. The diagnostic approach should routinely include laboratory tests, electroencephalogram (EEG) and neuroimaging. Cerebrospinal fluid (CSF) examination is indicated when central nervous system infection is suspected [GPP]. Brain MRI is the current standard of reference [level B]. When MRI is not available or contraindicated, computerized tomography (CT) can be applied [level C]. The first-line intravenous antiepileptic drug is phenytoin, the administration of which in adults should not exceed 50 mg/min to obtain serum levels between 10 and 20  $\mu\text{g/ml}$  [GPP]. When oral administration is possible, new antiepileptics could be considered, e.g. gabapentin or levetiracetam [GPP].

Status epilepticus must be managed in accordance with guidelines for the general population [39] [level A]. In most cases, antiepileptic therapy can be suspended after 3 months [level C].

## CPM

Central pontine myelinolysis is a symmetrical demyelinating lesion at the center of the pons seen usually in alcoholics and malnourished patients, attributed to a rapid correction of hyponatremia [40]. CPM has been reported in 1–8% of liver-transplanted patients [3,41–43]. The high incidence in OLT is likely favored by the usual hyponatremic 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. Clinical manifestations do not differ from non-liver-transplanted patients, including insidious misleading presentations [41] or paucisymptomatic pictures [44]. A high mortality has been reported [45,46].

### *Literature analysis*

Hyponatremia and an abrupt rise in serum sodium ( $> 18 \text{ mmol/l/24–48 h}$ ) are significantly related to the occurrence of CPM in liver-transplanted patients [45,46] [class IV]. There is no definite therapy for CPM. Sporadic suggestions include the use of steroids and intravenous immunoglobulins with some benefit. Re-inducing hyponatremia in the very early phase of CPM has also been proposed [47] [class IV]. Prevention is based on a slow correction of perioperative hyponatremia [45,46], not exceeding 8 mmol/day [40]. Transplantation at an early stage of the liver disease has also been suggested [46] [class IV]. MRI is currently the best investigation [48] [class IV]. Serial MRI could be needed because the appearance of the lesion may be delayed [43] [class IV].

## Recommendations

Given enough time before OLT, hyponatremia should be corrected slowly. The variations in serum sodium concentration must be carefully monitored and controlled before and during surgery to avoid major fluctuations [GPP]. If the patient is hyponatremic when undergoing OLT, a perioperative hourly correction rate at or below 0.5 mmol/h should be maintained. The correction rate should not exceed 8 mmol/day [GPP]. MRI should be performed early and repeated if negative [GPP].

## Neuromuscular disorders

Neuromuscular disorders present with focal or generalized weakness. Focal weakness includes

mononeuropathies, with an incidence of 2–13% [49–51] and brachial plexopathy, the incidence of which is 1–5.8% [3,51,52]. Axonal involvement is common. Invasive procedures, perioperative positioning and rarely compressive masses (e.g. hematoma) are the main causes. Generalized weakness occurs in 1.5–10% of patients [3,49,51,53–55] and consists of axonal or demyelinating polyneuropathy and necrotizing myopathy, mainly related to immunosuppression neurotoxicity [56–58] and critical illness [54,55,59]. Guillain-Barré syndrome [60,61] and chronic inflammatory demyelinating polyneuropathy [62,63] are also reported.

#### *Literature analysis*

No systematic studies have analyzed the risk factors for neuromuscular complications in OLT. Diabetes and alcoholism do not seem to increase the risk of perioperative mononeuritis [50] [class III]. High doses of corticosteroids and use of non-depolarizing neuromuscular blocking agents are reported to favor quadriplegia after OLT [53,54] [class III]. Diagnosis is mainly based on conventional electrophysiological study, muscular enzyme assessment and CSF examination. Nerve or muscle biopsy should also be considered. Prognosis is usually good [49,54,55] [class IV], but some patients need mechanical supports to walk [53]. Prevention of perioperative neuropathy is focused on careful perioperative nursing [64] [class IV]. Minimizing the use of corticosteroids and neuromuscular blocking agents in a critical illness setting has proven to be of help in preventing neuromuscular disorders [65] [class IV]. Treatment includes a change of immunosuppression therapy when neurotoxicity is the cause [57,58] [class IV], and conventional therapy in case of Guillain-Barré syndrome [60] or chronic inflammatory demyelinating polyneuropathy [62] [class II]. No specific treatment exists for critical illness in neuromuscular disorders. Customary general measures for critical illness usually applied in intensive care units (e.g. insulin therapy) can reduce mortality and morbidity [66] [class II].

### **Recommendations**

#### *Perioperative mononeuropathies*

Prevention implies caution during catheterization, avoiding blinded cannulations and external compressions by blood pressure cuff or tourniquet [GPP]. To reduce perioperative malpositioning it is indicated to maintain the arms at <90° of abduction, to maintain the arms at <30° of extension when combined with abduction, padding of the exposed nerves (i.e. at the level of fibular head, popliteal space, calcaneus, under forearms, under hands), frequent repositioning during prolonged surgery. Patients should be instructed to

avoid postures potentially compressing or stretching the nerves [GPP].

#### *Generalized weakness*

Prevention requires avoiding, when possible, the prolonged use of non-depolarizing neuromuscular blocking agents and minimizing the use of high-dose intravenous corticosteroids [level C]. In case of calcineurin inhibitor toxicity, prompt switching to a different agent (e.g. sirolimus) is recommended [GPP]. Customary general measures for critical illness, including aggressive insulin-therapy, and conventional management of Guillain-Barré syndrome and chronic inflammatory demyelinating polyneuropathy are indicated [level B].

### **Cerebrovascular disorders**

Acute cerebrovascular disorders occur in 2–6.5% of OLT recipients, mostly with cerebral hemorrhage [3,67,68], usually within 2 months after surgery [3,68,69]. 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 hypercholesterolemia, diabetes, and hypertension [68–70]. Perioperative events, such as cerebral hypoperfusion and massive transfusion, may also favor cerebrovascular injury [68,71]. Causes of cerebral bleeding include *Aspergillus* angiopathy and mycotic aneurysms [68,69].

#### *Literature analysis*

Adjustment of cerebrovascular risk factors before, during and post-OLT is the main preventive measure [68,70] [class IV].

Diagnosis and treatment are similar to that 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 antimicrobial therapy [70] [class III–IV].

### **Recommendations**

Prevention includes correction of coagulopathies before surgery (e.g. administration of platelets and blood products but with caution because of the risk of consumptive coagulopathy), avoiding perioperative cerebral hypoperfusion and control of cerebrovascular risk factors after OLT (especially hypertension) [GPP]. According to general guidelines, computed tomography (CT) scan is the preferred diagnostic test in early phases of acute cerebrovascular disorders, especially to detect haemorrhage [level C]. MRI, despite its greater sensitivity, could be not tolerated or not applicable

immediately after OLT, but it should be considered to characterize some vascular lesions or to rule out other etiologies [GPP].

A search for bacteriemia or fungemia to detect infection should be routinely applied [GPP]. General treatment of cerebrovascular disorders in OLT should not differ from that applied in the general population [GPP]. Concomitant antifungal treatment should be given in the presence of angiopathy related to central nervous system infections [level C].

### Central nervous system infections

Central nervous system infections in liver-transplanted patients are favoured by immunosuppression. The incidence is estimated in 5% [72,73], with a high mortality [43]. *Lysteria monocytogenes*, *Aspergillus fumigatus* and *Cryptococcus neoformans* are the most commonly involved pathogens [73]. Viral infections are very rare, related to herpesvirus-6 and cytomegalovirus [73]. Progressive multifocal leukoencephalopathy has been occasionally reported [58,74]. Most central nervous system infections are metastatic from other sites (mainly gastrointestinal tract and lung). Clinical patterns include meningitis, encephalitis, abscesses, or a combination.

#### Literature analysis

Neuroimaging, spinal tap after excluding increased intracranial pressure, and the search for signs of systemic infection are the core of diagnosis. Brain biopsy can be performed in individual cases [42,72] [class IV]. CSF polymerase chain reaction is crucial in detecting viral infections [75] [class I]. Prevention focuses on eradicating infection in donors and recipients and avoiding nosocomial contamination [72,76,77] [class III]. No data are available suggesting the need for specific prophylactic antimicrobial strategies for central nervous system infection. Treatment is based on guidelines for immunocompromised patients [75,78–83] and OLT centres experience [72,84] [class III, II]. 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) [85].

### 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, upon suspicion of the diag-

nosis without definitive proof is needed to control infection [GPP]. An exhaustive search for latent infection in donor and recipients 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 neurolisterosis consists of prolonged administration of ampicillin plus gentamicin; second choice include 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 i.v. every 12 h in two doses, then 4 mg/kg i.v. every 12 h, switching to oral dosing (same dosage) as tolerated and clinically justified; maintenance regimen consists of 200–300 mg orally every 12 h. Duration of intravenous therapy should be between 6 and 27 days, followed by oral administration for 4–24 weeks [level A]. In case of intolerance, contraindications or therapy failure: liposomal amphotericin B (1–5 mg/kg/day) or capsosungin 50 mg/day (loading dose: 70 mg day 1) or itraconazole (except after voriconazole) [level B]. Surgical resection may be considered. First-line treatment for cryptococcal meningitis is a combination of liposomal amphotericin B plus 5-flucytosin. Schedule treatment includes: induction with amphotericin B (0.7 mg/kg/day) and flucytosine (150 mg/kg/day) for 2 weeks, followed by consolidation with fluconazole for 8–10 weeks (400–800 mg/day), followed by 6–12 months at lower doses of fluconazole (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 a possible option [GPP].

These guidelines will be updated when necessary and in any case within 2 years. We declare that we have no conflict of interest in connection with this paper.

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