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EDITORIAL

Cerebral complications of solid organ transplantation

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Introduction

Solid organ transplantation (SOT) is a highly effective treatment in patients with end-stage organ failure, but is associated with a substantial risk of complications, including neurologic complications. Depending on the type of SOT and evaluated time frame, neurologic complications are described in between 10 and 21% of kidney transplant patients [1] and 33% of liver transplant patients in the perioperative period [2] and in 85% of heart transplant patients during 18 years of follow-up [3]. The spectrum of complications is broad, including postoperative delirium, peri-transplantation stroke, drug toxicity, central nervous system (CNS) infections and post-transplantation CNS lymphomas [4]. Here, we provide a practical approach to management of major neurologic complications in SOT patients admitted to the ICU.

Postoperative delirium and early complications

Postoperative delirium is a frequent complication of liver, heart and lung transplantation, occurring in 10%–36% of cases [3, 5–7], and seems to be less frequent after kidney transplantation [8]. In patients receiving liver transplantation for alcoholic liver disease, increased pre-transplantation serum level of ammonia and shorter duration of abstinence were identified as risk factors [9]. Data in liver and lung transplant recipients suggest that obesity, pre-transplant acute kidney injury, intraoperative complications and benzodiazepine exposure are important risk factors [5–7]. Postoperative delirium is associated with adverse outcome, including increased use of hospital resources, graft rejection and mortality. Perioperative cerebrovascular complications, mostly ischemic strokes, occur in 5% of patients after intrathoracic surgery (i.e., lungs and heart transplants) [3]. Multiple cortical and upper brainstem strokes can cause a decreased level of consciousness with few focal neurologic signs, resembling encephalopathy.

Neurotoxicity of immunosupressive drugs

Calcineurin inhibitors (CNI), namely ciclosporin A and tacrolimus, have neurologic side effects that can occur even in patients with normal serum trough levels, such as headache, tremor, delirium, seizures, thrombotic microangiopathies (TMA) and posterior reversible encephalopathy syndrome (PRES) [2]. Some of them are dose-dependent and may respond to CNI dose tapering, with an increased risk of subsequent transplant rejection [10]. In cases of non-severe toxicity, a strategy consisting of tapering and slowly (e.g., over days) replacing the CNI with another can be considered. Otherwise, CNI must be stopped and replaced by a non-CNI immunosuppressant (e.g., mTOR inhibitors or belatacept).

TMAs occurring after SOT are most often caused by CNI dose-dependent endothelial toxicity and usually only have hematologic and renal involvement [11]. When neurologic manifestations or other signs of TMA are present at diagnosis, and if renal involvement persists after CNI discontinuation, a diagnostic workup searching for an alternate cause of TMA is warranted, including ADAMTS13 (A Disintegrin And Metalloprotease with Thrombospondin type 1 repeat S-13) and complement studies (complement factors C3, C4, CH50, B, H, I and CD46). Therapeutic plasma exchanges should be started promptly if thrombotic thrombocytopenic purpura or atypical hemolytic uremic syndrome cannot be ruled out.

PRES after SOT may be due to CNI toxicity on cerebral vasculature, leading to vasogenic edema mainly affecting

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Table 1 Major neurologic complications of solid organ transplantation in ICU patients

Complication	Postoperative delirium	Stroke	PRES/CNI toxicity	Brain abscess(es)	Meningitis/ encephalitis	Post-transplantation CNS lymphoma
Peak incidence after SOT	1st month	1st month	0–2 months	6 months	6 months	6 months and beyond
Altered mental status	+	±	+	±	+	±
Fever	–	–	–	±	+	–
Focal signs	–	++	±	++	±	++
Convulsive seizures	–	±	++	+	+	+
CSF findings	Normal	Normal	Normal	Abnormal	Abnormal	Normal
Brain imaging	Normal	Cerebral infarction or hemorrhage	Acute white matter lesions or normal	Focal lesion(s) ± edema ± mass effect ± herniation ± intraventricular rupture	Normal or White and gray matter lesions	Focal lesion(s) ± edema ± mass effect ± herniation
Diagnostic workup	Electrolytes and renal/liver function tests Betalactam plasma levels CNI plasma levels Consider EEG*	CT or MRI[#]	MRI CNI plasma levels EEG*	Extra-neurologic samples[$] Contrast enhanced CT or MRI[#] Brain biopsy Consider EEG*	CSF cultures and PCR MRI[#] Consider EEG	MRI Brain biopsy Consider EEG*
Treatment	Restore homeostasis Taper or stop eliciting medication Antipsychotics or alpha-2 agonists for persistent hyperactive symptoms	Reperfusion therapy in acute phase Secondary prophylaxis Rehabilitation	Taper or stop eliciting medication Treat hypertension	Antimicrobial treatment	Antimicrobial treatment	Oncology consultation Chemo- or radiation therapy

PRES posterior reversible encephalopathy syndrome, *CNI* calcineurin inhibitors; CNS central nervous system, *SOT* solid organ transplantation; CSF cerebrospinal fluid, *MRI* magnetic resonance imaging, *EEG* electroencephalography, *PCR* polymerase chain reaction, *CNI* calcineurin inhibitor

*EEG is proposed to rule out (non-convulsive) seizures and/or periodic discharges in patients with altered mental status. When suspicion of seizures is high, continuous EEG monitoring is preferred instead of spot EEG

[#] MRI is preferred but, in some instances, CT may suffice initially (e.g., in identifying cerebral hemorrhage) because for logistic reasons CT is usually more readily available for ICU patients

[$] In case of extra-neurologic involvement (i.e., respiratory samples, skin biopsy)

the white matter and in the most severe cases to cytotoxic edema and hemorrhagic transformations [12]. Treatment should include correction of aggravating factors such as hypertension and acute kidney failure and replacement of CNI by another immunosuppressive agent. CNI neurotoxicity may be obscured by steroid and beta lactam side effects, which can induce encephalopathy, myoclonus and (non-convulsive) seizures.

Central nervous system infections

Although CNS infections are uncommon in the early postoperative phase, latent infections due to intense immunosuppressive treatment and donor-derived infections may be observed. If the SOT patient has successfully gone through the 1st month, the spectrum of complications changes with higher risk of opportunistic infections, with an incidence <5% in most studies [4]. The most frequent pathogens include fungi (*Aspergillus*), yeasts (*Cryptococcus*), *Toxoplasma gondii*, viruses (e.g., JC virus or varicella zoster virus) and bacteria (e.g., *Mycobacterium tuberculosis* or *Nocardia*). Moreover, the risk of bacterial meningitis is sevenfold higher and includes pathogens such as *Pseudomonas aeruginosa*, *Escherichia coli* and *L. monocytogenes* [13]. As cerebrospinal fluid (CSF) biochemical and cellular abnormalities can be mild in SOT patients with CNS infections, broad antimicrobial treatment covering bacterial and viral infections is advised in all patients pending microbiologic testing. Antifungal, tuberculosis and anti-helminthic treatment should be considered if the patient has risk factors for

such infections. The prognosis of CNS infections in SOT patients is generally poor [3].

Practical approach

A thorough multimodal evaluation is mandatory to rapidly identify the most frequent conditions observed in ICU patients (Table 1) [14]. The type of transplantation and time between transplantation and development of neurologic symptoms are the main determinants of which complications should be first considered. Second, the type and history of immunosuppressive therapy (i.e., CNI and steroid exposure) is important to consider as an intensified immunosuppressive regimen and use of tacrolimus are risk factors for opportunistic infections or neurotoxicity, respectively. Third, co-trimoxazole prophylaxis may not provide full protection against infections by *Listeria monocytogenes*, *Toxoplasma gondii* and *Nocardia* species.

Physicians should be aware of the masking effect of immunosuppressive therapy itself, as for instance fever is often absent, and account for renal or hepatic failure and associated metabolic disturbances and/or drug accumulation. Evaluation should include a search for complications outside the CNS, laboratory examination for metabolic derangement and trough CNI plasma levels. In all patients cranial imaging with contrast should be performed first. MRI is preferable to identify cerebral edema and PRES, stroke or brain abscess. When space-occupying lesions causing brain shift are not identified, lumbar puncture (LP) needs to be performed for suspected CNS infection. Electroencephalography to rule out (non-convulsive) seizure(s) or periodic discharges should be considered in any SOT patient with altered mental status, with PRES and CNS infections carrying the highest risk of seizures in this population [15]. Emergency neurosurgery should be considered in patients presenting with space-occupying brain lesions and risk of brain herniation. Stereotactic brain biopsy/neurosurgical resection of brain lesions to identify the causative organism and perform resistance testing should be considered in all patients presenting with focal parenchymatous abnormalities (e.g., brain abscess), a negative CSF diagnostic workup and the absence of extracranial foci of infection. Tapering immunosuppression should be discussed in case of suspected CNI toxicity or severe (CNS) infection(s), respectively. Research aiming at preventing immunosuppression-associated complications is needed to improve neurologic outcomes after transplantation.

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Compliance with ethical standards

Conflicts of interest

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