

Neurotoxicity of Immunosuppressive Therapies in Organ Transplantation

Daniela ANGHEL^{a,b}; Radu TANASESCU^{a,b,c}; Ana CAMPEANU^d; Ioana LUPESCU^{a,e}; Giulio PODDA^c; Ovidiu BAJENARU^{a,f}

^a"Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania

^bFundeni Clinical Institute, Department of Neurology, Bucharest, Romania

^cUniversity of Nottingham, Academic Division of Clinical Neurology, Nottingham, UK

^dColentina Clinical Hospital, Department of Neurology, Bucharest, Romania

^eFundeni Clinical Institute, Department of Radiology, Medical Imaging and Nuclear Medicine, Bucharest, Romania

^fEmergency University Hospital, Department of Neurology, Bucharest, Romania

ABSTRACT

Immunosuppressive agents have revolutionized clinical transplantation medicine, allowing the avoidance of immune system attack on the transplanted graft. Nevertheless, the use of medications such as cyclosporine, tacrolimus and others also brought the side effects of these drugs. Early identification of drug-induced neurotoxicity in transplanted patients and of its specific causes is important, not only because of patient's poor clinical status but because of concomitant systemic and metabolic disorders which may obscure symptoms. Treatment and prognosis are highly dependent on the type of complication and it's early recognition. This review focuses on the clinical entities of neurotoxicity caused by immunosuppressive drugs in transplanted patients.

Keywords: immunosuppressive drugs, posttransplant states, neurotoxicity

INTRODUCTION

Neurological complications are common after organ transplantation and are associated with significant morbidity. Neurotoxicity occurs when the exposure to toxic substances alters the normal activity of the nervous system. Approximately one-third

of transplant recipients experiences neurologic alterations (1,2). The most common early complication seen with all types of transplanted organ is neurotoxicity (3) attributable to immunosuppressive drugs, because they are characterized by a narrow therapeutic index (underdosing is associated with increased risk of rejection episodes and overdosing may exacerbate drug-related toxicity).

Address for correspondence:

Daniela Anghel, MD, Fundeni Clinical Institute, Department of Neurology, 258 Fundeni Avenue, District no. 2, 022328, Bucharest, Romania.
E-mail: anghellc@yahoo.com

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Immunosuppressive drugs differ by their mechanism of action, as shown in Table 1.

Protocols of immunosuppression depend on type of transplanted organ and are permanently changing, but most of them consist of a combination between calcineurin inhibitors, purine synthesis inhibitors and glucocorticoids or a combination between monoclonal antibodies and calcineurin inhibitors.

- 1) *Corticosteroids* modulate the lymphocyte actions but can cause neuropsychiatric symptoms, including insomnia, irritability, impaired concentration, mood changes, mania, psychosis, depression, and delirium/confusion, with onset typically within days to weeks. Treatment consists of lowering the dose and administering short regimens of low-dose neuroleptics (e.g. haloperidol, olanzapine, quetiapine, risperidone). Peripheral toxicity occurs after long term use, usually as a proximal myopathy, with incomplete reversibility after cessation of the drug.
- 2) *Mycophenolate mofetil* reduces the amplitude of immune response by inhibiting purine synthesis in lymphocytes. It has no neurotoxicity, but rarely causes headache.
- 3) *The biologic agents* include polyclonal and monoclonal antibodies with immunomodulatory/immunosuppressive effects. They are used for the induction of immunosuppression and for the treatment of graft rejection.

3a) *Polyclonal* antibodies induce lysis of lymphocytes. Horse antithymocyte globulin (ATGAM) and rabbit antithymocyte globulin (ATG, Thymoglobulin) are used for immunosuppression induction and treatment of acute graft rejection. They have adverse effects (fever, thrombocytopenia, leukopenia, hemolysis, respiratory distress, serum sickness, anaphylaxis), but they are important therapy for hyperimmunized patient and severe acute cellular rejection in renal transplantation. Some adverse effects are ameliorated with steroids, acetaminophen and diphenhydramine.

3b) The *monoclonal* antibodies used in transplanted patients include anti-CD3 antibody (muromonab), anti-CD25 antibody (basiliximab and daclizumab), anti-CD20 antibody (rituximab) and anti-CD52 antibody (alemtuzumab). Except for muromonab, their administration in transplanted patients is associated with a very low prevalence of neurologic adverse effects.

Muromonab-CD3 (Orthoklon OKT3) is directed to the CD3 portion of the T-cell receptor, blocking the T-cell activation. This agent is now replaced by other monoclonal antibodies, because it has important adverse effects: cytokine release syndrome (fever, dyspnea, wheezing, headache, hypotension, diarrhea, vomiting, nausea, tremor, generalized weakness) and posttransplant lymphoproliferative disorder

No.	Class of immunosuppressive drugs	Drugs	Mechanism of action
1.	Corticosteroids	Methylprednisolone Prednisone	Regulators of gene expression
2.	Antimetabolites	Mycophenolate mofetil	Inhibitors of <i>de novo</i> purine synthesis in lymphocytes
3.	Biologic agents	Polyclonal antibodies (ATGAM, Thymoglobulin) Monoclonal antibodies (Muromonab, Daclizumab, Basiliximab, Rituximab, Alemtuzumab)	Lysis of lymphocytes Blockers of T lymphocyte activation
4.	Calcineurin inhibitors	Cyclosporine A Tacrolimus	Inhibitors of an intracellular phosphatase required for interleukin 2 production in the T lymphocyte
5.	Non-calcineurin inhibitors	Sirolimus Everolimus	Inhibitors of mammalian target of rapamycin (mTOR) activation in lymphocytes, resulting in cell cycle arrest and blockade of T-cell proliferation

TABLE 1. Classification of immunosuppressive drugs used in organ transplantation.

(PTLD). The possible neurotoxic adverse events include headache, seizures, aseptic meningitis and encephalopathy.

4a) *Calcineurin inhibitors*. Cyclosporine A (CsA) and Tacrolimus (Tcl) act as the cornerstones of the majority of immunosuppressive protocols to prevent graft rejection. In the peripheral immune system, CsA binds a protein found in the cytosol of the lymphocyte: cyclophilin. This complex inhibits calcineurin activation, lowering the interleukin 2 production in the T-cell.

Calcineurin is also expressed in several areas of the brain: cerebral cortex, striatum, substantia nigra, cerebellum and hippocampus (4). Calcineurin is the only calcium-activated phosphatase in the brain and a major regulator of key proteins essential for synaptic transmission and neuronal excitability, involved in memory and synaptic plasticity (5).

Early calcineurin inhibitor-induced neurotoxicity is considered when neurological symptoms occur within 4 weeks after transplantation (6). As mentioned before, neurotoxicity can occur both at therapeutic and at high CsA or Tac levels. Sometimes, neurotoxicity can be only indirectly inferred from the resolution of the clinical symptoms when treatment is discontinued.

Mechanisms underlying calcineurin inhibitors neurotoxicity:

1. CsA and Tac are highly lipophilic and are bounded in plasma especially to low-density lipoprotein (LDL). Low cholesterol concentrations lead to increased free concentrations of drugs but also lead to an increase in the amount of LDL receptors expressed on the cell membrane of astrocytes (at the blood-brain barrier); therefore, increased uptake of drugs can lead to damage of the blood-brain barrier as well as the white matter.
2. Neurotoxicity may be related to endothelin, produced in excess in the presence of calcineurin inhibitors. If endothelial integrity is disrupted, CsA and Tac could gain access to astrocytes. Endothelin could gain access to the cerebral vascular smooth muscle, resulting in vasoconstriction and vasospasm (7,8). Elevated circulating endothelin could promote systemic hypertension. Under such conditions, local ischemia and consequent white matter edema could show typical transient alterations in the subcortical pari-

etal and occipital lobes, as observed in cases of acute hypertensive encephalopathy (9) or in posterior reversible encephalopathy (PRES).

3. Part of CsA and Tac toxicity may arise from alterations in mitochondrial function (10), such as decrease of mitochondrial energy production and the subsequent activation of anaerobic glycolysis, impaired cellular calcium buffering, activation of proteases and phospholipases, activation of nitric oxide synthetase and generation of free radicals, leading to either apoptotic or necrotic cell death depending upon the severity of the insult (11).
4. Subcortical edema that is present in PRES can be the result of a hyperperfusion insult promoted by endothelial cell damage with breakthrough of autoregulation in the posterior circulation, which has paucity of sympathetic innervation.

Neurotoxic effects can manifest either in the central or in the peripheral nervous system.

The **major central** neurotoxic effect of calcineurin inhibitors is posterior reversible leukoencephalopathy syndrome (PRES), typically distributed in the posterior regions of the white matter of the brain. Other major side effects include akinetic mutism, toxic encephalopathy, seizures.

The **minor central** effects include insomnia, visual symptoms, headache, tremor, paresthesiae and mood changes; they are more frequent than major effects, occurring in almost 40% of transplant patients.

Treatment of **central** neurotoxicity:

Major symptoms of neurotoxicity must be treated by reducing the doses of immunosuppressives or by conversion from CsA to Tac and vice versa. Using a combination of drugs (calcineurin inhibitors plus mycophenolate mofetil or sirolimus) allows lower dosages of CsA and Tac without impairing the immunosuppression efficacy. In our transplantation center, we usually switch to sirolimus (when possible) or significantly lower the doses of calcineurin inhibitors; rarely do we hold the dose until the resolution of neurologic symptoms. Sometimes irreversible deficits are seen, especially if the immunosuppressive regimen is not rapidly changed.

Minor symptoms of neurotoxicity are easily managed with symptomatic treatment. We use common analgesics for headache, low doses of

benzodiazepines for insomnia (clonazepamum, midazolamum), beta blockers for tremor (metoprololum, propranololum), antiepileptics for paresthesiae (carbamazepinum, gabapentinum).

Peripheral toxicity occurs weeks to months after starting immunosuppressive treatment. Both the nerve and the muscle may be involved (12). Axonal and demyelinating neuropathy have been reported. The more severe forms have been observed during Tac therapy, such as multifocal demyelinating neuropathy resembling chronic inflammatory demyelinating neuropathy (CIDP). Some patients may respond to intravenous immunoglobulins or plasma exchange.

Risk factors for the development of calcineurin inhibitors-related neurotoxicity are: the use of methylprednisolone, arterial hypertension, fluid overload, hypocholesterolemia because it increases brain uptake of immunosuppressant drugs and drug interactions (13), hypomagnesemia, pre-existing brain disease, pre-existing blood-brain barrier alterations, hepatic encephalopathy, concomitant treatments (metoclopramide), surgical time >7 hours, and post-transplant hyponatremia (6).

Prevention can be achieved by oral formulations of CsA and Tac, delayed-starting and minimum efficacious doses of immunosuppressives, strict monitoring of plasma levels, correction of electrolyte imbalance and attention to pharmacological interactions (14).

Toxic encephalopathy

Neurobehavioral disturbances may develop after exposure to drugs which disrupt or abolish neural transmission in white-matter tracts devoted to high cerebral functions. Mild cases mimic a psychiatric disorder with inattention, apathy, forgetfulness, changes in personality, but severe cases produce major impairment (akinetetic mutism, dementia, coma) or death (15). Acute psychotic episodes manifest with agitation, crying, repetition of illogical sentences, rambling speech, abnormal perception, confusion and autonomic dysfunction. Neurologic signs such as hemiparesis, sensory deficits, and visual loss are less prominent than changes in mental status.

MRI (magnetic resonance imaging) shows symmetrically reduced diffusion (DWI-diffusion-weighted imaging) in the periventricular

and supraventricular white matter; DWI findings can be entirely reversible. Distinction of this entity from PRES can be done, because PRES typically affects the cortex or subcortical white matter on FLAIR (fluid attenuated inversion recovery); the periventricular white matter immediately around the ventricle is not involved, except in severe cases in which the subcortical white matter is already involved and PRES only uncommonly involves reduced DWI (16).

Therapy is nonspecific, involving the replacement of the toxic immunosuppressive agent and symptomatic treatment. We use tiapridalium or quetiapinum as antipsychotics for acute psychotic episodes, lorazepamum or bromazepamum as sedatives for agitation and supportive measures for vital functions.

Seizures

Seizures can be partial or generalized, most frequently of the tonic-clonic type. They can occur with or without structural brain lesions and with or without EEG alterations within the inter-critical period. Their incidence has been declining due to closer monitoring of drug levels and cautious dose initiation (17).

Treatment. For urgent management of seizures intravenous phenytoin is the choice, the administration of which in adults should not exceed 50 mg/min to obtain serum levels between 10 and 20 µg/ml (18). For oral administration, gabapentin or levetiracetam could be used in liver transplantation and valproate or carbamazepine could be used in other than hepatic transplantation. Status epilepticus must be managed in accordance with guidelines for the general population (19). In most cases, antiepileptic therapy can be suspended after 3 months (18).

PRES

It can manifest any time after transplantation, usually in the first month. After transplantation, several PRES-related risk factors, such as sepsis, shock associated with multiple organ dysfunction, graft versus host disease (GVHD) coexist with CsA or Tac toxicity. Blood levels of immunosuppressives do not correlate with the severity of neurotoxicity. It was suggested that genetic differences in the CsA metabolism might be related to CsA toxicity at therapeutic blood levels in a case report (20).

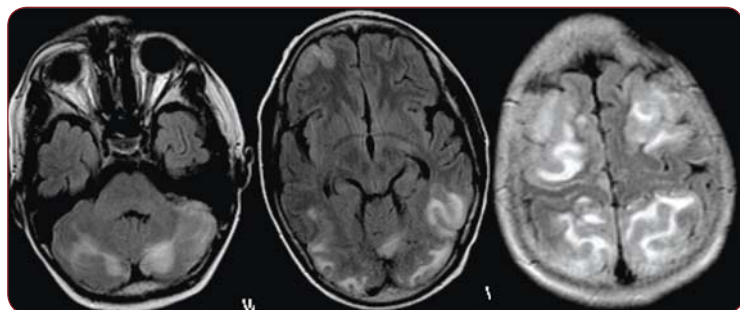


FIGURE 1. PRES in a liver transplanted patient: FLAIR hyperintensities in the subcortical and cortical regions of the bilateral parietooccipital lobes and cerebellar hemispheres (images from Fundeni Clinical Institute database).

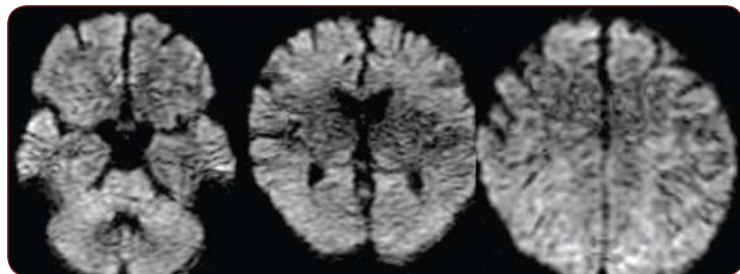
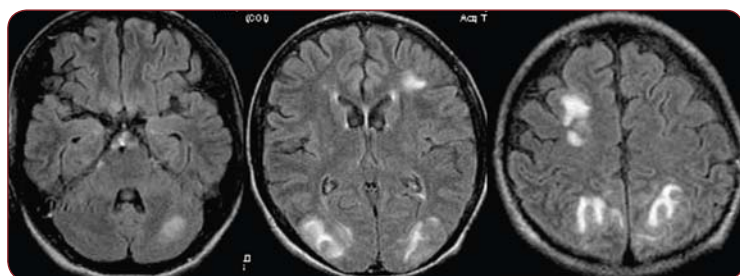


FIGURE 2. PRES in a renal transplanted patient (images from Fundeni Clinical Institute database).
Up: FLAIR images showing asymmetric hyperintensities in the left cerebellum and bilateral fronto-parieto-occipital lobes.
Above: DWI images showing normal signal in corresponding areas.

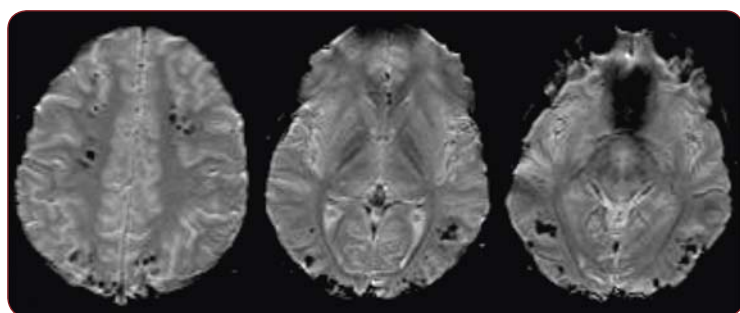


FIGURE 3. Sequelae of haemorrhagic PRES in a bone marrow transplanted patient. SWI GRE (susceptibility weighted imaging gradient echo) showing microbleeds in the fronto-parieto-occipital regions previously affected by PRES (images from Fundeni Clinical Institute database).

Clinical. Nausea, vomiting, headache, visual hallucinations, cortical blindness, confusion, disorientation, delusions, pyramidal motor weak-

ness, aphasia, ataxia and seizures are the most common initial clinical manifestations.

MRI should be performed early in the diagnostic evaluation of patients on calcineurin inhibitors who develop significant neuropsychic events (21). On T2-weighted and FLAIR MR images, hyperintensity in the subcortical and cortical regions of the bilateral parietooccipital lobes is typical (Figure 1) and resolves in few days or weeks. DWI is usually normal (Figure 2). Irreversible changes may appear in some parts of the lesions, reflecting intramyelinic or intracellular cytotoxic edema or hemorrhagic transformation (Figure 3). In patients with transplants, the hemorrhage complicating PRES is of three types (parenchymal haematoma, small minute haemorrhages <5 mm, subarachnoid haemorrhage) and occurs more frequently in patients with coagulopathy or after allogeneic bone marrow transplantation compared with solid-organ transplantation (22).

Differential diagnosis. When the lesions are predominantly or completely unilateral, the differential diagnosis should include neoplasm and encephalitis. Typical bilateral lesions must be differentiated from toxic leukoencephalopathy (as described above).

Treatment is the same as in toxic encephalopathy.

4b) Non-calcineurin inhibitors.

Sirolimus resembles Tac, but it does not affect calcineurin. It inhibits mammalian target of rapamycin (mTOR) activation in lymphocytes which causes cycle cell arrest and, finally blockade of T-cell proliferation, but it does not block T-cell activation. Rarely causes neurotoxicity, because it can alter cell metabolism of astrocytes, thus resulting in similar neurotoxicity as experienced by Tac and CsA (23): tremor, confusion, agitation and headache. It can delay wound healing, so it is generally not started until several weeks after a transplant.

Everolimus also inhibits mTOR activation. It is used for prophylaxis of organ rejection in adult patients receiving a kidney transplant, in combination with reduced doses of CsA. Rare adverse effects are dizziness, hypoesthesia, paresthesia, somnolence, and tremor. Treatment is symptomatic, concomitant with close monitoring of blood levels of the drug and of the accompanying CsA. □

CONCLUSIONS

1. Therapeutic drug monitoring cannot predict all adverse events associated with immuno-

suppressive drugs, especially with calcineurin inhibitors, because neurotoxicity can occur both at therapeutic and at high drug levels. Thus, recognition of prodromal signs such as tremulousness or headache is important for the early diagnosis and treatment.

2. Immediate diagnostic work-up, especially MRI neuroimaging, is required in any transplanted patient presenting with neurological symptoms.
3. Some cases of no reversibility have been described, either with coma and death, or

with occurrence of late epilepsy, regardless of the resolution of the initial lesions on neuroimaging.

4. There is significantly reduced survival rate for transplanted patients who experience neurotoxicity, also from neurologic complications but from discontinuation of certain immunosuppressive drugs, which may cause, in some circumstances, significant mortality due to rejection of the graft. ■

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