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VIEW

Neurological complications of solid organ transplantation

Complicações neurológicas no transplante de órgãos sólidos

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ABSTRACT

Solid organ transplantation is a significant development in the treatment of chronic kidney, liver, heart and lung diseases. This therapeutic approach has increased patient survival and improved quality of life. New surgical techniques and immunosuppressive drugs have been developed to achieve better outcomes. However, the variety of neurological complications following solid organ transplantation is broad and carries prognostic significance. Patients may have involvement of the central or peripheral nervous system due to multiple causes that can vary depending on time of onset after the surgical procedure, the transplanted organ, and the intensity and type of immunosuppressive therapy. Neurological manifestations following solid organ transplantation pose a diagnostic challenge to medical specialists despite extensive investigation. This review aimed to provide a practical approach to help neurologists and clinicians assess and manage solid organ transplant patients presenting with acute or chronic neurological manifestations.

Keywords: organ transplantation; neurological manifestations; central nervous system; peripheral nervous system.

RESUMO

O transplante de órgãos sólidos é um importante avanço no tratamento de doenças crônicas renal, hepática e cardíaca. Esta terapia tem aumentado a sobrevida e melhorado a qualidade de vida dos pacientes. Novas técnicas cirúrgicas e imunossupressores tem sido desenvolvidos para alcançar melhores desfechos. Entretanto, a variedade de complicações neurológicas que acompanham o transplante de órgãos sólidos é ampla, e carrega significado prognóstico. Pacientes podem ter acometimento do sistema nervoso central ou periférico devido a múltiplas causas que podem variar conforme o tempo após a realização da cirurgia, órgão transplantado e grau e tipo de terapia de imunossupressão. Manifestações neurológicas após o transplante de órgãos sólidos representam um desafio diagnóstico para médicos especialistas apesar de extensa investigação. O objetivo desta revisão é oferecer uma abordagem prática para ajudar neurologistas e clínicos a avaliar e manejar pacientes com transplante de órgãos sólidos que se apresentem com manifestações neurológicas agudas ou crônicas.

Palavras-chave: transplante de órgãos; manifestações neurológicas; sistema nervoso central; sistema nervoso periférico.

Solid organ transplantation is a significant development in the treatment of chronic kidney, liver, heart and lung diseases. This therapeutic approach has increased patient survival and improved quality of life. New surgical techniques and immunosuppressive drugs have been developed to achieve better outcomes[1].

Despite this major medical breakthrough, several complications may arise from transplantation. Neurological complications in solid-organ transplant patients may occur immediately after the surgical procedure, or after months or years, and increase morbidity and mortality in these patients[2]. The main neurological complications include infections, neoplasms, seizures, vascular disorders, psychiatric disorders and cognitive impairment, metabolic disturbances, and adverse drug reactions (Table 1).

This review aimed to provide a practical approach to help neurologists and clinicians assess and manage solid organ transplant patients presenting with acute or chronic neurological manifestations.

CENTRAL NERVOUS SYSTEM INFECTIONS

Organ transplant recipients have a high risk of opportunistic infections and the central nervous system (CNS) is frequently involved. However, in recent years, there has been a reduction in cases of opportunistic infections after

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organ transplantation[3]. This is a consequence of effective prophylactic strategies against opportunistic pathogens and a more prudent management for immunosuppression[3]. Headache, low-grade fever and mental status impairment are the most common clinical symptoms caused by opportunistic infections in organ transplant recipients[4,5].

In the early post-transplant period (one to two months), the most common infections are derived from the hospital environment. After the first month, viral infections predominate. Tardive infections may include: *Mycobacterium tuberculosis, Trypanosoma cruzi, Leishmania* species, *Strongyloides stercoralis, Cryptococcus neoformans, Histoplasma capsulatum, Coccidioides* and species of *Paracoccidioides*[6,7,8,9].

Table 1. Main neurological complications in solid organ transplant patients.

Central nervous system infections
Viral infections (herpes virus family and polyomavirus)
Bacterial infections (Nocardiosis, *Listeria monocytogenes* and *Mycobacterium tuberculosis*)
Fungal infections (Aspergillus, Mucormycosis, Cryptococcosis)
Protozoan infections (Toxoplasmosis)
Neuromuscular complications
Neuropathy
Myopathy
Neuromuscular junction disorders
Seizures
Immunosuppressant toxicity
Metabolic changes
Infections
Stroke
Tumors
Vascular neurologic complications
Posterior reversible encephalopathy syndrome (PRES)
Ischemic stroke
Intracerebral hemorrhage
Reversible cerebral vasoconstriction syndrome
Psychiatric and behavioral disorders
Depression
Anxiety
Bipolar disorders
Psychosis
Delirium
Substance abuse
Central nervous system post-transplant lymphoproliferative disorders (PTLD)
Neurological complications of immunosuppressive agents (Details in Table 3)
Other neurological manifestations
Altered consciousness and encephalopathy
Central pontine myelinolysis
Graft-versus-host disease
Myelopathies
Movement disorders
Headache
Visual and auditory disturbances

Differential diagnosis of infection in solid organ causative of transplantation patients

It is essential to differentiate the causative pathogens causative of the neurological condition given specific treatment varies and mortality is high. Neuroimaging features may contribute to the diagnosis[10]. Table 2 describes, in detail, the main infections associated with solid organ transplantation patients[11,12,13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28].

Viral infections

Viral infection of the CNS in post-transplantation patients can be divided into two etiological groups: human herpes virus family (herpes simplex virus [HSV], cytomegalovirus [CMV], Epstein-Barr virus [EBV], varicella-zoster virus [VZV], human herpes virus type 6 [HHV-6] and human herpes virus type 7 [HHV-7]) and polyomavirus[13,14,15,16,17,18].

Neurological manifestations include limbic encephalitis-like syndrome (HSV, CMV, HHV-6), rhombencephalitis, ventriculitis, myelitis, vascular involvement (VZV), and a multisystem post-transplant lymphoproliferative disorder (PTLD), which may involve the CNS and is associated with the EBV.[13,14,15,16,17,18].

Progressive multifocal leukoencephalopathy leads to demyelination after opportunistic infection of the JC virus[5]. The symptoms usually appear in the first year after transplantation, and include focal neurological deficit, sudden loss of consciousness and visual changes. The brain MRI shows asymmetric, non-enhancing, T2 hyperintense lesions – usually in the subcortical regions (Figure 1).[5] Cerebrospinal fluid (CSF) polymerase chain reaction (PCR) for JC virus can yield the diagnosis with sensitivity of approximately 75%.[5]

Bacterial infections

The main bacterial infections in immunosuppressed patients include nocardiosis, *Listeria monocytogenes* and *Mycobacterium tuberculosis*.

Nocardiosis is rare and may occur in up to 3.5% of transplant recipients[21]. High-dose corticosteroids are the major risk factor for this infection[11,21]. Brain abscess is the most common finding of this CNS infection (Figure 2) and common

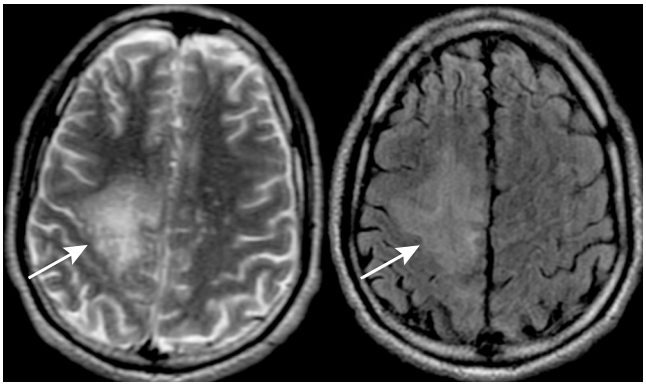

Figure 1. Brain MRI discloses subcortical lesions (hyperintense signal) with cortical preservation in a patient with JC virus infection.

Table 2. Detailed description of the main opportunistic infections of the central nervous system in organ transplant recipients.

Infection	Clinical symptoms	MRI findings	CSF analysis	Diagnosis	Treatment
			Viral infections		
Herpes virus family	Limbic encephalitis-like syndrome (HSV, CMV, HHV-6), rhombencephalitis (HHV-7), ventriculitis (CMV), myelitis (CMV, VZV, HHV-7), stroke (VZV), PTLD (EBV)	Bilateral lesions in the anterior hippocampus, uncus, and amygdala		CSF PCR	Depends on the herpes virus: acyclovir (HSV1, VZV), foscarnet, ganciclovir (CMV), and cidofovir
Polyomavirus		Subcortical lesions with cortical preservation		CSF PCR DNA	Discontinuation of immunosuppressant drugs
			Bacterial infections		
Nocardiosis	Fever, headache, conscious impairment and seizures			Positive culture (CSF, Bx)	Trimethoprim–sulfamethoxazole, imipenem or a third-generation cephalosporin and amikacin are treatment options. Reversal of immunosuppression is beneficial
Listeriosis	Meningitis or meningoencephalitis presenting with fever, headache, altered sensorium and seizures.[10,22] Cranial neuropathies, dysarthria, paresis, and ataxia occur in approximately 40% due to brainstem involvement (rhombencephalitis)	Nonspecific encephalitis	Polymorphonuclear or lymphocytic pleocytosis with elevated protein, and hypoglycorrhachia	CSF gram stain identifies *Listeria monocytogenes* in only 30-40% and CSF culture is often negative	Ampicillin or penicillin for 21 days
Neuro-tuberculosis	Meningitis complicated by hydrocephalus and vasculitis.	MRI demonstrates basilar meningeal enhancement (Figure 3) and abscesses and tuberculomas may present with enhancement with surrounding edema.	Lymphocytic pleocytosis with low glucose and elevated protein. CS acid-fast stains are positive in 10-40% of cases.	Diagnosis of tuberculosis can be established by tissue biopsy and culture of infected tissue. PCR assay is the recommended method to investigate infection with moderate sensitivity and high specificity	Empiric treatment with adjunctive dexamethasone is warranted in suspected cases, as well as reduction of immunosuppression with serial CSF monitoring
			Fungal infections		
Aspergillosis	Fever, altered mental status, seizures, stroke, and focal neurologic deficits	MRI demonstrates ring-enhancing or hemorrhagic lesions	Lymphocytic pleocytosis, elevated protein, fungal smears and cultures of CSF are usually negative	Serologic assays showing galactomannan antigen or 1,3-beta-d-glucan supports the diagnosis	Voriconazole is the first-line therapy for aspergillosis. Surgical management of aspergillomas is associated with better outcomes
CNS mucormycosis	Fever, headache, unilateral facial pain, nasal/sinus congestion, impaired vision, periorbital swelling, proptosis, and ophthalmoplegia	MRI shows cavernous sinus invasion or thrombosis, internal carotid artery thrombosis or intracerebral abscesses		The diagnosis can be established by histopathological examination and culture of necrotic tissue	Emergent intervention with surgical debridement, antifungal therapy, reversal of immunosuppression, and correction of hyperglycemia. Liposomal amphotericin B is the treatment of choice
Cryptococcosis	Fever, night sweats, weight loss, headache, impaired sensorium, nausea, and vomiting. Meningismus is infrequent	MRI may disclose mass lesions, cerebral edema or hydrocephalus	Elevated opening pressure with variable CSF mononuclear pleocytosis, elevated protein, and low glucose	Diagnosis is based on antigen detection in the CSF or serum or CSF culture	Lipid formulations of amphotericin B plus flucytosine for at least 2 weeks followed by consolidation and maintenance with fluconazole. Elevated intracranial pressure is managed with serial lumbar punctures and CSF shunts for drainage, Reduction of immunosuppression is desirable, preferably with the use of calcineurin inhibitors
			Protozoan infections		
Toxoplasmosis		MRI shows ring-enhancing lesions, edema or hemorrhage	CSF analysis show elevated toxoplasma-specific IgG titers or evidence of toxoplasma DNA	Serologic and imaging tests. A definite diagnosis can only be provided by histopathology, which is hardly ever necessary	Sulfadiazine and pyrimethamine is recommended on suspected infection

MRI: Magnetic resonance imaging; CSF: Cerebrospinal fluid; HSV: Herpes simplex virus; CMV: Cytomegalovirus; HHV-6: Human herpes virus type 6; HVV-7: Human herpes virus type 7; EBV: Epstein-Barr virus; PTLD: Post-transplantation lymphoproliferative disorder; PCR: Polymerase chain reaction; Bx: cerebral biopsy; CNS : central nervous system

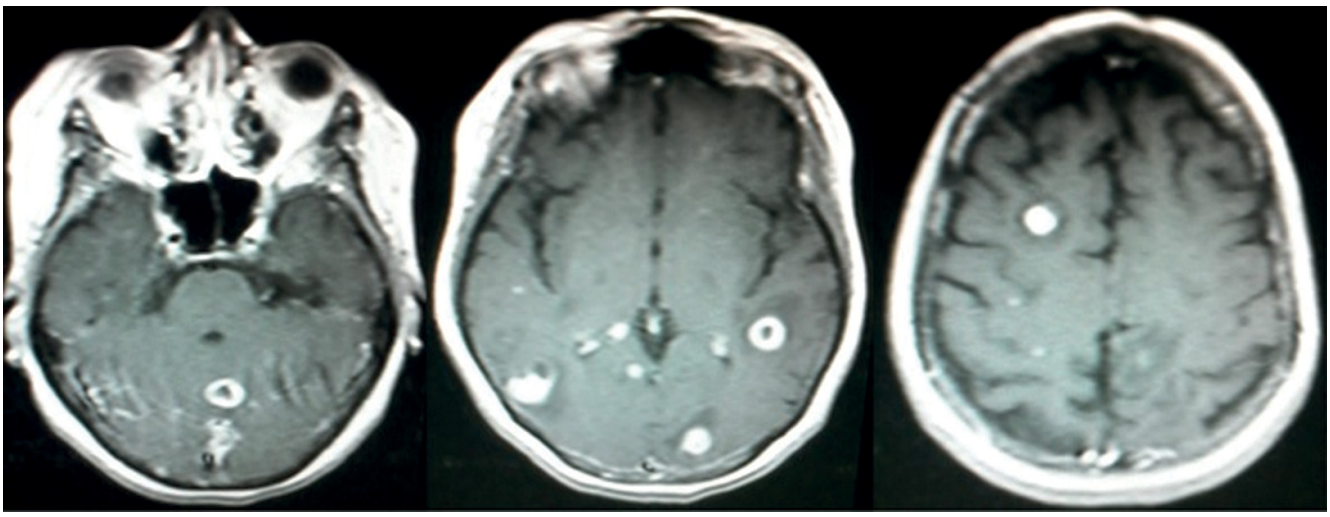

Figure 2. Multiple brain abscess in a patient with nocardiosis of the central nervous system.

symptoms of nocardiosis include fever, headache, impairment of consciousness and seizures. Treatment includes trimethoprim–sulfamethoxazole, imipenem or a third-generation cephalosporin and amikacin[21].

Listeria monocytogenes infection may cause meningitis or meningoencephalitis, presenting with fever, headache, altered mental status and seizures[22]. Cranial neuropathies, dysarthria, paresis, and ataxia occur in approximately 40% due to brainstem involvement (rhombencephalitis)[10,22]. CSF analysis usually demonstrates polymorphonuclear or lymphocytic pleocytosis with elevated protein levels, and hypoglycorrhachia. *Listeria monocytogenes* can be identified on the CSF gram stain in only 30–40% of cases[10,22].

Mycobacterium tuberculosis infection Symptoms of Mycobacterium include fever and altered mental status[9,23]. Meningitis can be complicated by hydrocephalus and vasculopathy. The MRI scans typically demonstrate meningeal enhancement. Abscesses and tuberculomas may be accompanied by ring enhancement with surrounding edema (Figure 3). PCR assay is the recommended method to investigate infection with moderate sensitivity and high specificity. Empiric treatment is warranted when CNS tuberculosis is suspected, and a four-drug regimen can be administered including isoniazid, rifampicin, ethambutol, and pyrazinamide[23].

Fungal infections

CNS infection caused by ***Aspergillus*** is clinically characterized by changes in consciousness, seizures, focal neurological deficit and, less commonly, meningitis and subarachnoid hemorrhage due to a mycotic aneurysm. Abscesses appear preferentially in the frontal and parietal lobes[3], but the cerebellum and brainstem can also be affected (Figure 4). Cerebral ischemia and hemorrhages may also appear due to vascular injuries from Aspergillus[3].

Cryptococcosis is a common late complication of transplant with subacute or chronic meningitis[26]. Meningismus

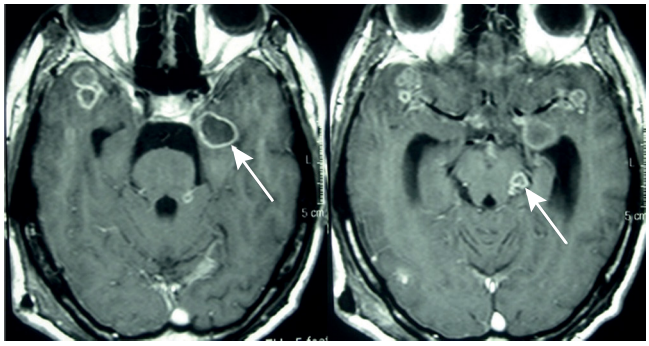

Figure 3. Axial-T1 weighted brain MRI shows multiple lesions at the base of the skull with gadolinium enhancement in a patient with tuberculosis of the nervous system.

is infrequent; however, increased intracranial pressure often occurs. Diagnosis is based on rapid antigen detection in the CSF and serum and isolation of the pathogen in CSF culture. Induction therapy consists of lipid formulations of amphotericin B plus flucytosine for at least two weeks followed by consolidation and maintenance therapy with fluconazole[26].

Protozoan infections

Toxoplasmosis occurs by reactivation of latent infection, after ingestion of contaminated food. *Toxoplasma gondii* lesions are frequently located in the basal ganglia and brain tissue with ring-enhancing abnormalities, edema or hemorrhage seen on MRI. Toxoplasmic meningoencephalitis is infrequently seen and may occur in the first three months after transplant. Empiric therapy with sulfadiazine and pyrimethamine is recommended on suspected infection. A presumptive diagnosis is based on seropositivity, clinical presentation, characteristic imaging, and response to therapy. The CSF analysis shows elevated toxoplasma-specific IgG titers or evidence of toxoplasma DNA, but a definite diagnosis can only be provided by histopathology, which is hardly ever necessary[27].

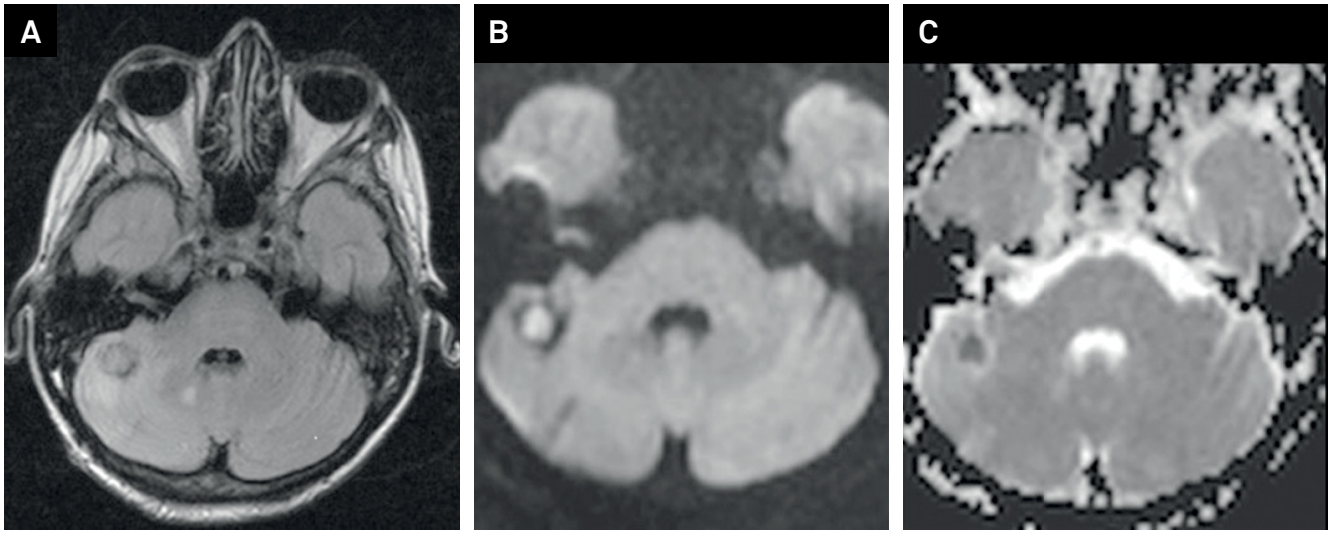

Figure 4. Brain abscess caused by *Aspergillus* involving the cerebellum in a transplant recipient.

NEUROMUSCULAR COMPLICATIONS

Neuropathies and myopathies are unusual complications following solid-organ transplantation. The reported frequency of neuromuscular disorders was 1%-13% in series of heart transplantation, 4% after liver grafting and up to 21% in lung recipients[1,2].

Mononeuropathy, plexopathy and polyneuropathy are likely associated with surgical and clinical complications following engraftment and immunosuppresion. In addition, prior organ failure, toxic and metabolic disturbances preceding the transplantation (diabetes, uremia, and alcohol intake) may predispose this patient population to nerve damage.[5] Surgical positioning and manipulation can lead to entrapment neuropathies (such as ulnar neuropathy and femoral neuropathy) or lower trunk brachial plexopathy following stretching stress related to thoracotomy in lung and heart transplantation. Lumbosacral plexopathy after kidney transplantation has also been described[1,2].

Phrenic mononeuropathy has been associated with delayed weaning from mechanical ventilation in combined heart-lung or isolated lung transplant patients, who can also present with recurrent laryngeal nerve injury. Femoral neuropathy has been related to kidney transplantation; and peroneal, ulnar, and median nerve dysfunction have been described after solid organ transplantation[1,2].

Immunosupressant drug toxicity is an uncommon cause of polyneuropathy. Case reports have described acute or chronic sensorimotor axonal polyneuropathy after tacrolimus tacrolimus exposure, with symptom improvement after drug discontinuation[25]. Cyclosporine has also been associated with axonal polyneuropathy in a few case reports[2].

Acute inflammatory demyelinating polyneuropathy or polyradiculopathy, also known as Guillain-Barré syndrome, in solid organ transplant patients has been associated with *Campylobacter jejuni* infection, as well as with cyclosporine neurotoxicity and prior or active CMV infection. Treatment includes intravenous immunoglobulin or plasmapheresis, substitution of the immunosuppressant drug or treatment with ganciclovir in selected cases[26]. An association between tacrolimus and Guillain-Barré syndrome after organ transplantation is not yet clear.

In a prospective study, chronic inflammatory demyelinating polyneuropathy (CIDP) was confirmed in 0.6% of 1,557 solid organ transplant recipients during eight years of follow-up. CIDP developed within the first year after liver, kidney, heart or lung transplantation. Immunosuppressive dose reduction before CIDP onset was reported in 60% of cases. Clinical improvement was achieved after treatment with intravenous immunoglobulin alone or combined with optimized immunosupressive therapy.[31] In addition to axonal injury, cyclosporine and tacrolimus toxicity has been implicated in sensorimotor demyelinating polyneuropathy resembling CIDP.[27]

Clinical complications following transplantation that require critical care support, neuromuscular junction blocking agents and steroid exposure (especially intravenously) are risk factors for critical illness myopathy and critical illness polyneuropathy. In addition, in critical care settings, the use of linezolid and other drugs can be associated with toxic neuropathy[2]. Critical illness myopathy manifests as difficulty in weaning from mechanical ventilation, subacute weakness while sparing eye movements, or even acute severe quadriparesis reported after liver transplantation[28].

Multiple factors are associated with the development of myopathy in transplant recipients. Myositis and rhabdomyolysis are frequently drug induced (azathioprine; combination of cyclosporine with colchicine or statin in kidney transplant recipients), associated with viral infections, or secondary to electrolyte imbalance. An inflammatory myopathy similar to idiopathic polymyositis with elevated serum creatine kinase has been reported

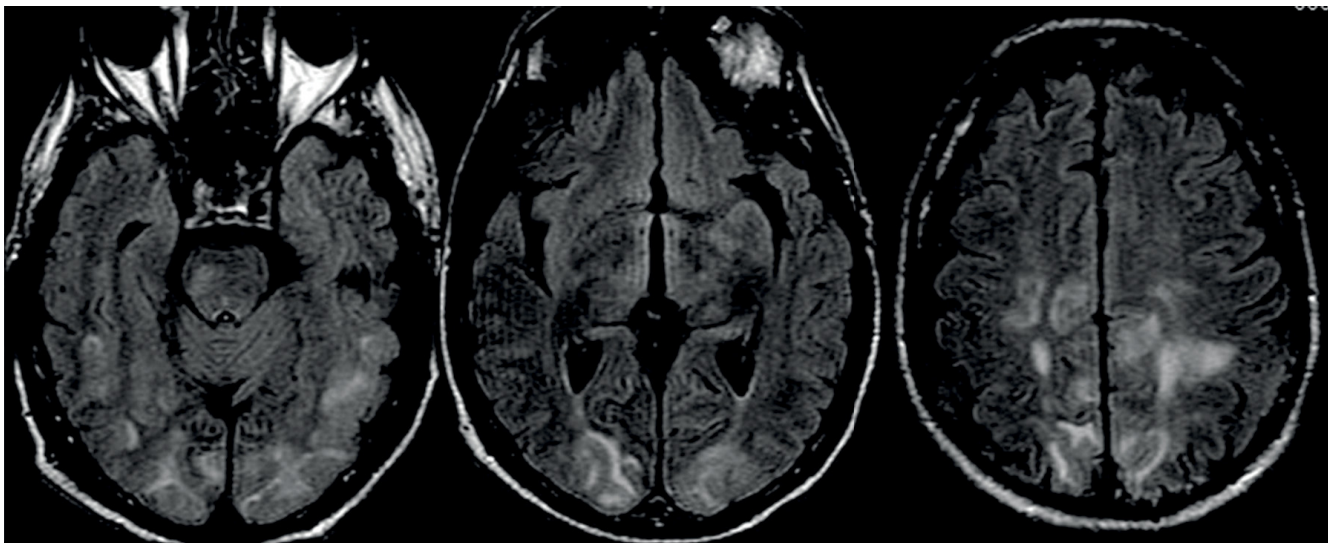

Figure 5. Patient with posterior reversible encephalopathy syndrome (PRES). The MRI demonstrates focal areas of symmetric brain edema with predominant involvement of posterior lobes.

following renal transplantation, and was successfully treated with high-dose steroid therapy. Myopathy secondary to steroid use has an insidious onset and normal creatine kinase levels.

Neuromuscular junction transmission impairment is not consistently reported in solid organ transplant recipients, in contrast to reports of myasthenia gravis following chronic graft-versus-host disease in hematopoietic stem cell transplantation.[28] Prolonged paralysis after neuromuscular junction blockade has been rarely reported in solid organ transplantation.[28]

SEIZURES

Seizures are common neurological complications after organ transplantation. They occur in 5–10% of transplant patients and are generally indicative of a metabolic or structural brain disorder[29]. The most common causes of seizures are immunosuppressant toxicity (especially associated with OKT3 and cyclosporine), metabolic changes, infections, stroke, and tumors[4,29].

Seizures most frequently occur within the first few weeks after transplant and may be generalized or partial, and are usually tonic-clonic[4]. Seizures associated with drug toxicity are preceded by subtle mental and behavioral changes and are often transient requiring no treatment other than reduction of toxic drugs. Although status epilepticus is rare, the clinical diagnosis may sometimes prove difficult and an EEG should be obtained if the patient remains unresponsive after the seizure. The differential diagnosis of seizures include delirium or non-epileptic movements like myoclonus (focal or multifocal) and tremors, usually secondary to metabolic or drug-induced derangements[4,29].

Patient evaluation should include MRI, CT scans, measurement of immunosuppressive drug levels, EEG and laboratory tests (sodium, calcium, magnesium and glucose). Additional tests include CSF analysis if an infection is suspected[29].

Patients who have had a single seizure should not be treated with antiepileptic drugs, especially if a rapidly reversible cause is identified on laboratory tests (e.g., hyponatremia or hypoglycemia). Benzodiazepines are the first-line agents used after the first seizure, and if patients require long-term treatment, other drugs may be selected[4,29].

Long-term treatment with antiepileptic drugs needs to be selected by a doctor, with the patient's consent, based on the etiology of the seizures, because it requires close monitoring of immunosuppressive therapy due to drug-drug interactions. The most traditional antiepileptic drugs (phenobarbital, phenytoin and carbamazepine) interfere with the metabolism of commonly-used immunosuppressive agents because of the induction of the hepatic cytochrome P450 system. Serum proteins (in particular, albumin) may be modified by several underlying clinical conditions, such as nutrition, drug interaction and electrolyte changes in transplanted patients; thus, monitoring of antiepileptic drug levels is recommended. The use of valproate should be avoided in liver transplant patients because of potential hepatotoxicity. Phenytoin has commonly been used (can be loaded intravenously), while gabapentin and levetiracetam should be considered as oral medications for their lack of hepatic enzyme induction and minimal interactions with immunosuppressive drugs[4,29].

The prognosis is usually favorable when a treatable and reversible cause is identified, but it is poor when a severe or irreversible cause, such as a tumor or systemic illness, is identified[4,29].

VASCULAR NEUROLOGIC COMPLICATIONS

Posterior reversible encephalopathy syndrome

Posterior reversible encephalopathy syndrome (PRES) is a neurotoxic state accompanied by a unique brain imaging pattern typically associated with a number of complex

clinical conditions including eclampsia/preeclampsia, allogenic bone marrow transplantation, solid organ transplantation, autoimmune diseases and chemotherapy. Posterior reversible encephalopathy syndrome is a leading neurological complication in solid organ transplantation, particularly in patients who have received tacrolimus or cyclosporin A.[30]

Clinical symptoms are broad and include headache, vision changes, paresis, hemianopsia, nausea, and altered mental status, which usually develop over a couple of days. Approximately 70% of patients present with hypertension. The syndrome occurs in 0.4–6% of solid organ transplant recipients, sometimes following infection or transplant rejection. Among kidney transplant recipients, PRES is typically a late complication, which develops in a setting of poorly-controlled hypertension and is associated with less extensive brain edema. In liver transplant recipients, PRES has an early onset (less than two months after transplantation) and is associated with extensive brain edema[30].

Brain imaging typically demonstrates focal areas of symmetric brain hemispheric edema (Figure 5). The parietal and occipital lobes are most commonly affected, followed by the frontal lobes, the inferior temporal-occipital junction and the cerebellum. Lesion confluence may develop as the extent of edema increases[30].

Treatment of PRES involves identifying and treating the underlying precipitating factor as well as brain edema and seizures. In transplant recipients, calcineurin inhibitors should be discontinued or, controversially, reduced. Symptoms and brain lesions will resolve in many cases, however irreversible damage may occur in selected patients in whom PRES is complicated by cerebral infarction or hemorrhage[30].

Stroke

Ischemic stroke and intracerebral hemorrhage have been reported as complications of both solid organ transplantation and hematopoietic stem cell transplantation. They typically occur in the setting of hypertension, diabetes, cardiac arrhythmias, coagulation disturbances, bacterial endocarditis, and accelerated atherosclerosis, which may be pre-existing or develop after transplantation.[31]

Ischemic strokes are more common after heart transplantation, with an incidence rate of 2-10%[31]. Higher stroke rates in cardiac transplant recipients are specifically associated with advanced age, diabetes mellitus, valvular disease as the indication for heart transplantation, preoperative use of left ventricular assist devices or intra-aortic balloon pump, and a prolonged cardiopulmonary bypass time[31]. Strokes occur in 2–3% of lung transplant recipients, whereas 5–10% of kidney transplant recipients may have a stroke due to the high burden of cardiovascular risk factors.

Ischemic stroke is rare in liver transplant recipients, with an estimated rate of 0-3%. However, because of underlying coagulopathy and thrombocytopenia, these patients have a higher risk of intracranial hemorrhage, with mortality rates of up to 80%. Intracranial hemorrhage is a late complication in kidney transplant patients and is rare in cardiac transplant recipients[31].

Reversible cerebral vasoconstriction syndrome

Reversible cerebral vasoconstriction syndrome comprises a group of conditions characterized by reversible multifocal narrowing of the cerebral arteries heralded by sudden (thunderclap), severe headaches with or without associated neurologic deficits[32]. Misdiagnose as primary cerebral vasculitis and aneurysmal subarachnoid hemorrhage is common because of overlapping clinical and angiographic features. However, unlike these more ominous conditions, reversible cerebral vasoconstriction syndrome is usually self-limited and headaches and vasoconstriction resolve over a period of days to weeks[32].

Reversible cerebral vasoconstriction syndrome includes Call-Fleming syndrome, migraine angiitis, postpartum angiopathy, and drug-induced vasospasm. Among the drugs associated with this syndrome are tacrolimus, cocaine, ecstasy, amphetamine derivatives, marijuana, cyclophosphamide, erythropoietin and intravenous immunoglobulins. Diagnostic criteria include the presence of segmental cerebral artery vasoconstriction in digital transfemoral angiography or indirect (CT or MRI) angiography; no evidence of aneurysmal subarachnoid hemorrhage; normal or near-normal CSF analysis (< 10 cells, protein < 80 mg and normal glucose level); severe acute headache with or without neurological signs or symptoms; and reversibility of angiographic abnormalities within 12 weeks[32].

PSYCHIATRIC AND BEHAVIORAL DISORDERS

Transplantation provides life-saving therapy to critically ill patients with end-stage organ failure. Specialized knowledge of mental health disorders is essential for optimal care of these patients[33].

Solid organ transplant recipients are at increased risk of a range of psychiatric complications including anxiety disorders, mood disorders, and psychosis. Common presentations include post-traumatic stress disorder, depression and anxiety states, mania, psychosis, delirium, and drug abuse. Patients with pretransplant psychiatric comorbidities are at particular risk of decompensation. Calcineurin inhibitor agents and corticosteroids may have very prominent behavioral effects[33]. We describe below the main psychiatric comorbidities seen in transplant recipients.

Depression

Depressive symptoms can affect the medical outcome of numerous conditions including cardiovascular diseases, diabetes mellitus, chronic obstructive pulmonary disease as well as kidney, heart or liver transplantation. Depressive symptoms have consistently been shown to be associated with higher mortality in these patients[33].

Cytomegalovirus infection and graft rejection are two of the most common causes of acute post-transplant depression[33]. Depression is also seen in the setting of bacterial

sepsis, abscess formation, diarrhea, fungal infection, herpes simplex encephalitis, tuberculosis, and cryptococcal infection. It is also a common finding in hepatitis C virus-related cirrhosis and a common complication of antiviral therapy[33].

Excessive weight gain or loss, altered immune function, increase in sedentary behaviors, changes in information processing, diminished perception of self-worth, unemployment, lethargy, pain and fatigue are among the factors that could cause depressive symptoms and interfere with motivation during rehabilitation[33].

Depression is treated with combined psychotherapy and psychopharmacology. The efficacy of medications may not be evident for six to eight weeks. It is important to consider long-term treatment for those with severe depression. Electroconvulsant therapy may be required in severe cases. The most commonly-used antidepressants are selective serotonin reuptake inhibitors. Patients with depression should not be excluded from transplantation, but it highlights the importance of preoperative assessment and treatment of this condition to optimize post-operative outcomes[33].

Anxiety

Anxiety is very common when post-transplant recipients are getting close to being discharged from hospital. They may have concerns about not being continuously observed by the transplant team[33].

Post-traumatic stress disorder may occur in response to organ transplantation events. Patients may experience delusions or hallucinations of life-threatening events related to their medical condition. Symptoms also include flashbacks, enhanced startle response and nightmares[33].

Benzodiazepines are helpful for immediate relief of anxiety and for prevention of panic attacks. The risk of dependency is of special concern in patients with a history of substance abuse. Buspirone is a good drug choice in these cases. Selective serotonin reuptake inhibitors and cognitive behavioral therapy are indicated for patients with persisting anxiety disorders[33].

Psychosis

The occurrence of hospitalized psychoses has independently been associated with increased risk of death and graft loss after renal transplantation, possibly mediated through medical non-adherence[34].

Most post-transplantation psychoses may result from stress-related exacerbations of a primary psychiatric disorder or abrupt discontinuation of mood stabilizers or antipsychotic medications[33]. In addition, several conditions predispose transplanted patients to an increased risk of psychosis: the use of high-dose corticosteroids, chronic illness-associated affective disorders, metabolic disturbances, and other immunosuppressive medications used in transplantation, such as calcineurin inhibitors, which have known neuropsychological side effects[34].

Emergency psychiatric consultation is indicated when psychotic symptoms interfere with medical management or are associated with suicidal ideation. The effectiveness of pharmacologic management has improved with the availability of newer atypical antipsychotic agents[34].

Delirium

Delirium is a sudden change in brain function and involves altered mental content and inattentiveness not associated with established dementia. Both hyperactive and hypoactive subtypes may be present after transplantation. Factors associated with this disorder are intraoperative complications, medication toxicity including calcineurin inhibitor-induced toxicity, drug-drug interactions, metabolic or neurologic complications, infection, drug or alcohol withdrawal, vitamin deficiency (thiamine, folate, and B12 vitamin), endocrinopathy, and hematologic disorders. Haloperidol and typical antipsychotic agents are recommended for agitation, delusions, and active hallucinations. Excessive sedation may occur in patients with severe hepatic or renal failure and the elderly. Brain imaging, EEG, and lumbar puncture may provide important information[34].

Bipolar disorders

The hallmark of this group of disorders is a propensity to develop profound changes in mood and behavior. Patients can do well post-transplant if their disorders are previously well controlled. Nevertheless, postoperative exacerbation of bipolar disorders can be triggered by operative stress or medical complications. A recurrence of life-threatening mania or depression has occurred among patients who had been symptom-free for as long as two decades. Prednisone may also precipitate hypomania, depression, or mixed mood disorder. A steroid-sparing immunosuppressive protocol is therefore indicated when feasible. Mood changes at any time can be unpredictable and disruptive to social support and doctor-patient communication. Emergency psychiatric intervention may be necessary to deal with the life-threatening risk of medication noncompliance[33].

Substance abuse

A recent meta-analysis demonstrated relapse rates as low as 2.5–5.6% of patients per year among transplanted individuals after histories of alcohol and/or illicit drug use[35]. Even those on methadone maintenance do not appear to relapse often while remaining on treatment. Methadone maintenance programs should not taper off methadone unless recommended by drug abuse counselors who will provide active follow-up support. Analgesic needs may increase because of tolerance or anxiety. Return to pre-established maintenance levels is an appropriate goal. Morbidity from relapse of tobacco use is common post-transplant and requires active treatment referral[35].

CENTRAL NERVOUS SYSTEM POST-TRANSPLANT LYMPHOPROLIFERATIVE DISORDERS

Central nervous system post-transplant lymphoproliferative disorders (PTLD) represent a spectrum of diseases characterized by lymphoid or plasmacytic proliferation that may occur in solid organ, bone marrow, or hematopoietic stem cell transplantation recipients. The disorder can be divided into a range of histological subtypes from reactive plasmacytic hyperplasia and polymorphic PTLD to monomorphic PTLD or malignant lymphoma. It is the second most common malignancy in post-transplant patients following skin cancer and is the first post-transplant malignancy in children. It usually occurs within the first year after transplant and is associated with EBV infection. Heart, lung and intestinal transplant recipients are at higher risk because they require intensive immunosuppression. Cyclosporine and tacrolimus may increase the risk of PTLD[36].

Post-transplant lymphoproliferative disorders rarely involve the CNS causing multifocal brain lesions with either a ring-enhancing or homogenous pattern. The majority of patients have a multifocal disease with a predilection for the periventricular/basal ganglia region[36]. A third of the patients may present with infratentorial involvement (Figure 6). The differential diagnosis is broad and includes infectious (abscess, toxoplasmosis) and neoplastic diseases (PTLD and others). The decision to perform less invasive diagnostic evaluations or proceed immediately to biopsy is controversial[36].

The optimal treatment of CNS PTLD is still not clearly defined. Patients may present with unaltered clinical status, and for that reason, the risks of treatment may be greater than those for immunocompetent patients with CNS lymphoma. Dose reduction or discontinuation of immunosuppressive agents is effective for approximately half of the PTLD patients. Radiotherapy is an option in selected patients[36].

NEUROLOGICAL COMPLICATIONS OF IMMUNOSUPPRESSIVE AGENTS

Immunosuppressive drugs currently used in clinical practice for transplant patients may cause peripheral and central neurological disorders. The mechanisms include direct drug effects or drug interactions. Side effects related to the treatment of infectious diseases are described above. Up to a third of transplant patients may have neurological side effects induced by immunosuppressive agents. The most common neurological manifestations include seizures, stroke, encephalitis, neuropathy, and acute encephalopathy. Three clinical syndromes related to neurological complications of immunosuppressive agents are noteworthy: PRES, immune reconstitution inflammatory syndrome, and PTLD[37].

The main immunosuppressive drugs for transplant patients are antiproliferative agents, calcineurin inhibitors and corticosteroids. Associated induction or maintenance drugs include monoclonal antibodies, polyclonal antibodies, cyclophosphamide, methotrexate, intravenous immunoglobulin, and rituximab[37]. Plasmapheresis can be used to treat some transplant patients. Table 3 shows the main neurological effects related to immunosuppressive agents.

OTHER NEUROLOGICAL MANIFESTATIONS

Altered consciousness and encephalopathy

Alterations of consciousness and encephalopathy are common after transplantation with manifestations ranging from confusion and delirium to stupor and coma. Multiple causes are involved and the spectrum of conditions with altered consciousness in transplant recipients depends on the time elapsed since transplantation. Anoxic brain injury is associated with the intraoperative procedure, and toxic and metabolic disturbances. Opportunistic infections are the most common complications causing altered consciousness[38].

Central pontine myelinolysis

Central pontine myelinolysis (CPM) is a non-inflammatory demyelinating disease of the pons, most commonly found in patients with chronic medical conditions such as alcohol dependence and often occurring following a rapid increase in serum sodium concentration[4]. A high proportion of post-transplant CPM cases can be traced to rapid correction of hyponatremia, often in the perioperative period or in association with high levels of cyclosporin A. The classic clinical spectrum of CPM is comprised of acute onset of tetraparesis, pseudobulbar palsy, dysphagia and stupor. The MRI shows lesions in the pons, which are hypointense on T1 and hyperintense on T2 and diffusion-weighted sequences (Figure 7). There is no specific therapy to reverse CPM[38].

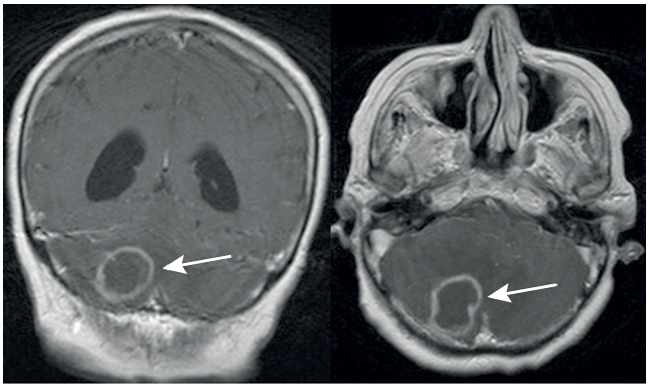

Figure 6. Brain MRI shows an expansive lesion with gadolinium enhancement in the cerebellum. Biopsy confirmed central nervous system post-transplant lymphoproliferative disorders (PTLD).

Table 3. Main neurological effects related to immunosuppressive agents in solid organ transplant patients.

Drugs	Neurological side effects
Antiproliferative agents	
Mycophenolate mofetil or sodium	Peripheral neuropathy, aseptic meningitis and PML
Azathioprine	Seizures
Calcineurin inhibitors	
Cyclosporin A	Myalgia and cramps, peripheral neuropathy, reflex sympathetic dystrophy, acute toxic encephalopathy, tremor, chorea, cerebellar ataxia, seizures, headache, depression and episodes of mania, sleep-wake cycle changes (insomnia), akinetic mutism and PRES
Tacrolimus	All related to cyclosporin A and the following: sensorineural hearing loss, central osmotic demyelination, optic neuropathy and CIDP-like syndrome and brachial plexopathy
Non-calcineurin inhibitors of proliferation sign	
Sirolimus	PRES, acute confusional syndrome, headache
Everolimus	Vertigo, tremor, hypoesthesia, paresthesia and somnolence
Corticosteroids	Psychiatric disorders, tremor, seizures, headache, pseudotumor cerebri and myopathy
Monoclonal antibodies (rituximab)	PML, myalgia, dizziness, and headache dementia with or without aseptic meningitis
Polyclonal antibodies (antithymocyte globulin and antilymphocytic globulins)	Opportunistic infections
Cyclophosphamide	Toxic encephalopathy
Methotrexate	Necrotizing cerebral microangiopathy, visual loss, seizures, leukoencephalopathy, acute transverse myelitis (especially if intrathecal), hyperintense signal on brain MRI
Intravenous immunoglobulin	Headache, diffuse paresthesias, myalgia, stroke, cerebral venous thrombosis and aseptic meningitis. Cases of Creutzfeldt-Jakob disease are described

PML: Progressive multifocal leukoencephalopathy; PRES: Posterior reversible encephalopathy syndrome; CIDP: Chronic inflammatory demyelinating polyradiculoneuropathy; MRI: Magnetic resonance imaging.

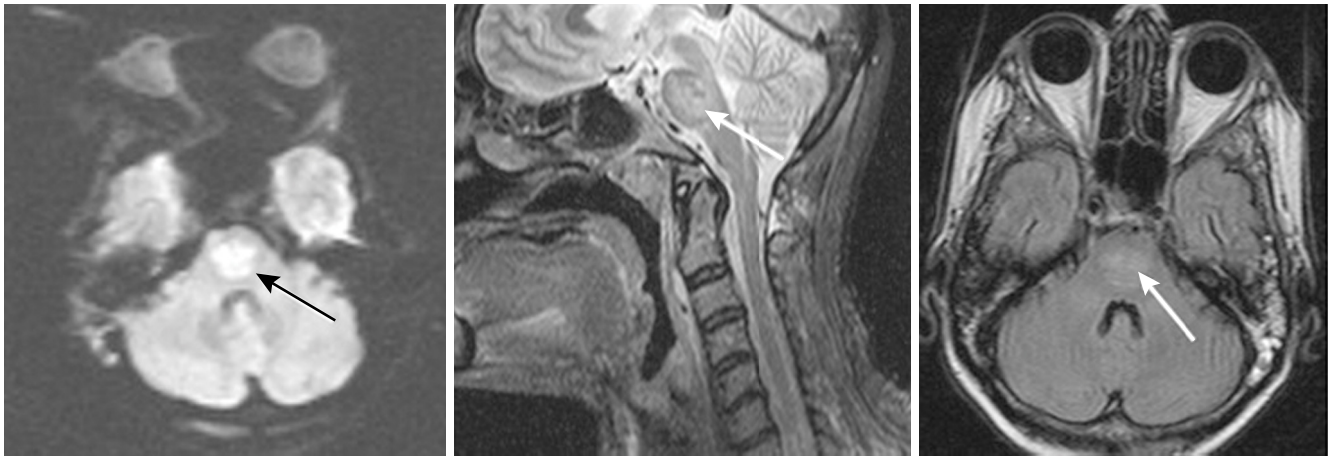

Figure 7. Brain MRI discloses a hyperintense signal in the pons, in a transplant recipient (liver transplantation) with pontine myelinolysis.

Graft-versus-host disease

Graft-versus-host disease is an immunological disorder caused when donor lymphocytes attack recipient tissues. This syndrome can affect many organ systems including the central and peripheral nervous systems. Neurological complications are seen almost exclusively in chronic graft-versus-host disease and include cerebral angiitis, cerebral lymphomononuclear infiltrates, polymyositis, and myasthenia gravis. Patients with CNS involvement of chronic graft-versus-host disease may present with seizures or focal neurological signs[38].

Myelopathies

Spinal cord involvement in transplant recipients is an unusual neurological manifestation. Some causes of spinal cord lesions in transplant patients include epidural abscess, hematoma, and viral infections. Human T-lymphotropic virus 1, HHV-6, HHV-7, VZV, EBV or CMV infection can lead to myelopathy or polyradiculopathy[38].

Movement disorders

Abnormal and involuntary movements after transplantation are usually associated with drug treatment. Tremor is

frequently associated with the use of calcineurin inhibitors (tacrolimus and cyclosporine); Parkinsonism is associated with hepatocerebral degeneration and liver failure; and myoclonus is particularly associated with opiate and antidepressant use[38].

Headache

Headache is often an underrated condition in transplant patients because of overlapping of other neurological and systemic complications. However, a new onset headache can be the first clinical manifestation of an opportunistic infection, brain neoplastic condition or neurotoxicity. As well, calcineurin inhibitors can aggravate pre-existing migraine[38].

Visual and auditory disturbances

Visual disturbances can be a symptom of cortical blindness associated with PRES and drug neurotoxicity. Ocular infections following fungal and viral infections require prompt treatment to prevent complications. Additionally, asymmetric bilateral demyelinating optic neuropathy can develop after tacrolimus use. Benign intracranial hypertension and optic disk edema has rarely been reported following renal transplantation[38,39].

Sensorineural hearing loss can occur in patients undergoing liver or renal transplantation and has been reported in association with both tacrolimus and cyclosporine use[38,39].

FINAL REMARKS

The variety of neurological manifestations following solid organ transplantation is broad and carries prognostic significance. Patients may have involvement of the central or peripheral nervous system due to multiple causes that can vary depending on time of onset after the surgical procedure, the transplanted organ, and intensity and type of immunosuppressive therapy. Neurological manifestations following solid organ transplantation pose a diagnostic challenge to medical specialists despite extensive investigations.

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