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REVIEW

Neurologic complications after solid organ transplantation

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Summary

Neurologic complications are common after solid organ transplantation and are associated with significant morbidity. Approximately one-third of transplant recipients experiences neurologic alterations with incidence ranging from 10% to 59%. The complications can be divided into such of those common to all types of transplant and others of those specific to transplanted organ. The most common complication seen with all types of transplanted organ is neurotoxicity attributable to immunosuppressive drugs, followed by seizures, opportunistic central nervous system (CNS) infections, cardiovascular events, encephalopathy and de novo CNS neoplasms. Amongst immunosuppressants, calcineurin inhibitors are the main drugs involved in neurotoxicity, leading to complications which ranges from mild symptoms, such as tremors and paresthesia to severe symptoms, such as disabling pain syndrome and leukoencephalopathy. Neurologic complications of liver transplantation are more common than that of other solid organ transplants (13–47%); encephalopathy is the most common CNS complication, followed by seizures; however, central pontine myelinolysis can appear in 1–8% of the patients leading to permanent disabilities or death. In kidney transplanted patients, stroke is the most common neurologic complication, whereas cerebral infarction and bleeding are more typical after heart transplantation. Metabolic, electrolyte and infectious anomalies represent common risk factors; however, identification of specific causes and early diagnosis are still difficult, because of patient's poor clinical status and concomitant systemic and metabolic disorders, which may obscure symptoms.

Introduction

Over the past two decades, remarkable advances have been made in the field of organ transplantation and improvements in surgical techniques and perioperative care have reduced the mortality and morbidity of transplantation. Neurologic complications are still common after organ transplantation, and are associated with a significant morbidity. Increased mortality in patients with severe neurologic complications after liver transplantation has been reported only in two studies [1,2]. Approximately, one-third of transplant recipients have neuropsychiatric complications and recent studies have shown an incidence ranging from 10% to 59% [3,4]. These neurologic complications can be divided into such of those common to all types of transplant and others of those specific to a given type of transplant. A summary of all the published studies reporting neurologic complications after solid organ transplantation is given in Table 1.

Common neurologic complications

Central nervous system (CNS) complications after solid organ transplantation not caused by or related to failure or impairment of the transplanted organ are mainly attributable to the immunosuppressive therapy and include seizures, opportunistic CNS infections, encephalopathy and cerebrovascular diseases.

Table 1. Incidence of neurologic complications after solid organ transplantation.

Organ	Author	Type of study	Age group	No. patients	Total (%)	Seizure (%)	Stroke (%)	I.H. (%)	CNS infections (%)	Encephalopathy (%)
Heart	Hotson 1976 [5]	C	Ad,P	83	65	6	7	2	29	ND
	Andrews 1990 [6]	C	Ad	90	8	2	3	2	0	ND
	Malheiros 2002 [7]	C	Ad	62	31	20	0	0	0	20
	Cemillan 2004 [8]	C	Ad	205	48	13	10	ND	2	16
	Marchioria 2005 [9]	C	Ad	48	35	ND	10	ND	4	ND
	Perez Miralles 2005 [10]	C	Ad	322	13.7	1.9	3.5	0.6	ND	ND
	Zierer 2007 [11]	C	Ad	200	23	3	5	ND	1	5
	Van de Beek [12]	C	Ad,P	313	19	2	2	<1	ND	9
Lung	Goldstein 1998 [13]	C	P	135	33	20	3	1	1	2
	Wong 1999 [14]	C	Ad,P	100	26	10	4	1	3	ND
Liver	Stein 1992 [15]	C	Ad,P	40	33	20	0	3	0	0
	Menegaux 1994 [2]	C	Ad	273	23	3	2	1	2	ND
	Menegaux 1994 [2]	C	P	118	8	3	0	1	0	ND
	Martinez 1998 [16]	A	Ad	200	ND	17	17	15	11	ND
	Martinez 1998 [16]	A	P	87	ND	24	37	30	11	ND
	Bronster 2000 [17]	C	Ad	463	20	8	0.6	1	1	11
	Ghaus 2001 [18]	C	Ad	45	70	20	ND	4	24	ND
	Marchioria 2005 [9]	C	Ad	241	61	ND	3	2	2	ND
	Saner 2006 [19]	C	Ad	174	25	3	2	5	ND	18
	Saner 2007 [20]	C	Ad	168	27	5	0.6	ND	0	18
	Erol 2007 [21]	C	P	40	35	17	ND	ND	ND	5
	Dhar 2008 [22]	C	Ad	101	32	4	0	0	0	28
Kidney	Adams 1986 [23]	C	Ad	467	30	6	6	1	4	ND
	Marchioria 2005 [9]	C	Ad	1097	21	ND	6	ND	13	ND
Pancreas–kidney	Marchioria 2005 [9]	C	Ad	15	73	ND	ND	ND	0	ND
Pancreas	Kiok 1988 [24]	C	Ad	15	ND	13	7	0	0	ND
Intestine	Zikovic 2000 [25]	C	Ad	54	77	17	5	ND	7	ND

I.H., intracranial hemorrhage; ND, not documented; C, clinical; A, autopsy; Ad, adult; P, pediatric.

Neurotoxicity related to immunosuppressants

Neurotoxicity related to immunosuppressive drugs, including cyclosporine, tacrolimus, OKT3 and corticosteroids, is the most common neurologic complication after solid organ transplantation. Rapamycin and mycophenolate mofetil are rarely associated with neurotoxicity [26,27] although recently cases of progressive multifocal leukoencephalopathy caused by the activation of JC virus have been reported in patients receiving mycophenolate mofetil.

Neurologic complications may also have to do with the recipient's pretransplant status, the type of organ transplanted and postoperative complications. Neurotoxicity associated with calcineurin inhibitors (CNI) is less common than nephrotoxicity or hypertension [28,29].

Calcineurin inhibitors

Cyclosporine and tacrolimus bind to immunophillins, which are low-molecular-weight-intracellular proteins that facilitate protein folding, intracellular transportation and the stability of multiprotein complexes. Neurotoxicity may derive from the same mechanism as the immunosuppressive effect of these drugs, by reducing substrates to cellular physiologic processes [30,31]. Both calcineurin inhibitors are very powerful vasoconstrictors, increasing the production of endothelin, with the release of thromboxane and impairment of nitric oxide/cyclic guanosine-3′,5′-monophosphate homeostasis, causing an excessive production of reactive oxygen species. The vasoconstriction may cause microvascular damage and disrupt the blood brain barrier. It has been demonstrated that the two drugs do not have exactly the same effects; accordingly, one may sometimes be used instead of the other when CNS symptoms occur, without losing the immunosuppressive effect [32]. CNIs also have a toxic effect on oligodendrocytes: glial cells develop intracytoplasmic inclusions when cultured with cyclosporine. This selective toxicity correlates with the white matter changes revealed by computed tomography (CT) and magnetic resonance imaging (MRI) [33]. Cyclosporine and tacrolimus appear to affect neuronal transmission in specific circuits via the following mechanisms: (i) inhibition of the gamma-amino butyric acid system, one of the brain's primary quietening neural systems, which may be the mechanism behind the increased seizure activity in transplant recipients; (ii) neuronal serotonin deple-

tion, which may explain depression and tremor; (iii) glutaminergic *N*-methyl-D-aspartate receptor inhibition, suggesting a possible role for delirium. Neurologic complications are more frequent and more severe while on tacrolimus than on cyclosporine [34]. Ranging from 10% to 28% of the patients on cyclosporine experience some sort of neurotoxic adverse event [13]. Mild symptoms are frequent and include tremor, neuralgia, peripheral neuropathy. A fine, postural tremor affecting the upper extremities and responding to beta-blockers is the most common minor CNS disorder. Severe symptoms affect up to 5% of transplant recipients and include psychoses, hallucinations, blindness, seizures, cerebellar ataxia, motor weakness and leukoencephalopathy [35].

Many of the symptoms of tacrolimus-induced neurotoxicity are much the same. Mild symptoms include tremor, insomnia, nightmares, headache, vertigo, dysesthesia, photophobia or mood disturbances. Severe manifestations include akinetic mutism, seizures, cortical blindness, focal deficits, psychosis and encephalopathy [30]. The treatment of immunosuppressive neurotoxicity consists in correction of electrolyte imbalance and hypertension, immunosuppressant dose reduction and switching from cyclosporine to tacrolimus or vice versa if necessary [36,37]. The recent introduction of novel combinations, such as CNI plus mycophenolate mofetil or sirolimus and everolimus, enables lower doses of cyclosporine or tacrolimus to be used without weakening the immunosuppressive effect [38]. These approaches lead in most cases to the disappearance of the symptoms and the reversal of neuroimaging anomalies [39].

Corticosteroids

The incidence of acute side-effects is 3–4% and the most common neurologic complication is behavioral disorders including confusion, mood disturbances, manic states and psychotic reactions [40]. The neurologic complications of corticosteroids are reversible with a reduction and/or withdrawal of their intravenous administration [41].

OKT3

OKT3 is a murine immunoglobulin monoclonal antibody directed against a T-cell surface molecule. OKT3 associated neurotoxicity is rarely reported. The most frequent OKT3-related side effect is a flu-like condition, with headache and fever, reported in more than 50% of patients. OKT3 is rarely associated with neurologic complications because of its poor neurotoxicity and its current limited clinical indications. From 5% to 10% of patients treated with OKT3 develop an acute aseptic meningeal syndrome [42]. OKT3 causes release of systemic proinflammatory cytokines, which are responsible of the flu-like syndrome and may be involved in the pathogenesis of the cerebral edema. These cytokines may be also involved in meningeal inflammation, which occurs in the aseptic meningeal syndrome [43,44]. Diffuse encephalopathy may rarely occur, with coma, seizures, psychosis and brain edema. OKT3 side-effects usually occur 24–48 h after starting the treatment. The course is favorable and symptoms regress without the need to discontinue the drug's administration.

Seizures

Seizures are the second most common neurologic complication after solid organ transplantation. The most common risk factors for seizures in transplant recipients are immunosuppressant toxicity, rapid electrolytic or osmolar changes, CNS infections, and ischemic or hemorrhagic brain lesions [45,46]. Seizures may be partial or generalized, and are usually tonic-clonic. The clinical diagnosis of nonconvulsive status epilepticus may sometimes prove difficult, so EEG helps to identify the syndrome and in the differential diagnosis with metabolic encephalopathy.

Computed tomography, MRI and laboratory tests are needed to establish the etiology of seizures and enable metabolic, toxic and infectious causes to be ruled out. Additional tests should be performed to rule out hypomagnesemia, hyponatremia and hypoglycemia, and to determine drug levels. Cerebrospinal fluid assay should be considered when seizures are associated with signs of meningismus.

Preventive measures focus on controlling the metabolic parameters and proper drug management. Treating seizures in transplant recipients can be difficult because of the interference between most antiepileptic and immunosuppressive drugs and the usual need of intravenous therapy. Phenytoin is the preferred intravenous anticonvulsant, while gabapentin and levetiracetam should be considered as oral anticonvulsants for their efficacy and lack of hepatic induction [47,48]. Antiepileptic drugs are strongly protein-bound, while the unbound free drug in the serum is the active part. Serum proteins are often altered in transplant recipients so the free drug concentrations may be significantly higher than that in normal serum. Routine monitoring of the free phenytoin is expensive but should nonetheless be considered in these patients. Levels of immunosuppressive drugs should be carefully monitored during anticonvulsant therapy because of the common liver cytochrome involved in the metabolism of both drugs.

Encephalopathy

Encephalopathy presents with a set of symptoms progressing from a mildly altered consciousness to delirium and coma. It is often associated with headache, impaired

vision, tremor, asterixis, multifocal myoclonus, chorea and sometimes seizures. Common causes of encephalopathy include neurotoxicity from nonimmunosuppressive drugs, various metabolic derangements, CNS or systemic infections, and stroke. Immunosuppressant-related encephalopathy has been also described with cyclosporine [49], tacrolimus [50] and, to a lesser extent, OKT3 [51]. Neurotoxicity is usually associated with higher serum concentrations, but may become apparent at serum levels within the therapeutic range. Common signs are tremor, headache, and cerebellar or extrapyramidal signs [35,52]. The most serious complication is reversible posterior leukoencephalopathy, presenting with nausea, hematemesis, headache, loss of vision, seizures and altered consciousness [50], associated with subcortical and deep white-matter changes [53,54]. The spontaneous resolution of the syndrome is probably associated with the spontaneous reduction in hemodynamic disorders. Metabolic encephalopathy is common in transplant recipients and may be attributable to electrolyte and glucose imbalance. In particular, hypercalcemia, hypermagnesemia, hypo- and hypernatremia, hypo- and hyperosmolarity are known to cause metabolic encephalopathy. Clinical signs are sleep disorders, apathy, disorientation in space and time, delirium, acute psychotic episodes with agitation, crying, dysperceptive disorders, and autonomic dysfunction. Diagnosis of encephalopathy is mainly clinical; electroencephalogram can reveal slowing of rhythm and appearance of theta activity. Treatment of encephalopathy focuses on correction of electrolyte and glucose imbalance and optimization of levels of immunosuppressive drugs.

Infections

Central nervous system infections are documented in a mean of 5–10% patients after solid organ transplantation and are associated with a high mortality rate [55]. CNS infections usually occur 2–6 months after transplantation, mainly because of immunosuppression and usually involve systemic infections, especially those affecting the lung and gastrointestinal tract. The clinical syndromes may include acute, subacute or chronic meningitis and encephalitis, and focal deficits because of brain abscesses. As the usual signs of infection are blunted in immunosuppressed patients and infections with uncommon pathogens often occur, it may be difficult to reach an early diagnosis. There is a correlation between the time elapsing after transplantation and the pathogen involved in the infection: bacterial infections occur in the first 2 months after transplantation, while viral and opportunistic infections are more common 6 months after transplantation. Opportunistic bacterial infections include pathogens such as *Nocardia*, *Mycobacterium tuberculosis* and *Listeria monocytogenes*. Fungi are often *Cryptococcus neoformans*, *Aspergillus fumigatus*, *Candida*, *Pneumocystis carinii*. Common viruses include cytomegalovirus (CMV), Varicella-Zoster virus and Epstein–Barr virus (EBV), herpes viruses 1 and 2 (HSV 1 and 2) and BK/JC polyoma virus are less common. Diagnosis of CNS infections is based on searching of systemic signs of infections, neuroimaging, lumbar puncture, and eventually brain biopsy. Cerebral spinal fluid (CSF) polymerase chain reaction is necessary to detect viruses in the liquor.

Bacterial infections

Infections caused by *Nocardia* have been documented in 1–6% of solid organ transplant recipients [56]. The primary route of entry is the lung and the CNS is the most frequent site of secondary dissemination, in the form of single or multiple brain abscesses. These are rarely caused by *M. tuberculosis*: approximately 1% of transplant recipients with *M. tuberculosis* have been found to have brain abscesses [57]. *Listeria monocytogenes* may present with isolated bacteremia or meningitis any time after transplantation, though most infections occur in the late post-transplant period. Meningitis is the most common form of CNS involvement, but a brainstem encephalitis syndrome characterized by cranial nerve palsy, sensory-motor and cerebellar signs caused by *Listeria* has also occasionally been reported [58].

Fungal infections

Candida infections are common after transplantation, especially in the recipients of liver, lung, heart–lung and pancreas, but CNS lesions are infrequent. *Aspergillus* is the agent most frequently responsible for brain abscesses in organ transplant recipients. The most common neurologic symptoms of *Aspergillus* are an altered mental state (86%), seizures (41%), and focal neurologic deficits (32%), while meningeal signs are less common (19%) [59]. Concurrent lung involvement has been reported in 83–90% of patients with CNS lesions, suggesting that the lung is, here again, the route of entry and the CNS the site of secondary dissemination [59]. *Aspergillus* invasion of the blood vessels with subsequent ischemic or hemorrhagic infarctions, and solitary or multiple brain abscesses are the main neuropathologic findings [60]. Infections caused by *Cryptococcus* are rare and have been reported in 0.3–6% of transplant patients [61,62]. Subacute meningitis is the usual presentation of cryptococcal infection, with symptoms developing over a period of 2–90 days.

Viral infections

Among HSV, HHV-6 is the most neuroinvasive and it can cause focal encephalitis. Despite frequent occurrence of systemic CMV infections, encephalitis is uncommon.

Reactivation of the JC polyoma virus and oligodendrocyte infection results in progressive multifocal leukoencephalopathy. Clinical signs include severe and rapidly progressive dementia, ataxia, visual disturbances and other focal neurologic deficits, generally progressing to a vegetative state within 6 months. Unfortunately, all therapeutic regimens are still in the experimental phase. It is important to distinguish between the progressive multifocal leukoencephalopathy related to tacrolimus or cyclosporine from central pontine myelinolysis because the former is usually reversible [63].

Cerebrovascular events

Strokes are a rare but significant cause of morbidity and mortality in transplant recipients. They may be related to the presence of bacterial endocarditis, hypercoagulable states, atherosclerosis, vasculitis and cardiac arrhythmias. Strokes may also be caused by the perioperative detachment of arterial emboli from carotid or intracranial arteries. The main preventive measure is the adjustment of cerebrovascular risk factors before, during and after transplantation. Diagnosis of stroke is made both by clinical symptoms and brain CT scan or MRI.

De novo CNS malignancies

Organ transplant recipients have a three- to fourfold higher incidence of malignant disease compared with the general population [64], because of their reduced immunosurveillance and high incidence of infections involving oncogenic viruses. The most common CNS neoplasms are lymphoma and glioma. The incidence of post-transplant lymphoproliferative disorders has been estimated at less than 2% (with higher rates in the pediatric population) and 27% of cases involve the CNS and meningi [65–67]. Patients undergoing heart–lung or liver–bowel transplantation are at highest risk (5%), while the risk is lower with liver, cardiac and bone marrow allografts (1–2%), and lowest with kidney transplantation (<1%) [65]. Many of the reported cases of CNS lymphomas are associated with prior EBV infections [68]: this condition is estimated to occur in 3% of liver recipients [69] and in 1–2% of kidney recipients [70]. The clinical manifestations vary and the diagnosis is based on neuroradiologic findings and liquor analysis, but it is often cerebral biopsy that enables the final diagnosis. Local radiotherapy is the treatment of choice, sometimes associated with other measures, such as chemotherapy and antiviral therapy for EBV-related lymphomas.

Organ-specific neurologic complications

Heart

Neurologic complications occur in 50–70% of heart transplant recipients and are the primary cause of death in 20% of these patients [10]. Neurologic complications in such patients are influenced by their primary disease and prior cardiovascular and CNS status, the surgical procedure and postoperative course, and post-transplant medication. The most common complication is ischemic stroke, reported in 3–10% of the patients [5,6,9–11], followed by drug toxicity. Valve disease as the reason for the transplant is associated with ischemic stroke; diabetes mellitus and renal failure are associated with seizures [10]. Perioperative hemodynamic instability giving rise to cerebral ischemia and metabolic disorders secondary to multiple organ failure are the determining factors for encephalopathy. After heart transplantation, patients show residual frontal hypoperfusion on SPECT with 99mTc-hexamethyl-propylene-amineoxime [71] and these cerebral anomalies may be because of long-standing cerebral hypoperfusion resulting from severe heart disease, or microemboli caused by a cardiovascular bypass, which is a known cause of encephalopathy in heart recipients (Fig. 1). While awaiting heart transplantation, moreover, some patients are treated with artificial hearts and ventricular assist devices, which require anticoagulant therapy and carry an intrinsic risk of cardioembolic events and intracranial hemorrhage [72]. Patients with end-stage heart failure have a high prevalence of cognitive impairments attributable to a decreased brain perfusion secondary to poor cardiac function and these conditions may be partially improved by cardiac transplantation [73]. Cardiac arrest and prolonged global CNS ischemia may lead to anoxic encephalopathy.

Lung

The neurologic complications of lung transplantation are similar to those seen in heart-transplanted patients. The incidence in the pediatric population is 45% and the most common presenting symptoms are seizures, followed by encephalopathy, headache, depression and focal neurologic etiologies, followed by stroke, and metabolic and infectious causes [14].

Kidney

Central nervous system complications after kidney transplantation are reported in 6–21% of recipients [9,23]. Stroke may occur in 8% of renal transplant recipients and may be facilitated by hypertension, diabetes and accelerated atherosclerosis, which may be acquired during dialysis

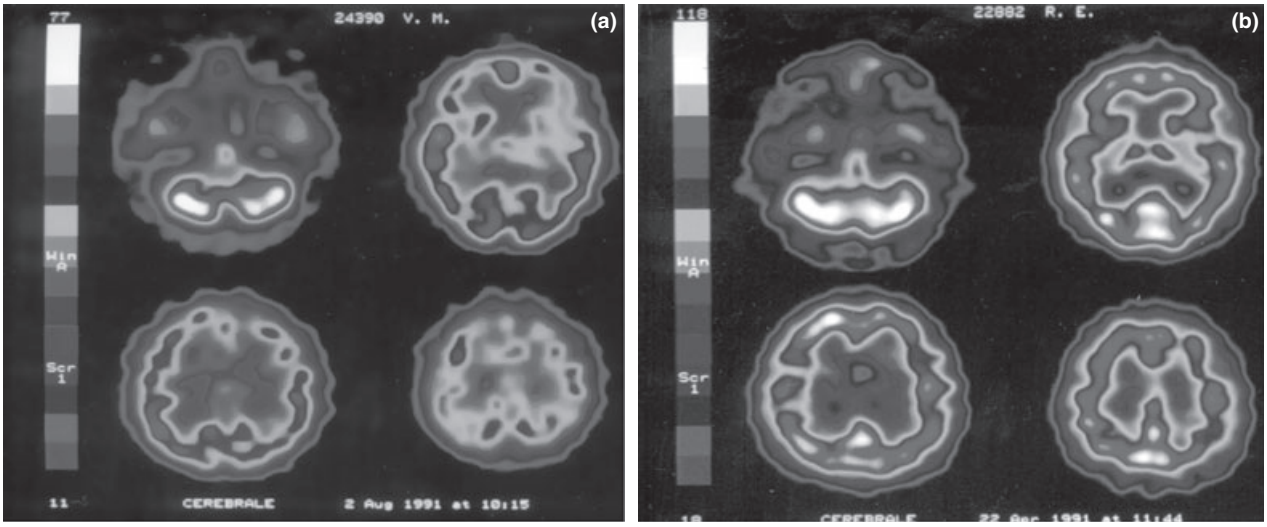

Figure 1 99mTc-HM-PAO single-photon emission computed tomography shows residual defect 1 year after heart transplantation (a) compared to control (b).

or after transplantation [74]. Peripheral mononeuritis and polyneuritis may also occur. An acute femoral neuropathy can develop in 2% of the patients as a result of perioperative nerve compression by retractors or nerve ischemia. Patients complain of weakness in the thigh and pain or sensory deficits on the thigh and inner calf. Most patients have an excellent chance of recovery [74–76]. Guillain Barre syndrome may also develop, associated in some cases with CMV or *Campylobacter jejuni* infection. Infections represent the most frequent neurologic complication. Acute meningitis, usually caused by *L. monocytogenes*, subacute and chronic meningitis caused by *C. neoformans*, focal brain infections caused by *A. fumigatus*, *Toxoplasma gondii* or *Nocardia asteroids*, and progressive dementia caused by Polyoma J virus are the most common CNS infections in kidney transplant recipients [74].

Liver

Neurologic complications of liver transplantation are more common than other solid organ transplants, ranging from 4% to 70% in the published series [2,9,15–21]. Living donor liver transplantation is associated with a significantly lower incidence of neurologic complications than in patients who receive a cadaveric graft [19]. This may be because of a better graft quality, shorter cold ischemia time and recipient's better baseline conditions at the time of transplantation. The reason why liver transplantation is associated with such a high risk of neurologic complications is attributable to the complexity of the surgical procedure, the unfavorable conditions of patients awaiting transplantation (malnutrition, ionic disorders, coagulopathy) and hepatic encephalopathy before the transplant [17,29]. Liver cirrhosis patients without any overt encephalopathy may have mild cognitive alterations, defined as minimal hepatic encephalopathy. It is important to identify this neuropsychiatric syndrome in patients awaiting liver transplantation because it may correlate with residual cognitive deficits seen in transplanted patients [77,78]. The combination of spectral electroencephalogram (ECG), PSE neuropsychologic battery and testing partial pressure of ammonia before transplantation helps to detect minimal hepatic encephalopathy and may enable its adequate treatment prior to surgery, which includes advising patients not to drive and adjusting their priority on the waiting list for liver transplantation [79]. Cirrhotic patients have also revealed alterations in cortical perfusion on 99mTc-HM-PAO single photon emission computed tomography and 18F-Fluorodeoxyglucose positron emission tomography [80,81]. Cerebral blood flow is lower in patients with alcoholic or viral cirrhosis than in cholestatic liver disease [82], and it is lower in alcoholics with cirrhosis than in patients with cirrhosis of other etiology when evaluated by 18F-fluorodeoxyglucose positron emission tomography [80]. The cerebral anomalies are found mainly in the frontal lobe and may be because of potentially irreversible damage caused by alcohol abuse even in the absence of significant cerebral atrophy. When evaluated by PET, patients with alcohol abuse may have metabolic deficiencies in the frontal lobe even after 4 years of abstinence [81]. Patients with cholestatic liver disease seem to have less cerebral impairment than viral or alcoholic patients but they show the same hypoperfusion of the caudatus, thalamus and cerebellum. Cholestasis may

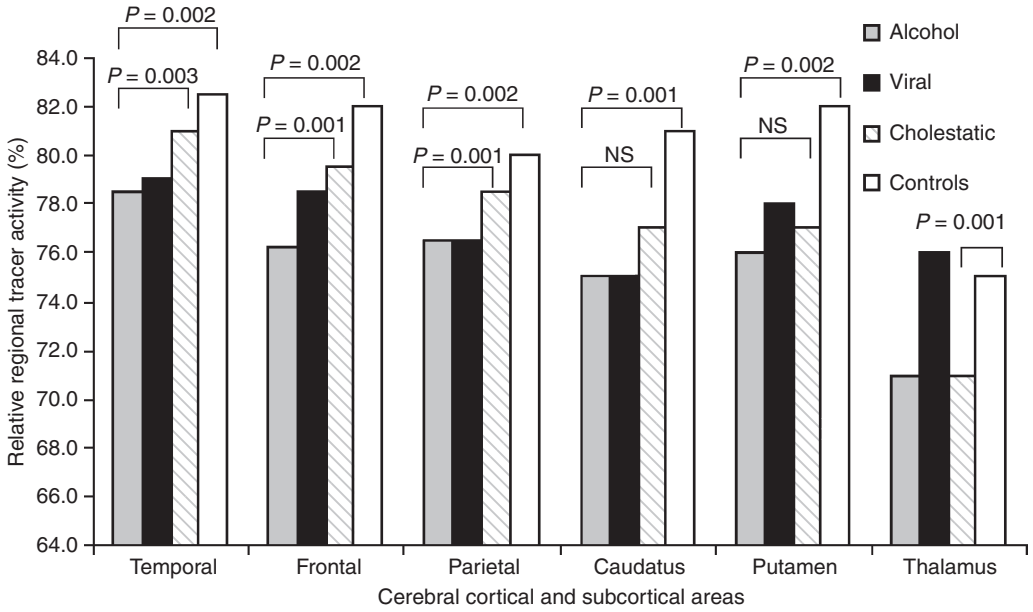

Figure 2 99-TC-hexamethylpropylene-amine-oxime regional brain activity in patients divided by etiology of liver cirrhosis and controls. Patients with cholestatic liver disease show cortical perfusion no different from controls and significantly better than in other etiologies of liver cirrhosis.

reduce the permeability of the blood brain barrier by altering the cholesterol content in the membrane, thereby reducing the neuronal damage caused by ammonia [83] (Fig. 2). Liver transplantation normalizes cerebral blood flow, although the frontal cortex remains significantly more impaired in patients with alcoholic cirrhosis than in those with nonalcoholic cirrhosis [80,81]. Encephalopathy is the most common CNS complication, followed by seizures [17]. Its causes are numerous, including anoxia, primary graft nonfunction, renal failure, rejection, sepsis, central pontine myelinolysis (CPM) and drugs [28]. CPM is a symmetrically demyelinating lesion at the center of the pons, usually seen in alcoholics and malnourished patients, attributed to a rapid correction of hyponatremia [84]. CPM has been reported in 1–8% of patients. Although CPM is occasionally reversible, the clinical course often progresses to death over days to weeks.

Seizures are the second most common neurologic complication reported after liver transplantation, with an incidence of 25–45%. The etiology of seizures in liver recipients is usually related to a CNS lesion such as stroke, or to CPM or CNS infections. Acute cerebrovascular disorders occur in 2–6.5% of liver transplant recipients, mostly with brain hemorrhage [85], which typically occurs in the frontal and parietal lobes, and less commonly in the subcortical areas [86]. Several risk factors are recognized, including those associated directly with liver failure (e.g. coagulopathy) and those secondary to immunosuppressive therapy, such as hypercholesterolemia, diabetes and hypertension. Cerebral ischemia may be caused by cerebral edema, an increase in intracranial pressure or arterial embolism. The incidence of CNS infections is estimated at 5%, with a high related mortality [87]. *Listeria monocytogenes*, *A. fumigatus* and *C. neoformans* are the most commonly involved pathogens; viral infections are rare, and relate to HSV and CMV [87]. CMV, hepatitis B virus or hepatitis C virus may occasionally cause fulminant systemic failure with secondary CNS involvement [88]. The clinical syndromes include meningitis, meningo-encephalitis, encephalitis and focal deficits caused by brain abscesses, frequently caused by *Aspergillus*.

Pancreas

Major CNS complications of pancreas transplantation include hypoxic encephalopathy (20%), cerebral and spinal-cord infarction (7%), and seizures (13%) [24]. These appear to be closely associated with cardiovascular collapse or cardiac arrest, often occurring after septic, hemorrhagic or additional surgical-anesthetic stress suffered some time after the transplantation. There are associations between visual hallucinations and cyclosporine therapy, between CSF pleocytosis and OK3 therapy, and between compressive neuropathy and surgical anesthesia. It is difficult to distinguish the complications attributable to pancreas transplantation from those caused by the natural history of the underlying diabetes [89].

Intestines

Neurologic complications of intestinal transplantation seem to be more common than that with other solid organ transplants, but are similar in the spectrum of signs and symptoms [25].

Conclusions

Neurologic complications are common after solid organ transplantation. Differences in their incidence could depend on different cohort studies and underlying medical conditions in recipients awaiting transplantation of different solid organs. The most common complication, seen with all types of organ being transplanted, is neurotoxicity caused by immunosuppressive drugs, followed by seizures, opportunistic CNS infections, cardiovascular events, encephalopathy and de novo CNS neoplasms. Stroke is more common after kidney transplantation, while encephalopathy, seizures and CPM are characteristic of liver transplantation. Cerebral infarction, embolization and bleeding are more typical after heart transplantation. Metabolic, electrolyte and infectious anomalies are common risk factors for the onset of neurologic complications after solid organ transplantation, but further studies are needed to clarify the full spectrum of risk factors. Diagnosis and management are often made more difficult by the patient's poor clinical status, and because systemic and metabolic disorders may obscure symptoms of an underlying CNS lesion. Evidence-based guidelines on this issue are currently lacking.

Although few evidences are available to correlate post-transplantation parameters with risk of developing neurologic complications, an extensive evaluation is recommended to optimize the post-transplantation management. Preventive measures could be the use of CNI-sparing regimen in patients with high risk of CNS complications after transplantation and attention to postoperative care.

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