Organ Transplant Recipients and Critical Care Seizures

15

Deena M. Nasr, Sara Hocker, and Eelco F.M. Wijdicks

Introduction

Seizures are the second most common central nervous system complication in solid organ transplant recipients. They are second to encephalopathy in liver, intestinal, and lung transplantation and stroke in cardiac and renal transplant recipients [1]. The incidence of seizures among solid organ transplant (SOT) recipients is wide with reports ranging from 1 to 13%, and 2 to 20% in hematopoietic stem cell transplant (HSCT) recipients [2, 3] (Table 15.1). Such a wide disparity in prevalence is not easily explained and may be related to a premorbid condition, use of certain immunosuppressive drugs, and control of hypertension causing posterior reversible encephalopathy syndrome. In most series it is unclear how the diagnosis of seizures was made or confirmed.

Seizures may be focal or generalized in onset. They are essentially a non-specific symptom of cerebral dysfunction. In the setting of organ transplantation, they may result from drug-induced neurotoxicity, metabolic/electrolyte disturbances, central nervous system (CNS) infections, malignant hypertension, ischemic or hemorrhage stroke, or CNS malignancy.

D.M. Nasr
Department of Neurology, Mayo Clinic, Rochester, MN, USA
e-mail: Nasr.Deena@mayo.edu

S. Hocker (✉)
Division of Critical Care Neurology, Mayo Clinic,
200 First Street S.W., Rochester, MN 55905, USA
e-mail: Hocker.Sara@mayo.edu

E.F.M. Wijdicks
Division of Critical Care Neurology, Mayo Clinic,
Rochester, MN, USA
e-mail: Wijde@mayo.edu

The general approach to the evaluation of seizures in this population differs little from the general population. The priorities are: (1) to abort the seizure in order to minimize neurologic and systemic morbidity, (2) to minimize seizure recurrence by identifying and treating the etiology when possible, and (3) to determine if there is need for long-term antiepileptic drugs (AEDs). A few additional considerations specific to this patient population also apply and are outlined in this chapter.

Initial Patient Evaluation and Treatment

In the acute setting, the primary goal is to abort the seizure. Because most seizures are self-limited, there is a tendency to think that most patients will not require emergent treatment and can be observed, however, seizures in these fragile postoperative patients may lead to major systemic complications (aspiration, myocardial demand ischemia, rhabdomyolysis). We opt for a short two week course with an antiepileptic with a good safety profile such as levetiracetam. Obviously in the case of recurrent seizures or status epilepticus, emergent pharmacologic treatment with intravenous AEDs is recommended.

Most post-transplant seizures respond to first line treatment with benzodiazepines with preferred agents being lorazepam or midazolam [4]. When seizures continue despite benzodiazepine administration efforts should be made to rapidly identify and correct any readily reversible precipitating factors (i.e., severe hyponatremia) and a second line intravenous AED should be administered. Options include phenytoin, fosphenytoin, valproic acid, phenobarbital, or levetiracetam [5].

The next step is to find a possible cause of the seizure (Table 15.2). This is especially pertinent in transplant patients who are immunosuppressed with antirejection medications and therefore at higher risk for infections and neurotoxicity related to the antirejection drugs. Investigation of serum electrolyte levels including magnesium, sodium, calcium,

P.N. Varelas, J. Claassen (eds.), *Seizures in Critical Care*, Current Clinical Neurology, DOI 10.1007/978-3-319-49557-6_15

Table 15.1 Incidence of seizures in organ transplant patients

Transplant organ	Incidence of seizures (%)
Liver	4–8 [79–82]
Bone marrow transplant	2–20 [2–3, 83–85]
Heart	2–9 [76, 86–88]
Kidney	2–6 [1, 89]
Lung	6–10 [90–91]
Pancreas	13 [92]
Intestinal	17 [93]

Table 15.2 Possible causes of seizures in transplant recipients

Cerebrovascular events • Arterial ischemic infarcts • Intracranial hemorrhage • Cerebral venous thrombosis	**Malignancy** • B-cell lymphoma • Post-transplant lymphoproliferative disorder
CNS infection *Bacterial* • Nocardia • Listeria • Tuberculosis *Viral* • JC virus • Herpes Viruses (HSV, CMV, VZV, EBV, HHV-6) *Fungal* • Aspergillus • Candida • Cryptococcus *Parasite* • Toxoplasmosis	**Medication induced neurotoxicity** *Antirejection agents* • CNIs: Tacrolimus, cyclosporin A • OKT3 (muronmonab-CD3) • Chemotherapy: busulfan and carmustine *Antibiotics* • Quinolone Class • Carbapenem class *Analgesics* • Meperidine **Metabolic derangements** • Hyponatremia • Hypocalcemia • Hypomagnesemia • Hypoglycemia • Hyperammonemia

and glucose as well as a complete blood count with differential, ammonia, blood cultures, and antirejection medication levels should be performed.

Because seizures are comparatively more common in CNS infections associated with transplantations an infectious evaluation should be initiated if seizures occur one month after transplantation (CNS infections are exceedingly rare in the postoperative period). A history of preceding headache, confusion, signs of increased intracranial pressure including transient visual obscurations, morning headaches, or signs of meningismus on examination justifies a lumbar puncture but immunosuppressed post-transplant patients should undergo neuroimaging prior to lumbar puncture. Empiric antimicrobial therapy should be started while neuroimaging and lumbar puncture are performed.

Because of their immunosuppressed status, imaging is strongly considered in these patients, even when a clear trigger (i.e., severe hypocalcemia) is present. A non-contrast CT is the first investigational step to rule out the presence of a lesion that may require emergent intervention. Non-contrast CT can also be useful in detecting the typical vasogenic edema of posterior reversible encephalopathy syndrome (PRES) (Fig. 15.1), a mass-like lesion such as brain abscess, intracerebral hemorrhage, or diffuse cerebral edema.

If initial investigations are unrevealing, MRI with contrast can be considered. Smaller brain abscesses, empyema, septic emboli, pachymeningeal or leptomeningeal enhancement, brainstem infarctions, radiologic signs of PRES, and central pontine myelinolysis are more readily identified on MRI compared with CT [5].

An electroencephalogram (EEG) is not performed in most settings due to the fact that the majority of seizures last less than 1 min and patients recover quickly from these seizures. However, patients who remain persistently encephalopathic following a seizure will need an urgent EEG in order to determine if the patient is in nonconvulsive status epilepticus. Because undefined rhythmic movements are so common in the postoperative period an EEG can also be useful to characterize the nature of uncertain "spells" of unresponsiveness or abnormal movements. For example, to differentiate multifocal myoclonus (seen in metabolic encephalopathy) or tremors from seizures in unresponsive patients or in patients awakening from anesthesia [5].

Seizures in Transplant Patients: Specific Causes

Drug-Induced Seizures

Immunosuppressant agents such as cyclosporine, tacrolimus, mycophenolate mofetil, and corticosteroids are universally administered following organ transplantation to reduce the risk of rejection and improve graft survival. In the acute post-transplant period, induction agents can be used including thymoglobulin, OKT3, and basiliximab. These are followed with maintenance steroids, mycophenolate mofetil, or calcineurin inhibitors such as cyclosporine or tacrolimus. Most transplant patients are then continued on a long-term regimen consisting of a calcineurin inhibitor or mycophenolate mofetil [6].

Because of the narrow therapeutic windows of antirejection drugs and the higher propensity for metabolic derangements in the post-transplant period, drug toxicity from calcineurin inhibitors or mycophenolate mofetil can be considered as a potential cause for seizures. Post-transplant drug-induced encephalopathy affects up to 40% of patients with the incidence peaking within the early postoperative period due to high loading doses [7, 8]. Drug toxicity from antirejection agents is the most common cause of seizures and is the cause in about 25% of cases [9]. The calcineurin inhibitors have been mostly responsible for most drug-induced seizures due to their mechanism of action. They inhibit calcium signaling pathways that are essential to T-cell activations. However, calcineurin also plays an essential role

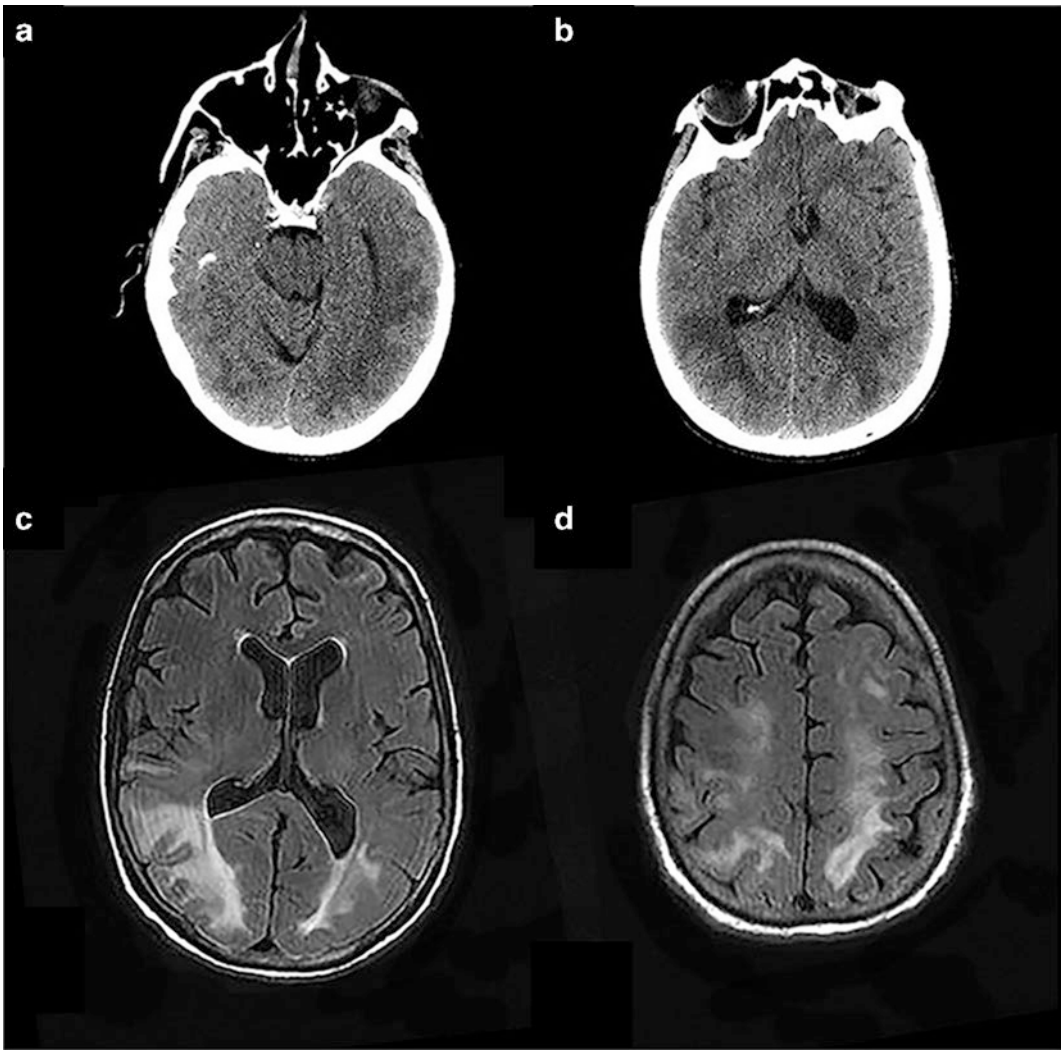

Fig 15.1 (**a**, **b**) Computed tomography and (**c**, **d**) magnetic resonance imaging fluid attenuated inversion recovery (FLAIR/T2 weighted sequences demonstrating a typical pattern of vasogenic edema associated with PRES). The edema is bilateral, asymmetric, predominantly subcortical, and preferentially affecting the posterior regions and frontal lobes

in regulating neuron excitability, blood–brain barrier permeability, and sympathetic activation [9]. The neurotoxic effects of calcineurin inhibitors may be potentiated by pre-existing disruption of the blood–brain barrier in the perioperative period due to hepatic encephalopathy or perioperative hypotension [10]. Ultimately, these disruptions can lead to vasogenic edema, posterior reversible encephalopathy syndrome (PRES), and seizures.

The diagnostic criteria for CNI induced toxicity include development of seizures or encephalopathy in patients receiving CNIs who have high serum trough levels of the drug at the time of symptoms onset and rapid increase in drug levels prior to symptomatic presentation. Neurotoxicity from CNIs is more commonly seen in the first month of post-transplant care due to the higher intravenous dosing [11]. Postural tremors and headaches are the most common symptoms encountered and can be seen with tacrolimus neurotoxicity. However, both tacrolimus and cyclosporine neurotoxicity can manifest with focal or generalized tonic-clonic seizures that can be seen with or without the presence of posterior reversible encephalopathy syndrome (PRES). Risk factors for CNI toxicity include hepatic dysfunction, hypertension, low magnesium levels, and administration of medications such as corticosteroids, amphotericin, and ganciclovir which inhibit drug metabolism [12]. While it is important to monitor drug levels during the early phase of maintenance immunosuppression while on these therapies, it has been demonstrated that no correlation exists between seizures and drug levels themselves [13]. Rather, it is the rapid increase in drug levels that is thought to be a provoking cause. In addition, levels of metabolites, rather than the drug itself, can be associated with seizures.

Over the past several years, there has been a switch from cyclosporine to tacrolimus as the antirejection agent of choice in organ transplant patients. Tacrolimus is associated with lower rates of hypertension, acute rejection, and possibly a better neurotoxicity profile as compared to cyclosporine. The incidence of seizures is similar when comparing the two drugs [14].

Newer agents such as sirolimus and everolimus have been introduced to be used as either first line agents or calcineurin inhibitor (CNI) sparing agents in cases of neurotoxicity. Despite their similar appearing names, these medications are mammalian target of rapamycin (mTOR) inhibitors, not CNIs. There has not been any compelling evidence to suggest that sirolimus itself potentiates seizures. However, there have been few case reports of PRES associated with sirolimus, predominantly in association with hypertensive crises [15, 16].

In cases of neurotoxicity, the primary treatment strategy is reducing the dose or changing the offending agent [17, 13, 18]. This decision should not be taken lightly as it puts the transplanted organ at potential risk for rejection. Various strategies exist for restarting the antirejection transplant regimen including transitioning one CNI to another or an alternative agent such as an mTOR inhibitor or muromonab-CD3 (OKT3) [19]. OKT3 is a murine immunoglobulin monoclonal antibody that is rarely used today for very limited indications such as acute steroid-resistant rejection of allogenic renal, cardiac and liver transplant patients. Neurotoxicity is uncommon with the most commonly reported manifestation being the development of an aseptic meningitis within 72 h of administration [20]. It is in this context that seizures have, rarely, been reported.

Busulfan is commonly used to condition patients in preparation of hematopoietic stem cell transplantation. This agent has been frequently reported to cause seizures in HSCT patients. This complication typically occurs in the 3rd or 4th day of administration and appears to be dose dependent [21, 22]. Although hard evidence is lacking regarding seizure prophylaxis, it has become a generally accepted practice when initiating high-dose busulfan. This is complicated by the fact that the seizure prophylaxis must not have any interaction or toxicity with the conditioning regimen, interfere with the donor cells, or interact with other medications that the patient is receiving. Phenytoin is not an ideal agent for prevention of seizures in this setting due to the risk of toxicity and its ability to induce busulfan metabolism. Current data support the use of benzodiazepines such as clonazepam or lorazepam as seizure prophylaxis. Levetiracetam is another promising agent due to its limited drug–drug interactions and adverse effects.

A number of other agents, both chemotherapeutic and immunosuppressive, have been associated with seizures in transplant patients. Carmustine is a chemotherapeutic agent used in preparation of HSCT. This agent has been associated with seizures in a number of studies [23, 24]. Azathioprine and mycophenolate mofetil have also been associated with seizures in the post-transplant setting [25].

Many antibiotics used to treat infections in immunosuppressed patients are associated with reductions in seizure threshold. Quinolone antibiotics have a variable effect on the seizure threshold. Trovafloxacin has the greatest potential for seizure induction and levofloxacin has the lowest rate of seizure induction. Imipenem and meropenem have also been associated with seizures in prior studies [26, 27]. While the overall risk of seizures in these patients is low, close monitoring of transplant patients on these drugs is recommended [27] and they should probably be avoided entirely in patients with pre-existing epilepsy [28].

Post-transplant pain is often managed with opioid medications such as meperidine [29]. Meperidine has a high central nervous system depressant effect, however, its metabolite is normeperidine, which has twice the CNS neurotoxic effect of meperidine and is a CNS excitatory agent. Accumulation of normeperidine in the CNS can result in generalized seizures, myoclonus, tremors, and hyperreflexia. These effects cannot be reversed by opioid antagonists. Risk factors for meperidine related seizures include hepatic or renal dysfunction [30].

Management in the setting of drug-induced seizures is primarily cessation of the drug after which recurrent seizures are not expected. If seizures recur after the suspected causal drug has been discontinued and sufficient time to allow five half-lives of the drug has passed, an alternative cause for the seizures should be sought.

Acute Metabolic Change

An acute metabolic change should be considered in all patients with post-transplant seizures as in many cases, these disturbances are easily reversible. Metabolic disturbances can result from acute electrolyte imbalances in the early postoperative period. Delayed onset idiopathic hyperammonemia has also been reported and can result in refractory seizures, however, this rare complication is not easily reversible [31].

Hyponatremia and hypo-osmolality can contribute to seizures in the early postoperative period [32]. In one study of seizures in children who seized within 24 h following a kidney transplant, the patients with seizures had more pronounced shifts in sodium levels and serum osmolality that those without seizures [32]. Renal transplant patients are particularly prone to hyponatremia and shifts in serum osmolality due to their high rates of postoperative polyuria. This is due to renal tubular dysfunction and can be exacerbated by aggressive fluid resuscitation. Severe hyponatremia as a result of post-transplant polyuria can result in generalized tonic-clonic seizures [33]. Low sodium levels have also been associated with

seizure events in cystic fibrosis patients following lung transplant [34] and rapid changes in sodium levels have been associated with seizures in liver transplant patients [35]. Treatment is often correction with hypertonic saline, however, care must be taken to not reverse the hyponatremia too quickly otherwise the patient will be at risk for the development of central pontine myelinolysis (CPM) [36, 37].

Hypomagnesemia is another well-established risk factor for seizures in the post-transplant population [35]. This is especially true in the liver transplant population where hypomagnesemia is an independent risk factor of seizures as well as in patients receiving small bowel transplants and HSCT [35, 38, 39]. Hypomagnesemia can potentiate the effects of drug-induced neurotoxicity [40] and can also result from cyclosporine induced renal wasting [41, 42]. Hypomagnesemia frequently presents with muscle weakness prior to its more serious manifestations such as behavioral changes and seizures. Reversal of the electrolyte deficiency is the only way to prevent further seizures in these patients.

Hypocalcemia is another side effect of CNIs such as cyclosporine. Like hypomagnesemia, it is due to increased excretion of the electrolyte in the urine. Hypocalcemia occurs with a nadir level at about one week post-transplant [43]. Hypocalcemia has been shown to be a predictor of PRES in patients with chronic kidney disease, including transplant patients [44].

Hypoglycemia induced seizures are also not uncommon and may be most likely to occur in patients receiving combined pancreas-renal transplants.

Idiopathic hyperammonemia is a rare complication in organ transplant recipients but is often devastating [31, 45]. This most commonly occurs while patients are severely neutropenic. Patients present with acute lethargy, confusion, seizures, and then progress to coma. Serologic evaluation demonstrates ammonia levels over 200 μmol/L with mild elevation of liver enzymes [45]. Patients with liver failure or who are receiving valproic acid can also experience high serum ammonia levels. Imaging evaluation of these patients demonstrates diffuse cerebral edema. There are no pharmacologic treatments for idiopathic hyperammonemia although some have reported success with lactulose, nonabsorbable antibiotics, dialysis or sodium benzoate for trapping, and removal of ammonia [31, 46].

CNS Infections

Infections most commonly occur one to six months following solid organ transplantation [47]. In the first month following the transplant, patients are at high risk for pneumonia or wound infection. Patients with hematopoietic stem cell transplant are at higher risk of opportunist infections in the first month as they are under maximal immunosuppression during this period. This is in contrast to solid organ transplant patients who are not on maximal therapy until about 1 month following the transplant. Beyond 6 months, patients who have not experienced rejection, poor graft function, or GVHD are generally given a lower dose of immunosuppressants and are thus at a lower risk for infectious complications. However, those who are maintained on high doses of immunosuppressant agent remain susceptible to many typical and opportunistic infections [47].

A CNS infection should be considered in any patient with headache, mental status changes, or seizure [47]. It is important to keep in mind that initial CSF studies may be underwhelming and even the imaging manifestations of a CNS infection may not be striking. Both the development of an inflammatory response in the CSF and formation of an abscess require a robust immune response; thus many of these patients may have only a mild CSF pleocytosis or a more phlegmon appearing lesion in their brain rather than an organized, diffusion restricting walled off fluid collection [47].

Bacterial infections account for a substantial proportion of infections in this population. Special consideration should be given to opportunistic infections such as Listeria and Nocardiosis. Nocardiosis presents as a pulmonary infection that is diagnosed with sputum, skin, or brain tissue and can present with a mass lesion. CNS involvement occurs in 50% of the cases and can present with fevers, meningismus, focal deficits, and seizures. It has been reported in <5% of renal transplant patients (1–6% of solid organ transplants [47–49]). Listeria presents with gastrointestinal symptoms, fevers, focal deficits, and seizures. Diagnosis is made by identification of gram positive bacilli in the CSF or blood.

Immunosuppressed patients are at high risk for opportunistic fungal infections such as aspergillosis, candidiasis, and cryptococcosis. All three of these fungal infections can present with disseminated pulmonary infiltrates and nodules while candida and cryptococcosis can also present in the lungs. These infections can manifest clinically as meningitis or with more focal symptoms suggestive of an abscess, both of which can lead to seizures [47]. Aspergillosis is unique in that it can present with septic and hemorrhagic infarctions. Presentation of fungal CNS infections includes encephalopathy (90%), focal neurological deficits (33%), seizures (40%), and meningeal signs (20%) [50]. Diagnosis depends on CSF and blood cultures and rarely, brain histology.

Opportunistic viral infections include herpes virus infections such as cytomegalovirus (CMV), Epstein–Barr virus (EBV), varicella-zoster virus (VZV), human herpes virus-6 (HHV-6), and herpes simplex virus (HSV) as well as JC virus induced progressive multifocal leukoencephalopathy (PML) [51]. These are generally the result of reactivation or primary infection and present with meningitis or limbic encephalitis. Mass lesions can be seen in the setting of EBV induced post-transplant lymphoproliferative disease (PTLD)

as well as in the setting of JC induced PML [51]. These viral infections are diagnosed with CSF and blood culture as well as by identification of virus specific serologies or antibodies in the CSF. Treatments for herpes virus infections include acyclovir, ganciclovir or foscarnet, and cytarabine for PML. These infections are particularly a problem in HSCT recipients and can cause headache, confusion, and seizures several weeks after transplantation due to limbic encephalitis [51].

Other opportunistic infections that can affect organ transplant recipients include toxoplasmosis and tuberculosis. Toxoplasmosis can present with meningitis and abscess formation and is diagnosed with serology and CSF markers. Tuberculosis can present with basilar meningitis, abscess, "tuberculomas," and is diagnosed with CSF culture, smear, and serology [51].

One of the chief difficulties complicating the management of CNS infections is the interaction between many of the pharmacologic agents used to treat them with antirejection drugs and AEDs. For this reason, consulting a pharmacist and a careful risks/benefits may be helpful; however, adequate treatment of the infection must take priority over other considerations.

Post-transplant Malignancy

B-cell lymphoma and PTLD are the most common brain tumors seen in transplant recipients [52, 53]. These are most common after liver and small bowel transplants. PTLD is typically associated with EBV infection and should be considered in patients presenting with de novo seizures years following transplant (extreme cases 6 months post-transplantation have been reported. Lymphoma and PTLD in immunocompromised patients typically present with multiple periventricular ring enhancing lesions, similar to toxoplasmosis [52, 53]. Classically, increased uptake on SPECT or FDG/PET has been used to differentiate CNS lymphoma or PTLD from toxoplasmosis. In cases of high clinical suspicion, biopsy is recommended, followed by initiation of corticosteroids to reduce edema. In addition, reduction of immunosuppression therapy is advised [52, 53].

Posterior Reversible Encephalopathy Syndrome

PRES is a usually reversible neurologic syndrome of subcortical vasogenic brain edema in patients with acute neurologic symptoms (i.e., encephalopathy, headache, seizures, and visual disturbances) in the setting of renal failure, blood pressure fluctuations, autoimmune disorders, or cytotoxic drug administration (i.e., CNI therapy). PRES occurs in up to 2% of solid organ transplant recipients and up to 10% of patients receiving hematopoietic stem cell transplants [54, 55]. Most cases of PRES occur within 30 days of transplant as it is during this time that derangements in drug levels, blood pressure, and other metabolic changes are most common [54–56]. However, late cases have been reported in renal transplant patients with malignant hypertension. Liver transplant patients are also at high risk of PRES due to blood–brain barrier disruption from hepatic encephalopathy [57]. Seizures occur in the majority of patients with PRES [54–56, 58]. One recent study demonstrated that up to half of seizures in heart transplants were attributable to PRES [59]. Seizures in the setting of PRES are typically generalized tonic-clonic seizures or less commonly, status epilepticus. EEG may show slowing, reflective of the encephalopathy, and periodic discharges, most frequently affecting the bioccipital regions. It is thought that a substantial proportion of CNI induced seizures are due to PRES [54, 55]. The diagnosis of PRES is generally made by a combination of both clinical and radiologic findings. Imaging is primarily useful to exclude alternative etiologies, but also often confirms the diagnosis. CT may show vasogenic primarily subcortical edema which is typically bilateral and asymmetric. MRI, particularly FLAIR/T2 sequences, is more sensitive for the demonstration of vasogenic edema (Fig. 15.1) and may also show areas of associated restricted diffusion. Associated intracranial hemorrhage is not incompatible with a diagnosis of PRES and is in fact present in 10–25% of cases. Kidney transplant patients tend to develop PRES later (>1 year) when compared with liver transplant patients [60]. Treatment of PRES is focused primarily on reversal of the underlying cause, whether that is CNI neurotoxicity, acute on chronic kidney injury, or hypertension [61]. The majority of cases resolve within 2 weeks.

Cerebrovascular Disease

Cerebrovascular diseases including ischemic infarctions and intracranial hemorrhages most commonly occur within the first month post-transplant. Because acute symptomatic seizures may complicate cerebrovascular events, prompt neuroimaging should be performed in all patients with new-onset seizure, especially those having focal neurological signs. Most studies quote a 2–4% incidence of these complications with higher rates in elderly patients and those with pre-transplant diabetes. In cardiac and renal transplant recipients acute ischemic stroke can occur in up to 3–10%, and 8% of patients, respectively [62, 63]. In orthotopic heart transplant patients, 15% (12 of 82 consecutive patients) had seizures, with the most common etiology being postoperative stroke [64]. In kidney transplant patients, acute ischemic stroke tends to occur several years following transplant. Most poststroke seizures are focal and typically easily aborted with intravenous phenytoin, fosphenytoin, and valproic acid. However, status epilepticus can develop in 16–25% of all patients with poststroke seizures [65].

Acute hemorrhage is more common in patients who have undergone bone marrow or liver transplantation. Up to 7% of liver transplant patients suffer from acute cerebrovascular disease, a majority of which are hemorrhagic [66, 67]. There is often a concomitant coagulopathy due to the underlying liver disease. Hemorrhage typically occurs in the frontal and parietal lobes and less commonly in the subcortical areas. Intracranial hemorrhage secondary to thrombocytopenia and infarction or hemorrhage secondary to fungal infection can occur in up to 3% of BMT patients [65]. Cerebral venous thrombosis has also been reported in the HSCT population [68–70] and the most common presentation in those cases is seizures. The etiology and pathophysiology of this complication is unknown.

Seizures in Transplant Patients: Treatment

Goals of treatment in the acute setting were discussed previously and the management of status epilepticus is discussed in a separate chapter. Many of the etiologies discussed above are reversible upon cessation of the offending process (i.e., infection, hypertension, PRES, mass effect, etc.), and therefore do not require long-term AED therapy. However, there are some cases where long-term seizure control with AEDs is required. In patients who have recurrent seizures or a patient with a single seizure and a structural epileptogenic focus identified by neuroimaging, pharmacologic therapy should be initiated. Some patients can have their AEDs discontinued after 3 months without risk of recurrence, such as those with seizures in the setting of PRES. Patients with uncontrollable metabolic imbalances or structural CNS lesions may require even longer term AED therapy [5].

The primary considerations in selecting AEDs are efficacy and safety, in particular minimizing drug–drug interactions and effects on other organ systems. The pharmacokinetics and pharmacodynamics of AEDs and their effect on immunosuppressant agent metabolism need to be carefully considered. The ideal AEDs are those with minimal protein binding and minimal effects on induction or inhibition of drug metabolism pathways, especially among patients with liver transplants. For patients with renal transplants, AED agents may require dose adjustments due to variability in excretion. A number of AEDs have a more favorable profile in transplant patients with seizures and provide broad coverage in that they can treat both partial and generalized seizures.

Phenytoin and fosphenytoin are generally considered first line agents in the setting of recurrent seizures or status epilepticus. The benefit of these agents is that they are efficacious and can be loaded intravenously. Close blood pressure monitoring should be performed during administration of an IV load of these medications as they can cause hypotension. Also, it is important to consider that these agents can induce CNI metabolism which leads to lower doses of CNI and more vigilant titration of the agent is required to maintain therapeutic levels. Some transplant recipients may have hypoalbuminemia, and under those circumstances lower doses should be used as protein binding would be reduced. We advise that phenytoin levels be monitored by checking both free and total levels, as many of these patients have hypoalbuminemia and the total phenytoin level may not reflect the amount of free active drug.

Phenobarbital may be a good option in HSCT patients as it is one of a few AEDs that does not cause bone marrow suppression. Patients should be closely monitored during administration of a loading dose as it can be complicated by hypotension and respiratory depression. This agent can also interact with CNIs by inducing the CYP450 enzymes.

Valproate, which does not induce CYP450, was historically used to treat seizures in renal transplant patients, but is now discouraged due to the association with hepatic failure [5, 71]. This medication is also highly protein bound and lower doses should be considered in patients with reduced binding proteins. There have also been reports of valproic acid causing a coagulopathy by platelet dysfunction akin to von Willebrand disease and the drug should be avoided altogether in liver transplant recipients [72].

Levetiracetam has been gaining popularity for post-transplant seizures due to its broad spectrum efficacy and the fact that it is not extensively protein bound, or metabolized through the liver and lacks drug–drug interactions [71]. There is very sparse data on the efficacy of this medication in transplant recipients [73]. Levetiracetam can be taken orally or intravenously in patients of all ages and, when loaded, reaches therapeutic levels hours after the first dose. It does not affect CNI metabolism. Patients with impaired renal function may require a dosage decrease as it is primarily excreted through the urine [5]. It is also important to note that this medication is dialyzable and supplemental doses should be given after dialysis.

Lacosamide is another emerging option. It has been approved for refractory focal seizures and is available in both IV and oral formulations [74]. It has no known drug–drug interactions. It is primarily excreted in the urine and therefore must be renally dosed. Caution is advised in patients with severe cardiac disease or conduction defects and HSCT as it can cause PR prolongation, AV block, irregular atrial rhythms, and bone marrow suppression. Lacosamide has not been studied in the transplant patient population for monotherapy and its high cost may be preclusive in some patients (5).

If oral formulations are feasible, gabapentin and pregabalin may be considered. Similar to lacosamide these are approved for focal seizures and efficacy of monotherapy has not been established. The side effect profile is generally benign and does not cause any myelosuppression. They also require renal dosing as they are primarily excreted through urine. These agents do not have any known drug–drug interactions, are not heavily protein bound, and do not induce CYP450 enzymes.

Carbamazepine (CBZ) is generally not recommended as initial therapy. It can be used to treat focal seizures. It is heavily protein bound, and strongly induces CYP450 enzymes thereby lowering CNI levels. Close monitoring of CBZ levels should be considered in the first two weeks of administration as this agent has been known to undergo auto induction. Both 10,11 epoxide metabolite and CBZ levels should be performed in patients with liver failure if there is suspicion for medication toxicity as these patients can develop CBZ toxicity secondary to accumulation of the active metabolite despite normal CBZ levels. One of its notable side effects is hyponatremia secondary to SIADH which may be especially problematic in transplant recipients who are already pre-disposed to electrolyte disturbances. Oxcarbazepine is a structural derivative of carbamazepine and has similar indications as CBZ. It is a milder CYP450 inducer but has a higher risk of producing hyponatremia as compared with CBZ.

Topiramate, lamotrigine, and zonisamide may be considered in generalized and focal seizures. They all have hepatic metabolism. Topiramate has dose dependent liver enzyme inducing properties at doses above 200 mg. These agents should be used with caution given the potential for drug–drug interactions.

Seizures in Transplant Patients: Significance for Outcome

Although some studies suggest that seizures are associated with worse outcomes in HSCT and cardiac transplant recipients [3, 75, 76] one should consider that prognosis is dependent on a number of factors. Seizure duration, etiology, and failure to respond to the initial AED are each important factors impacting prognosis. A general principle is that patients with seizures resulting from CNS infection, cerebrovascular insults, or CNS malignancy will have worse outcomes than those with seizures resulting from drug toxicity or metabolic disturbances. This was demonstrated in previous studies on HSCT and liver recipients [77, 78]. Post-transplant seizures should be considered in context and rarely should influence decision about goals of care unless they are truly treatment refractory as can be the case with delayed onset idiopathic hyperammonemia.

References

1. Adams Jr HP et al. Stroke in renal transplant recipients. Arch Neurol. 1986;43(2):113–5.
2. Bhatt VR et al. Central nervous system complications and outcomes after allogeneic hematopoietic stem cell transplantation. Clin Lymphoma, Myeloma Leuk. 2015;15(10):606–11.
3. Zhang XH et al. Epileptic seizures in patients following allogeneic hematopoietic stem cell transplantation: a retrospective analysis of incidence, risk factors, and survival rates. Clin Transplant. 2013; 27(1):80–9.
4. Lowenstein DH, Alldredge BK. Status epilepticus. N Engl J Med. 1998;338(14):970–6.
5. Shepard PW, St Louis EK. Seizure treatment in transplant patients. Curr Treat Options Neurol. 2012;14(4):332–47.
6. Moini M, Schilsky ML, Tichy EM. Review on immunosuppression in liver transplantation. World J Hepatol. 2015;7(10):1355–68.
7. Zivkovic SA. Neurologic complications after liver transplantation. World J Hepatol. 2013;5(8):409–16.
8. Pless M, Zivkovic SA. Neurologic complications of transplantation. The Neurologist. 2002;8(2):107–20.
9. Dhar R, Human T. Central nervous system complications after transplantation. Neurol Clin. 2011;29(4):943–72.
10. Butterworth RF. Pathogenesis of hepatic encephalopathy and brain edema in acute liver failure. J Clin Exp Hepatol. 2015;5(Suppl 1):S96–S103.
11. Zivkovic SA, Abdel-Hamid H. Neurologic manifestations of transplant complications. Neurol Clin. 2010;28(1):235–51.
12. van Gelder T, van Schaik RH, Hesselink DA. Pharmacogenetics and immunosuppressive drugs in solid organ transplantation. Nat Rev Nephrol. 2014;10(12):725–31.
13. Wijdicks EF et al. FK506-induced neurotoxicity in liver transplantation. Ann Neurol. 1994;35(4):498–501.
14. Kelly PA, Burckart GJ, Venkataramanan R. Tacrolimus: a new immunosuppressive agent. Am J Health-System Pharm: AJHP: Off J Am Soc of Health-System Pharmacists. 1995;52(14):1521–35.
15. Moskowitz A et al. Posterior reversible encephalopathy syndrome due to sirolimus. Bone Marrow Transplant. 2007;39(10):653–4.
16. Qin W et al. Rapamycin-induced posterior reversible encephalopathy in a kidney transplantation patient. Int Urol Nephrol. 2011;43(3):913–6.
17. Small SL et al. Immunosuppression-induced leukoencephalopathy from tacrolimus (FK506). Ann Neurol. 1996;40(4):575–80.
18. Wijdicks EF, Wiesner RH, Krom RA. Neurotoxicity in liver transplant recipients with cyclosporine immunosuppression. Neurology. 1995;45(11):1962–4.
19. Jimenez-Perez M et al. Efficacy and safety of monotherapy with mycophenolate mofetil in liver transplantation. Transplant Proc. 2006;38(8):2480–1.
20. Martin MA et al. Nosocomial aseptic meningitis associated with administration of OKT3. JAMA. 1988;259(13):2002–5.
21. De La Camara R et al. High dose busulfan and seizures. Bone Marrow Transplant. 1991;7(5):363–4.
22. Murphy CP, Harden EA, Thompson JM. Generalized seizures secondary to high-dose busulfan therapy. Ann Pharmacother. 1992;26(1):30–1.
23. Snider S, Bashir R, Bierman P. Neurologic complications after high-dose chemotherapy and autologous bone marrow transplantation for Hodgkin's disease. Neurology. 1994;44(4):681–4.
24. Ferrucci PF et al. Evaluation of acute toxicities associated with autologous peripheral blood progenitor cell reinfusion in patients undergoing high-dose chemotherapy. Bone Marrow Transplant. 2000;25(2):173–7.
25. Melvin JJ, Huntley Hardison H. Immunomodulatory treatments in epilepsy. Semin Pediatr Neurol. 2014;21(3):232–7.
26. Vaughn BV et al. Seizures in lung transplant recipients. Epilepsia. 1996;37(12):1175–9.
27. Turhal NS. Cyclosporin A and imipenem associated seizure activity in allogeneic bone marrow transplantation patients. J Chemother. 1999;11(5):410–3.
28. Kushner JM, Peckman HJ, Snyder CR. Seizures associated with fluoroquinolones. Ann Pharmacother. 2001;35(10):1194–8.
29. Lee SH et al. Prospective, randomized study of ropivacaine wound infusion versus intrathecal morphine with intravenous fentanyl for analgesia in living donors for liver transplantation. Liver Transplant: Off Publ Am Assoc Study Liver Dis Int Liver Transplant Soc. 2013;19(9):1036–45.

30. Eker HE et al. Meperidine induced seizure in a patient with lyme borreliosis. J Clin Med Res. 2009;1(5):302–4.
31. Hocker S, Rabinstein AA, Wijdicks EF. Pearls & oy-sters: status epilepticus from hyperammonemia after lung transplant. Neurology. 2011;77(10):e54–6.
32. Drake K, Nehus E, Goebel J. Hyponatremia, hypo-osmolality, and seizures in children early post-kidney transplant. Pediatr Transplant. 2015;19(7):698–703.
33. Montas SM et al. More is not always better: a case postrenal transplant large volume diuresis, hyponatremia, and postoperative seizure. Transplant Int: Off J Eur Soc Organ Transplant. 2006;19(1):85–6.
34. Goldstein AB et al. Cystic fibrosis patients with and without central nervous system complications following lung transplantation. Pediatr Pulmonol. 2000;30(3):203–6.
35. Pinero F et al. Neurological events after liver transplantation: a single-center experience. Transplant Int: Off J Eur Soc Organ Transplant. 2014;27(12):1244–52.
36. Wszolek ZK et al. Pontine and extrapontine myelinolysis following liver transplantation. Relationship to serum sodium. Transplantation. 1989;48(6):1006–12.
37. Crivellin C et al. Risk factors for central pontine and extrapontine myelinolysis after liver transplantation: a single-center study. Transplantation. 2015;99(6):1257–64.
38. Philibert D et al. Incidence and severity of early electrolyte abnormalities following autologous haematopoietic stem cell transplantation. Nephrol Dial Transplant: Off Publ Eur Dial Transplant Assoc - Eur Renal Assoc. 2008;23(1):359–63.
39. Beier UH et al. Electrolyte imbalances in pediatric living related small bowel transplantation. Transplantation. 2008;85(2):217–23.
40. Al-Rasheed AK et al. Cyclosporine A neurotoxicity in a patient with idiopathic renal magnesium wasting. Pediatr Neurol. 2000;23(4):353–6.
41. Lee CH, Kim GH. Electrolyte and acid-base disturbances induced by clacineurin inhibitors. Electrolyte & Blood Pressure: E & BP. 2007;5(2):126–30.
42. Wijdicks EF. Neurotoxicity of immunosuppressive drugs. Liver Transplant: Off Publ Am Assoc Study Liver Dis Int Liver Transplant Soc. 2001;7(11):937–42.
43. Nobata H et al. Hypocalcemia immediately after renal transplantation. Clin Transplant. 2013;27(6):E644–8.
44. Gera DN et al. Posterior reversible encephalopathy syndrome in children with kidney disease. Indian J Nephrol. 2014;24(1):28–34.
45. Uygun V et al. Idiopathic hyperammonemia after hematopoietic stem cell transplantation: a case report. Pediatr Transplant. 2015;19(4):E104–5.
46. Matoori S, Leroux JC. Recent advances in the treatment of hyperammonemia. Adv Drug Delivery Rev. 2015;90:55–68.
47. Wright AJ, Fishman JA. Central nervous system syndromes in solid organ transplant recipients. Clin Infect Dis: Off Publ Infect Dis Soc Am. 2014;59(7):1001–11.
48. Chapman SW, Wilson JP. Nocardiosis in transplant recipients. Semin Respir infect. 1990;5(1):74–9.
49. Clark NM, Reid GE. Nocardia infections in solid organ transplantation. Am J Transplant: Off J Am Soc Transplant Am Soc Transplant Surg. 2013;13(Suppl 4):83–92.
50. Torre-Cisneros J et al. CNS aspergillosis in organ transplantation: a clinicopathological study. J Neurol Neurosurg Psychiatry. 1993;56(2):188–93.
51. Cohen BA, Stosor V. Opportunistic infections of the central nervous system in the transplant patient. Curr Neurol Neurosci Rep. 2013;13(9):376.
52. Al-Mansour Z, Nelson BP, Evens AM. Post-transplant lymphoproliferative disease (PTLD): risk factors, diagnosis, and current treatment strategies. Curr Hematol Malig Rep. 2013;8(3):173–83.
53. Korfel A, Schlegel U. Diagnosis and treatment of primary CNS lymphoma. Nat Rev Neurol. 2013;9(6):317–27.
54. Masetti R et al. PRES in children undergoing hematopoietic stem cell or solid organ transplantation. Pediatrics. 2015;135(5):890–901.
55. Potluri K, Holt D, Hou S. Neurologic complications in renal transplantation. Handb Clin Neurol. 2014;121:1245–55.
56. Heroux A, Pamboukian SV. Neurologic aspects of heart transplantation. Handb Clin Neurol. 2014;121:1229–36.
57. Chavarria L, Cordoba J. Encephalopathy and liver transplantation. Metab Brain Dis. 2013;28(2):285–92.
58. Cruz Jr RJ et al. Posterior reversible encephalopathy syndrome in liver transplant patients: clinical presentation, risk factors and initial management. Am J Transplant Off J Am Transplant Am Soc Transplant Surg. 2012;12(8):2228–36.
59. Navarro V et al. Incidence and risk factors for seizures after heart transplantation. J Neurol. 2010;257(4):563–8.
60. Bartynski WS et al. Posterior reversible encephalopathy syndrome after solid organ transplantation. AJNR Am J Neuroradiol. 2008;29(5):924–30.
61. Fugate JE, Rabinstein AA. Posterior reversible encephalopathy syndrome: clinical and radiological manifestations, pathophysiology, and outstanding questions. The Lancet Neurol. 2015;14(9):914–25.
62. Kim JM et al. Central nervous system complications after liver transplantation. J Clin Neurosci: Off J Neurosurg Soc Australas. 2015;22(8):1355–9.
63. Mour G, Wu C. Neurologic complications after kidney transplantation. Semin Nephrol. 2015;35(4):323–34.
64. Grigg MM et al. The etiology of seizures after cardiac transplantation. Transplant Proc. 1988;20(3 Suppl 3):937–44.
65. Coplin WM et al. Stroke after bone marrow transplantation: frequency, aetiology and outcome. Brain J Neurol. 2001;124(Pt 5):1043–51.
66. Wijdicks EF et al. Intracerebral hemorrhage in liver transplant recipients. Mayo Clin Proc. 1995;70(5):443–6.
67. Guarino M et al. EFNS guidelines on management of neurological problems in liver transplantation. Eur J Neurol: Off J Eur Fed Neurolog Soc. 2006;13(1):2–9.
68. Harvey CJ et al. MR angiographic diagnosis of cerebral venous sinus thrombosis following allogeneic bone marrow transplantation. Bone Marrow Transplant. 2000;25(7):791–5.
69. Motohashi K et al. Cerebral venous sinus thrombosis after allogeneic stem cell transplantation. Int J Hematol. 2010;91(1):154–6.
70. Bertz H et al. Sinus venous thrombosis: an unusual cause for neurologic symptoms after bone marrow transplantation under immunosuppression. Transplantation. 1998;66(2):241–4.
71. Chabolla DR, Wszolek ZK. Pharmacologic management of seizures in organ transplant. Neurology. 2006;67(12 Suppl 4):S34–8.
72. Kreuz W et al. Valproate therapy induces von Willebrand disease type I. Epilepsia. 1992;33(1):178–84.
73. Glass GA et al. Levetiracetam for seizures after liver transplantation. Neurology. 2005;64(6):1084–5.
74. Ben-Menachem E et al. Efficacy and safety of oral lacosamide as adjunctive therapy in adults with partial-onset seizures. Epilepsia. 2007;48(7):1308–17.
75. Cordelli DM et al. Etiology, characteristics and outcome of seizures after pediatric hematopoietic stem cell transplantation. Seizure. 2014;23(2):140–5.
76. van de Beek D et al. Effect of neurologic complications on outcome after heart transplant. Arch Neurol. 2008;65(2):226–31.
77. Wijdicks EF et al. Causes and outcome of seizures in liver transplant recipients. Neurology. 1996;47(6):1523–5.
78. Choi EJ et al. New-onset seizures after liver transplantation: clinical implications and prognosis in survivors. Eur Neurol. 2004;52(4):230–6.

79. Saner FH et al. Severe neurological events following liver transplantation. Arch Med Res. 2007;38(1):75–9.
80. Dhar R, Young GB, Marotta P. Perioperative neurological complications after liver transplantation are best predicted by pretransplant hepatic encephalopathy. Neurocrit care. 2008;8(2):253–8.
81. Bronster DJ et al. Central nervous system complications in liver transplant recipients–incidence, timing, and long-term follow-up. Clin Transplant. 2000;14(1):1–7.
82. Lewis MB, Howdle PD. Neurologic complications of liver transplantation in adults. Neurology. 2003;61(9):1174–8.
83. Denier C et al. Spectrum and prognosis of neurologic complications after hematopoietic transplantation. Neurology. 2006;67(11):1990–7.
84. Siegal D et al. Central nervous system complications after allogeneic hematopoietic stem cell transplantation: incidence, manifestations, and clinical significance. Biol Blood Marrow Transplant J Am Soc Blood Marrow Transplant. 2007;13(11):1369–79.
85. Sostak P et al. Prospective evaluation of neurological complications after allogeneic bone marrow transplantation. Neurology. 2003;60(5):842–8.
86. Munoz P et al. Infectious and non-infectious neurologic complications in heart transplant recipients. Medicine. 2010;89(3):166–75.
87. Mayer TO et al. Contrasting the neurologic complications of cardiac transplantation in adults and children. J Child Neurol. 2002;17(3):195–9.
88. Zierer A et al. Significance of neurologic complications in the modern era of cardiac transplantation. Ann Thorac Surg. 2007;83(5):1684–90.
89. Yardimci N et al. Neurologic complications after renal transplant. Exp Clin Transplant: Off J Middle East Soc Organ Transplant. 2008;6(3):224–8.
90. Mateen FJ et al. Neurological complications following adult lung transplantation. Am J Transplant. 2010;10(4):908–14.
91. Goldstein LS et al. Central nervous system complications after lung transplantation. J Heart Lung Transplant Off Publ Int Soc Heart Transplant. 1998;17(2):185–91.
92. Kiok MC. Neurologic complications of pancreas transplants. Neurol Clin. 1988;6(2):367–76.
93. Zivkovic SA et al. The clinical spectrum of neurologic disorders after intestinal and multivisceral transplantation. Clin Transplant. 2010;24(2):164–8.