An approach to neurological disorders in a kidney transplant recipient

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Abstract

Kidney transplantation is the preferred modality of choice for treatment in patients with end-stage kidney disease. However, there are associated complications that arise from immunosuppressive medications, infections, and associated co-morbidities. Neurological disorders frequently develop in kidney transplant patients, in turn, increasing the associated morbidity and mortality. This review discusses the common neurological disorders following kidney transplantation, including infections, cognitive decline, drug-related, malignancy, seizure, and other neurological complications.

Introduction

Kidney transplantation is the desired modality of treatment in patients of end-stage kidney disease (ESRD). It offers better survival and quality of life as compared to hemodialysis and peritoneal dialysis. Despite these advantages, transplant recipients are susceptible to complications that impede the quality of life and add to the financial burden. Neurological diseases frequently develop in kidney transplant recipients and increase morbidity. Neurological diseases after kidney transplantation are frequently underdiagnosed and have been reported in up to 30% to 60% of patients. (1) Noteworthy, in a systematic review and meta-analysis by Mohammadi et al., the total prevalence of neurological disorders in 4674 patients following kidney transplantation was 7.9% (2)

This review attempts to classify the neurologic complications in kidney transplant recipients (KTR) under the following categories: (a) pre-existing neurological conditions (b) early neurological complications (c) subacute and d) late neurological complications and highlights various neurological complications related to infections, medications, malignancies and other comorbid conditions.

Pre-existing neurological disease

Neurological disease in renal failure may not be unveiled until transplantation. Associated co-morbidities like vascular calcification, malnutrition, chronic inflammation, cerebrovascular accidents, diabetes mellitus, hypertension, and other underlying diseases such as systemic
lupus erythematosus predispose these patients to neurological syndromes. Ischemic stroke is responsible for both acute neurological deficits or subclinical, gradually worsening cognitive impairments. Diabetes mellitus affects peripheral nerves resulting in painful sensory neuropathy. Systemic lupus erythematosus has a wide spectrum of neurological manifestations, for example, headache, seizures, chorea, with cognitive dysfunction, myelopathy, meningitis, and mononeuropathy. (3) Patients with infections like HIV can experience dementia, neuropathies, and vacuolar myelopathy. (4) Longstanding uremia causes axonal, symmetrical, sensorimotor, length-dependent, polyneuropathy that does not entirely resolve even after the improvement of renal function. Autonomic dysfunction is another complication of uremia, which causes orthostatic hypotension, impotence, heart rate variability, exercise intolerance, and gastrointestinal intolerance. (5) Factors like age, diabetes mellitus, inflammation, stroke, oxidative stress, and decreased cerebral perfusion, leading to cerebral ischemia during hemodialysis, make ESRD patients more vulnerable to cognitive impairment and dementia as compared to the general population. (6)

Neurological illnesses may manifest at any time post-transplantation. Immediate neurological complications occurring post-renal transplantation surgery are associated with several diagnostic possibilities. They can affect both the central nervous system (CNS) and the peripheral nervous system (PNS).

**CNS Dysfunction:** Following transplant surgery, KTR may exhibit mild symptoms like behavioral changes and confusion due to perioperative sedation, but they may be as severe as encephalopathy or coma resulting from hypoxic-ischemic insult. The patients requiring intensive care unit (ICU) may develop psychosis within 2–5 days after surgery. Neuroimaging with computed tomography (C.T.) scan or magnetic resonance imaging (MRI) scan aid in diagnosis. (7) Psychosis usually resolves with environmental reorientation; rarely neuroleptics are required.

**Electrolyte Imbalance:** Abnormalities in electrolytes and acid-base is a regular finding after renal transplantation. The most frequent post-transplant metabolic disturbances are dysnatremia, hyperkalemia, hypomagnesemia, hypophosphatemia, and metabolic acidosis. Serum sodium of less than 120 mEq/L may lead to confusion, disorientation, or generalized tonic-clonic seizures. Severe hypomagnesemia may also manifest as confusion, muscle
weakness, tremor, tetany, and seizures. (8) The correction of existing electrolyte imbalance improves attributable neurological symptoms. Sodium correction should be done meticulously as a rapid correction (> 10 mEq/L over 24 hours) may lead to central pontine myelinolysis.

**Hypertensive encephalopathy:** Hypertensive encephalopathy in the immediate post-transplant period is caused by uncontrolled high blood pressure. It may result from drugs (steroids/ calcineurin inhibitor), allograft rejection, renal artery stenosis, or volume overload. (9) Hypertensive encephalopathy is often associated with posterior reversible encephalopathy syndrome (PRES). It has characteristic findings on MRI, which includes vasogenic edema in bilateral deep cortical and subcortical regions of the parietal and occipital lobes. Other risk factors contributing to PRES are young age, high doses of corticosteroids, calcineurin inhibitors (CNI), and longstanding uremia before transplant. PRES usually presents with convulsion, headache, visual defects, and altered mental state. Management involves the removal of offending drugs and anti-hypertensive medication for blood pressure control. (10)

**Peripheral nervous system dysfunction:** During renal transplantation, the incidence of peripheral nerve injuries is seen in up to 5% of patients. (11) The femoral nerve, lateral femoral cutaneous nerve, and the lumbosacral plexus are the commonly affected sites. (12) Damage to the nerve can occur either by compression by a local hematoma formation or stretching of the nerve from prolonged retraction. Rarely, acute femoral neuropathy may develop in 0.1–3% of patients. (13) It may not be noticed until the patient attempts to ambulate and is typically apparent within 24–48 hours post-surgery. Ischemia, due to the “steal phenomenon” during anastomosis of the renal graft artery to the internal iliac artery, is another mechanism of nerve damage as the proximal end-to-end anastomosis diverts blood away from the vasa nervosum. (14) On examination, unilateral weakness on knee extension, absent patellar reflex, and decreased sensation on the anterior medial aspect of the thigh may be found. The patient may also complain of numbness over the lateral aspect of the thigh due to injury of the lateral femoral cutaneous nerve, which is present in 2.4% of patients in one series. (15) Lumbosacral plexopathy can also occur in cases where the internal iliac artery is used for graft revascularization. The patient complains of pain in the buttock, and examination reveals weakness of ankle dorsiflexion or proximal leg weakness. Neuropathies are usually self-limiting and resolve entirely, which can take several months; however, there may be incomplete recovery. (12-13,16)
Seizure

The reported incidence of seizure in KTRs is approximately 17.6%. (17) Seizure in a KTR may be related to numerous etiologies such as electrolyte disorders, withdrawal of antiepileptic drugs, CNI toxicity including PRES, liver dysfunction, cerebrovascular accidents, infections, and brain tumors. Convulsions are commonly reported during the immediate 24 hours post-transplant surgery; they are usually due to changes in plasma osmotic pressure and serum sodium. (18) For identification of etiology imaging with C.T. or MRI head are helpful. The electroencephalogram plays an essential role in excluding non-epileptic seizures (such as myoclonus) and determines the type of seizure. To rule out an infectious cause, CSF analysis should be performed. An approach to a seizure in a KTR is illustrated in figure 1. The mainstay for seizure management in a KTR is to identify and treat the underlying etiology in addition to initiating antiepileptic drug (AED). The selection of an AED for a KTR is complicated by factors like drug interactions, tolerability, metabolism, and excretion. Drugs like barbiturates, phenytoin, and carbamazepine have significant drug interactions with immunosuppressive medications, as they induce hepatic cytochrome P450 enzymes leading to increase in the metabolism of CNIs and steroids (19) Newer AEDs like levetiracetam, lacosamide, gabapentin, and pregabalin have favorable side effect profiles and minimal drug interactions. A brief summary of the pharmacokinetics of important AEDs is shown in table 1.

Subacute neurological complications

Infections

About 5-10 percent of KTRs suffer from CNS related infections at any time post-transplantation, resulting in a mortality rate of 44-77%. (20) Infections account for more than thirty percent of patients manifesting with signs and symptoms of the neurological illness (21). The probability of infection from a pathogen varies with the duration post-transplantation. Infections in the early post-transplantation period (<1 month) are usually nosocomial (acquired pathogens) or donor-derived. Subsequently, after five months, infections due to opportunistic organisms develop. (22) The risk of developing an infection depends on two crucial factors: 1) epidemiologic exposure (from the community or hospital) with the organism; 2) net immunosuppressive state of the patient. Decreased T-cell immunity owing to immunosuppressive medications is primarily responsible for infectious complications.
Treatment of graft rejection, diabetes mellitus, malnutrition, and poor graft functions are other important contributing factors. (23) Clinical presentation of these patients varies from fever, meningismus, headache to the altered sensorium, and seizure. In KTR, the diagnosis of CNS infection may be challenging as they may present with minimal signs and symptoms attributable to immunosuppressive therapy. CNS infections can be categorized as meningitis, encephalitis, and focal brain abscess. Table 2 summarizes common CNS infections experienced in KTR, with methods of diagnosis and treatment strategies. (22-24)

**Progressive Multifocal Leukoencephalopathy (PML)**

PML is a fatal and cataclysmic condition of CNS caused by the John Cunningham virus, a human polyoma family virus. The incidence of PML after kidney transplantation is 0.027%, with a median time of seventeen-month following transplant. (25) Visual deficits, mental deficits (cognitive changes, emotional liability, and memory loss), motor weakness, and seizure are the usual complaints in patients with PML. Still, it can be relentlessly progressive and devastating, causing mortality within months to a year. Its spread to the brain results in cerebral white matter demyelination and oligodendrocytes lysis. MRIs show multifocal, asymmetric lesions in cortical and subcortical areas with a minute or no mass effect or enhancement typically involving parieto-occipital regions. (26) Brain biopsy is the gold standard method for diagnosis, but diagnosis can also be made by CSF analysis for J.C. virus DNA by PCR technique. (27) Patients with PML have a fatal outcome, and currently, there is no effective treatment strategy. However, cytarabine and interferons have been tried in PML with no clear success. (28-29)

**Drug toxicity**

Calcineurin Inhibitors: Tacrolimus (Tac) and Cyclosporine (CsA) form the backbone of immunosuppression in a KTR. They inhibit calcineurin activation and block interleukin-2 production. The overall estimated frequency of neurological adverse effects may vary from 10%-28%. (30) Various published studies have shown that tacrolimus is more frequently and severely associated with neurotoxicity as compared to cyclosporine. (31) The timing of CNS side effects is usually within the first month after initiation, and they are more frequent at higher
doses; however, they can occur even at therapeutic levels (32). The severity of symptoms ranges from mild such as tremor, ataxia, agitation, confusion, and nightmares to severe as encephalopathy, convulsion, and coma. Visual hallucinations and cortical blindness may also seldom occur in a KTR on CNI. (33) (Table 3) CsA and Tac may have deleterious effects on the peripheral nervous system. Both the nerve and the muscle can get affected. Cases of axonal, demyelinating, and multifocal demyelinating neuropathy have been reported to be more severe with tacrolimus. (34)

Mechanisms of neurotoxicity:

- Calcineurin is also expressed in several areas of the brain: cerebral cortex, striatum, substantia nigra, cerebellum, and hippocampus. Both CsA and Tac are highly lipophilic and bound to low-density lipoprotein, so they can cross the blood-brain barrier and damage the white matter. (35)
- CNIs cause an increase in endothelin expression and decrease nitric oxide production. By disrupting endothelin integrity, CsA and Tac gain access to astrocytes and cerebral vascular smooth muscle, invoking vasoconstriction and vasospasm. (36)
- Disruption of the blood-brain barrier and cytotoxic effect on the vascular endothelium results in leakage of fluid into the interstitium, resulting in vasogenic edema.
- CsA and Tac may also cause neurotoxicity by alteration in mitochondrial function and ensuing apoptotic or necrotic cell death from activation of anaerobic glycolysis, proteases, phospholipases, and generation of free radicals. (37)

Predisposing factors for the development of CNI induced neurotoxicities are advanced liver failure, low cholesterol levels, elevated CsA or tac blood levels, hypomagnesemia, and steroids. (33) The use of delayed-release formulations, minimum therapeutic doses, strict monitoring of blood levels, and vigilance to pharmacological interactions may reduce drug-induced neurotoxicity. Some times change CNI to mTOR inhibitors, or belatacept may be required in case of severe and no improvement in symptoms.

- **Posterior Reversible Encephalopathy Syndrome**

The overall estimated incidence of PRES in solid organ transplantation recipients is 0.5%–5% and is more common with the use of tacrolimus. (38) MRI brain findings in PRES have been
already mentioned above. The characteristic subcortical edema is the result of endothelial cell damage promoted by loss of autoregulation in the posterior circulation. The following criteria may help establish the diagnosis of calcineurin inhibitors associated PRES: (1) clinical features (headache, changes in mental status, seizures and visual disturbances) after excluding other possible causes such as infection, metabolic disorders, and structural CNS lesions and (2) characteristic findings C.T. or MRI brain of subcortical white matter lesions. (39) This syndrome is potentially reversible and should be diagnosed as early as possible. It usually responds to cessation or lowering the dose of the drug, additionally controlling hypertension and convulsions.

- **Calcineurin-Induced Pain Syndrome**

Calcineurin-induced pain syndrome is characterized by incapacitating bilateral leg pain sparing the hip areas. The reported incidence in transplant patients is 2% to 14% and usually presents within the first year post-transplantation. (40) The most common affected areas are knee and feet. Symptoms may worsen with physical activity, stress and may improve with resting. Imaging studies show bone marrow edema in affected areas. The exact mechanism is yet to be elucidated, but it is postulated that calcineurin inhibitors affect sensory neural function by regulating two-pore potassium channels, leading to an alteration in neuronal resting membrane potential. The syndrome usually is self-resolving, but according to some anecdotal reports, calcium channel blockers are beneficial. (41)

**Corticosteroids** can cause neuropsychiatric symptoms, such as insomnia, impaired concentration, mood changes, irritability, mania, psychosis, and depression. Symptoms usually begin within days to weeks after treatment initiation. With long term use, the peripheral nervous system can also be involved, and proximal myopathy can occur, which may not completely resolve after cessation of the drug. (42)

**Mycophenolate mofetil** (MMF) is rarely associated with neurotoxicity. Headache is one of the few side effects associated with the use of MMF. (43)

**Mammalian Target of Rapamycin Inhibitors** (mTOR inhibitors) - Neurotoxicity is infrequent with sirolimus and everolimus. Few cases of reflex sympathetic dystrophy and PRES have been reported with sirolimus and everolimus, respectively. (44,45)

**Bortezomib** can cause painful sensory neuropathy. (46)
Neurologic side effects of immunosuppressants used in kidney transplantation (Table 4)

**Chronic neurological complications**

**Cerebrovascular Disease**

Cerebrovascular accidents (CVA), including ischaemic, hemorrhagic stroke, and transient ischemic attacks, are the most common chronic neurological complication in a KTR. U.S. Renal Data System data showed that the incidence of CVA in a KTR is 5% during the first year post-transplant and 9.4% in the second year. (47) A study done on 1600 KTRs revealed that 60.3% of patients died with a functioning graft, and stroke was the second-highest cause of mortality after infections. (48) Cerebral hemorrhages can be catastrophic and fatal. Various factors like long-term use of steroids, hypertension, diabetes mellitus, smoking, old age, poor graft function, obesity, dyslipidemia, and peripheral arterial disease contribute to accelerated atherosclerosis and increased risk of stroke in a KTR. Patients with polycystic kidney disease are at a higher risk of developing a hemorrhagic stroke. (49) In a KTR with ischemic stroke, other possibilities like fungal infections (aspergillosis and mucormycosis) should also be excluded as the hyphae can invade cerebral arteries with distal embolization. Correction of reversible risk factors like treatment of hypertension and dyslipidemia, cessation of smoking and alcohol, controlling diabetes is crucial in improving outcomes. The use of anticoagulation to prevent cardioembolism in patients with atrial fibrillation should be considered as per risk to benefit assessment. (50)

**Cognition**

Improvement in cognitive function following kidney transplantation is variable, as some studies suggested improvement only to some extent, and others have indicated exacerbation of cognitive decline. (51) Impairment in multiple domains like verbal learning, memory, and executive functioning was found to be higher in KTR as compared to the general population. (52) Cognitive impairment adversely impacts daily living. Defective memory and executive function may lead to a breach in adherence to immunosuppressive medications. It also diminishes the quality of life and employment rates while escalating hospital admissions, financial burden, morbidity, and mortality. Metabolic and vascular changes due to prolonged exposure to comorbid medical conditions, developed during the dialysis period, neurotoxicity
from medications such as CNI or steroids, diabetes, higher baseline frailty, malnutrition, are some important factors responsible for cognitive impairment in a KTR. (53) Improved graft function results in amelioration of processing speed, convergent thinking, executive, and attention functioning. (54) Treatment of cognitive impairment involves comprehensive care and is usually supportive. It includes management of chronic comorbid conditions, treatment of other associated factors such as depression, optimal effective immunosuppression strategies. Polypharmacy and the use of psychotropic drugs should be deterred.

**CNS Malignancy**

Various CNS malignancies, including post-transplant lymphoproliferative disorders (PTLD), oligodendrogliomas, astrocytomas, lymphomas, and glioblastomas, have been reported in previously published literature in post-transplantation settings. (55) Of all PTLD cases, CNS is involved in approximately 7–15% of cases. (56) In a study by Snanoudj R et al. done in 25 KTRs, the median duration of diagnosis post-transplant was eighteen months. (57) In contrast to this, an analysis of 34 patients of primary CNS lymphoma by Cavaliere et al. reported a median time of 4.4 years post-transplantation. The most common presenting symptom was a focal neurological deficit. (58) Other symptoms are headache, seizures associated with raised intracranial pressure. Less frequently, visual defects and spinal cord lesions may be present. Two critical factors determining the risk of development of primary CNS lymphoma are (1) immunosuppression load of the patient; and (2) Epstein–Barr virus seropositivity. According to some studies, female sex, high lactate dehydrogenase level, poor performance status, and resistance to initial therapy are predictors of inferior survival. Treatment strategies typically involve reduction or cessation of immunosuppression medications and the use of rituximab. Systemic and intrathecal chemotherapy, radiation, and surgery may be used adjunctively according to the stage of malignancy. (59)

**Conclusion**

Neurological manifestations in a post-kidney transplant recipient is a common and frequent cause of mortality and morbidity. It is rewarding to identify the cause and guide the treatment accordingly. Multiple etiologies need to be considered, and infection is the commonest cause in post-transplant settings. A good physical examination and history help to identify most of these.
Author Contributions

P Meena: Writing - original draft
V Bhargava: Resources; Software; Writing - review and editing
D Rana: Resources; Supervision
A Bhalla: Conceptualization; Formal analysis
A Gupta: Supervision; Validation

Disclosure

All authors have nothing to disclose.

References


Legends

Table 1. Summary Of The Pharmacokinetics Of Antiepileptic Drugs.

Table 2. Common Cns Infections Post Renal Transplantation.

Table 3: Neurological Side Effects Of Calcineurin Inhibitors.

Table 4. Neurologic Side Effects Of Immunosuppressants Used In Kidney Transplantation.

Figure 1: An Approach To Seizure In A Renal Allograft Recipient.
Table 1. Summary of the pharmacokinetics of antiepileptic drugs.

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Metabolism</th>
<th>Route of Elimination</th>
<th>Renal toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inducers of cytochrome P450 (CYP) enzymes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>Inducer of CYP3A</td>
<td>Hepatic/renal</td>
<td>Interstitial nephritis; anemia; hypovitaminosis D</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Inducer of CYP3A, metabolized by CYP2C9</td>
<td>Renal -&lt;5%</td>
<td>Acute interstitial nephritis; decrease ADH release</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Inducer of CYP3A</td>
<td>Hepatic</td>
<td>Acute interstitial nephritis; hyponatremia (SIADH)</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Induces CYP34A</td>
<td>Hepatic</td>
<td>Acute interstitial nephritis</td>
</tr>
<tr>
<td>Topiramate</td>
<td>weak inducer of CYP3A4</td>
<td>Renal</td>
<td>Renal tubular acidosis; nephrolithiasis</td>
</tr>
<tr>
<td><strong>Inhibitors of cytochrome P450 (CYP) Enzymes</strong></td>
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<tr>
<td>Valproate</td>
<td>Hepatic(CYP450) metabolism,inhibit CYP2C9</td>
<td>Hepatic</td>
<td>Tubulointerstitial nephritis; Fanconi syndrome.</td>
</tr>
<tr>
<td>Felbamate</td>
<td>Inhibit CYP450</td>
<td>Renal</td>
<td>Rare incidence of renal stone</td>
</tr>
<tr>
<td><strong>No drug interactions</strong></td>
<td></td>
<td></td>
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<tr>
<td>Gabapentin</td>
<td>None</td>
<td>Renal</td>
<td>-</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>None</td>
<td>Renal</td>
<td>Hypokalemia; hypomagnesemia</td>
</tr>
</tbody>
</table>
Table 2. Common CNS Infections Post Renal Transplantation

<table>
<thead>
<tr>
<th>Disease</th>
<th>Organism</th>
<th>Diagnosis</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meningitis</td>
<td>Bacterial</td>
<td>Listeria monocytogenes, Haemophilus influenza, Neisseria meningitides, and Streptococcus pneumonia.</td>
<td>Cerebrospinal fluid (CSF) pleocytosis, increased protein, and reduced glucose.</td>
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<td></td>
<td></td>
<td></td>
<td>Gram stain positive.</td>
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<td></td>
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<td></td>
<td>Rapid antigen latex agglutination test.</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>PCR for Neisseria meningitides and Streptococcus pneumoniae.</td>
</tr>
<tr>
<td></td>
<td>Fungal</td>
<td>Mycobacterium tuberculosis</td>
<td>CSF- Acid-fast bacilli +</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Raised adenosine deaminase</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Raises total leucocyte with lymphocyte predominance, low glucose, increased protein.</td>
</tr>
<tr>
<td></td>
<td>Fungal</td>
<td>CSF- lymphocytic or monocytic pleocytosis, elevated protein, and low glucose.</td>
<td>CSF cryptococcal antigen, India ink.</td>
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<tr>
<td></td>
<td></td>
<td>Cryptococcus neoformans</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Galactomannan assay.</td>
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<td></td>
<td></td>
<td></td>
<td>(1,3)-beta-D-glucan assay.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>DNA PCR assay in serum or BAL samples.</td>
</tr>
<tr>
<td><strong>Candida spp</strong></td>
<td>Branching, septated hyphae</td>
<td>Fluconazole, Echinocandin or Amphotericin B</td>
<td></td>
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<tr>
<td><strong>Cytomegalovirus</strong></td>
<td>Pseudohyphae and budding yeast</td>
<td>Ganciclovir</td>
<td></td>
</tr>
<tr>
<td><strong>Varicella-zoster virus</strong></td>
<td>CSF PCR positive, MRI-Enhancing ventriculoencephalitis</td>
<td>Ganciclovir</td>
<td></td>
</tr>
<tr>
<td><strong>Human herpes virus-6</strong></td>
<td>MRI- Mixed lesion (ischemic or hemorrhagic infarcts), Demyelinating lesions at grey-white matter junction, CSF PCR positive</td>
<td>Ganciclovir or Foscarnet</td>
<td></td>
</tr>
<tr>
<td><strong>Toxoplasma Gondii</strong></td>
<td>MRI- Multiple ring-enhancing lesions, predilection to basal ganglia, thalami, and corticomedullary junction</td>
<td>Pyrimethamine and folinic acid</td>
<td></td>
</tr>
</tbody>
</table>

**Encephalitis:**
- Headache, seizures, focal neurological deficit, altered mental status, cranial nerve palsy
- Cytomegalovirus:
  - CSF PCR positive
  - MRI-Enhancing ventriculoencephalitis
- Varicella-zoster virus:
  - MRI- Mixed lesion (ischemic or hemorrhagic infarcts)
  - Demyelinating lesions at grey-white matter junction
  - CSF PCR positive
- Human herpes virus-6:
  - CSF PCR positive
  - Focal or diffuse encephalitis
- Toxoplasma Gondii:
  - MRI- Multiple ring-enhancing lesions, predilection to basal ganglia, thalami, and corticomedullary junction
| Headaches, seizures, and focal neurological deficits |
|---|---|---|
| **Bacterial** | *Nocardia asteroides* | · Gram-positive, weakly acid-fast, branching rod-shaped bacteria  
· MRI- Single or multiple lesions with contrast enhancement and little mass effect |
| **Fungal** | Mucormycosis, Aspergillosis, Candida Cryptococcosis, | Begin with paranasal sinuses, producing periorbital edema and may invade the intracavernous carotid artery, Cerebral artery emboli, mycotic aneurysm and stroke |

| Trimethoprim/sulfonmethoxazole and neurosurgical intervention |
|---|---|---|
| Antifungals |

**Table 3: Neurological Side Effects Of Calcineurin Inhibitors**

<table>
<thead>
<tr>
<th>Severity</th>
<th>Central toxicity</th>
<th>Peripheral toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Minor</strong></td>
<td>Insomnia, visual disturbances, headache, and mood changes</td>
<td>Paresthesias, peripheral neuropathy, and myopathy.</td>
</tr>
<tr>
<td><strong>Major</strong></td>
<td>PRES, akinetic mutism, toxic encephalopathy, and convulsions</td>
<td>Axonal and demyelinating neuropathy, Guillain–Barré syndrome.</td>
</tr>
</tbody>
</table>
## Table 4. Neurologic Side Effects Of Immunosuppressants used in Kidney Transplantation

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Calcineurin inhibitors</strong></td>
<td><em>Mild:</em> Tremor, headache, insomnia, vivid dream imagery, photophobia</td>
</tr>
<tr>
<td></td>
<td><em>Moderate:</em> visual and cortical disturbances</td>
</tr>
<tr>
<td></td>
<td><em>Severe:</em> Encephalopathy, convulsion, coma, and flaccid quadriplegia</td>
</tr>
<tr>
<td><strong>Steroids</strong></td>
<td>Insomnia, anxiety, psychosis, myopathy, mania, depression</td>
</tr>
<tr>
<td><strong>Bortezomib</strong></td>
<td>Distal peripheral neuropathy</td>
</tr>
<tr>
<td><strong>Mammalian target of rapamycin inhibitor</strong></td>
<td>Sympathetic dystrophy, rarely PRES and possible potentiation of calcineurin-inhibitor toxicity</td>
</tr>
<tr>
<td><strong>Belatacept</strong></td>
<td>Central neurological system</td>
</tr>
<tr>
<td></td>
<td>Post-transplant lymphoproliferative disorder</td>
</tr>
<tr>
<td><strong>Alemtuzumab</strong></td>
<td>Sensorimotor polyneuropathy and myelitis</td>
</tr>
<tr>
<td><strong>Rituximab</strong></td>
<td>Progressive multifocal leukoencephalopathy</td>
</tr>
</tbody>
</table>
Figure 1: An Approach To Seizure In A Renal Allograft Recipient.

- Seizure
  - Electrolyte disorder
  - Blood glucose levels
  - Head imaging
  - CSF analysis
  - EEG
  - Reversible cause identified: Treatment of etiology
  - Cause: uncertain: Levetriacetam, Lacosamide, Gabapentin