Review Article

Neurologic complications of kidney transplantation

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Abstract: Renal transplant is the most common organ transplant in the United States, and the frequency of kidney transplants continues to rise as transplant offers improved survival and quality of life compared to dialysis. However, complications are not uncommon and patients frequently encounter issues requiring hospitalization, especially in the first year postoperatively. Complications that arise are typically related to surgical complications, immunosuppressive medications, or infection due to immunosuppression. Neurological complications are fairly common post-operatively, and are associated with increased morbidity and mortality in this population. This review discusses the most common etiologies of neurological complications after kidney transplant, including infection, malignancy, medication related, acute neuropathy, and other neurological pathology.

Keywords: Kidney transplantation; nervous system diseases; immunosuppression

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Introduction

Kidney transplantation is the most common solid organ transplant in the United States, with over 17,000 transplants performed annually while over 100,000 patients remain on the waiting list (1). This number has continued to rise over the past years as kidney transplantation offers improved survival and quality of life compared to hemodialysis for the majority of patients with end-stage renal disease, and is ultimately more cost-effective over the course of patients' lives. However, during the first year after transplant, patients frequently encounter complications requiring hospitalization, typically due to immunosuppressive medications or infection due to chronic immunosuppression. Neurological complications are a common issue after kidney transplant, with between 30–60% of patients experiencing some neurological complication (2). Neurological complications are associated with increased morbidity and mortality and should be kept on the differential for all post-transplant patients. This review discusses the most common etiologies of neurological complication after kidney transplant: infection, malignancy, medication, surgical complications, seizure, and stroke.

Infection

CNS infection accounts for a significant percentage of neurological complications after solid organ transplant, including in kidney recipients. Infection is of specific concern in the post-operative patient as immunosuppressive regimens alter both the typical presentation and types of organisms observed. CNS infection (including meningitis, encephalitis, and abscess) has significant morbidity and mortality in renal transplant patients, and symptoms can range from non-specific (such as headache, fever, and altered mental status) to focal neurologic deficits and coma. When attempting to identify a causative organism, the post-surgical timeline is important as there is a correlation between time post-transplant and likely organisms (3). In general, classification of post-operative infections can be divided into the first month after transplant, one to six months after transplant, and beyond 6 months (*Table 1*).

Table 1 Typical organisms after renal transplant by time period (3-6)

Time after transplant	Likely organisms	Typical presentation	Diagnosis	Treatment
First month	*Streptococcus pneumoniae, Neisseria meningitidis, Listeria monocytogenes, Haemophilus influenza*	Nonspecific; ranging from headache, fever, meningismus, altered mental status	CSF with neutrophilic predominance, decreased glucose, elevated protein	Empiric treatment including ceftriaxone, vancomycin, ampicillin, narrowing therapy after culture results
	Aspergillus fumigatus	Nonspecific; seen with comorbid respiratory disease	Antigen or antibody present in CSF, branching hyphae visualized in CSF	Antifungals including voriconazole, amphotericin
	Candida species	Disseminated fungemia with CNS symptoms	Pseudohyphae visualized in CSF, PCR, positive culture	Fluconazole Amphotericin can be considered in severely ill or neutropenic patients
1–6 months	*Mycobacterium tuberculosis*	Non-specific; consider in patients from endemic areas, travel or exposure history, or history of latent infection	CSF Acid Fast Bacteria stain may miss the diagnosis. Interferon-Gamma Release Assay as screen. Decreased glucose, leukocytosis with lymphocytic predominance, increased protein, and increased adenosine deaminase	Multiple drug therapy including isoniazid, rifampin, ethambutol, pyrazinamide
	Cytomegalovirus	Non-specific, but may include symptoms of retinitis, GI manifestations	CSF PCR	Ganciclovir, foscarnet
	Varicella Zoster Virus	Encephalitis, headache, altered mental status, seizure. May or may not have skin manifestations	PCR of CSF, may require multiple samples to rule out as it can initially be negative	Intravenous acyclovir with appropriate hydration. Can consider valacyclovir prophylaxis after infection fully treated to prevent reactivation
6 months and beyond	*Cryptococcus neoformans*	Nonspecific; fever, headache	CSF PCR, antigen, culture	Amphotericin, flucytosine. Will need continued treatment with fluconazole for life even after CSF culture negative. Poor prognosis
	Toxoplasma gondii	Altered mental status, seizure, focal neuro signs	Serum toxoplasma IgG, supportive imaging findings include ring-enhancing lesions	Pyrimethamine with leucovorin Prophylaxis can include Trimethoprim-Sulfamethoxazole or pyrimethamine with leucovorin if cannot tolerate TMP-SMX
	JC virus	AMS, seizure, focal neuro signs	CSF PCR	No treatment. Consider reducing immunosuppression. Poor prognosis

CNS, central nervous system; GI, gastrointestinal; CSF, cerebrospinal fluid; PCR, polymerase chain reaction.

Management of infection in post-transplant patients typical involves initiation of empiric anti-microbial therapy (antibiotics, antivirals or anti-fungal therapy) with narrowing of agents after the causative organism is determined and decreasing or stopping entirely the immunosuppression regimen (4). As many symptoms of CNS infection in this population are nonspecific, determining whether these symptoms are caused by

infection or a non-infectious etiology may be challenging. In general, work-up will include CSF culture and analysis including PCR, blood cultures, and brain imaging.

In the immediate post-operative period, CNS infection is most often caused by typical bacterial organisms although opportunistic infections from environmental organisms and reactivation of latent tuberculosis infection can occur. Typical bacteria causing neurological infection include *Streptococcus pneumoniae*, *Neisseria meningitidis*, *Listeria monocytogenes*, *and Haemophilus influenza* (5). Common presentation of these patients includes headache, fever, malaise, altered mental status, and meningismus. Opportunistic infections including *Mycobacterium tuberculosis*, *Aspergillus fumigatus*, and *Candida* species can also occur. Tuberculosis is rare as a primary infection post-operatively, but immunosuppression can cause reactivation of latent infection. These patients will have similar presentation to typical bacterial meningitis but may have radiographic evidence of lesions and CSF analysis will reveal very low glucose with a lymphocytic pleocytosis (compared to neutrophilic predominance in typical bacterial infection) with positive acid fast staining and culture (6). *Aspergillus fumigatus* is a fungus present in the environment, and infections are associated with pre-existing respiratory disease. CNS infection with *Aspergillus* is associated with multiple lesions on CT or MRI and diagnosis may be made via antigen, serology, or fungal culture. Finally, CNS infection with *Candida* species can be seen in patients with disseminated fungemia due to immunosuppression.

Risk of infection is highest from one to six months after transplantation as immunosuppression becomes maximally effective and dominant organisms shift to more atypical pathogens. These include viruses and the previously discussed opportunistic bacteria and fungi. Cytomegalovirus (CMV) is the most common opportunistic infection in kidney transplant recipients, present in up to 8% of patients. This prevalence has decreased due to improved recognition of donor and recipient seropositivity and prophylactic treatment (7). Risk is highest with donor seropositivity and recipient seronegativity, induction immunosuppression, and older donors (8). Infection may occur as a primary infection, reinfection of latent recipient infection, or most commonly donor-derived. Symptoms are generally nonspecific in CNS infection, but more characteristic systemic features include leukopenia, thrombocytopenia, and evidence of infection of other tissues with CMV such as retinitis, pneumonitis, or GI disease. Finally, CMV infection has been implicated in case reports of post-operative Guillain Barrè syndrome (9-13). Guillain-Barre Syndrome (GBS) is an auto-immune disease affecting the peripheral nervous system. The exact mechanisms of GBS is unknown but is posited to involve humoral and cell-mediated autoimmunity in response to some antigenic trigger, infectious or otherwise. GBS typically presents as an ascending paralysis and sensory loss with areflexia and can progress to respiratory failure as symptoms spread proximally. Treatment includes respiratory support, rehabilitation, and immunotherapy with plasmapheresis and/or intravenous immunoglobulins (14). Primary infection with Epstein Barr Virus (EBV) is a rare complication after renal transplant, but reactivation can occur and EBV is a significant cause of morbidity and mortality due to its association with post-transplant lymphoproliferative disorder (PTLD) discussed later in this review. Other viruses affecting the nervous system that can sometimes be seen in this post-operative period include human herpes virus 6 (HHV6), varicella zoster (VZV), and BK Polyoma Virus.

After 6 months, immunosuppressive regimens tend to decrease in intensity and overall risk of infection decreases. However, infection with rare atypical organisms can still occur with chronic immunosuppression, and organisms such as *Cryptococcus neoformans*, *Toxoplasma gondii*, tuberculosis, and JC virus (causing progressive multifocal leukoencephalopathy) may be seen.

Malignancy

Solid organ transplant recipients have a four-fold increased incidence of malignancy compared to the general population, and this is believed to be due to decreased immune surveillance and an increased susceptibility to oncogenic viruses due to immunosuppression (15). Post-operative primary CNS tumor is uncommon after renal transplant with the exception of PTLD affecting the CNS. While renal transplant is associated with lower rates of PTLD compared to most organ systems, a small percentage (1–2%) of kidney recipients will develop this complication (16). The two largest risk factors for development of PTLD after renal transplant are immunosuppression and Epstein Bar Virus serostatus. Immunosuppression is associated with increases in PTLD after transplant; incidence of PTLD is highest in the first year after transplant, the time of most intense immunosuppression, and rates decline significantly after this. Furthermore, rates of PTLD are significantly higher in solid organ transplants requiring a greater degree of

immunosuppression (such as heart) compared to kidney (17). Finally, induction therapy is associated with increased risk of PTLD (18). While the association between EBV and PTLD is now better understood, the pathogenic mechanism is still largely unknown. There is an increased risk (up to twenty-four fold) of PTLD among EBV-negative recipients of EBV-positive donor organs (19). The majority of PTLD tumors in transplant patients contain the EBV genome, suggesting a pathogenic role for the virus. However, EBV negative PTLD has been documented a minority (30%) of PTLD patients and the EBV genome can also be found in patients with this tumor who are not immunosuppressed (20). It is unclear whether these populations represent distinct disease entities.

Medications

Recipients of kidney transplant require immunosuppressive therapy in order to prevent rejection of the transplanted organ. Immunosuppression can be divided into induction and maintenance therapy with additional potential treatment of acute rejection. Induction therapy is given around the time of transplantation, is generally more potent with greater immunosuppression than maintenance therapy, and is done in order to prevent acute rejection. In contrast, maintenance immunosuppression is typically initiated at the time of transplant but continued long-term for the duration of the graft. Typical agents may include glucocorticoids, calcineurin inhibitors (CNIs), anti-metabolic agents, and mTOR inhibitors. Choice of agents will vary based on patients' individual factors including risk for rejection and balancing potential side effects.

Induction agents

Induction therapy agents work via depletion of T-cells resulting in blunted immune response. Medications used for induction include anti-thymocyte globulins, alemtuzumab (a humanized recombinant monoclonal antibody against CD25), and basiliximab (an IL-2R antagonist). None of these agents have specific neurotoxicities as common adverse effects. Antilymphocyte antibodies (ATG, Atgam, and alemtuzumab) may cause cytokine release syndrome, a systemic inflammatory response caused by initial immune cell activation (21). This is mentioned here as common symptoms (including fever, nausea, vomiting, diarrhea, tachycardia, hypotension, and seizures) are nonspecific and can mimic those of CNS infection after transplant. Basiliximab has not been associated with cytokine release syndrome and is overall well tolerated for kidney transplant induction therapy (22).

Maintenance agents

Corticosteroids

Glucocorticoids are used in both induction and maintenance therapy for their immunosuppression, as well as for the treatment of acute rejection. These drugs function via multiple pathways, with inhibition of various cytokines including Il-1, Il-2, IL-6, TNF-A, and IFN-gamma. The most commonly used glucocorticoids used for renal transplant patients are oral prednisolone, prednisone, and intravenous methylprednisolone. These agents are not ideal for maintenance therapy because of the well characterized side effects of chronic steroid use, including multiple adverse neurological symptoms. Thankfully, most if not all neurological complications of corticosteroids are reversible with reduction or withdrawal of the offending agent. One of the most common neurological side effects of glucocorticoid use is steroid-induced myopathy. Glucocorticoids have a direct catabolic effect on skeletal muscle (23). Patients with steroid myopathy typically present with gradual onset of proximal muscle weakness with atrophy. Lower extremities are usually affected first and more severely than the upper extremities. It is usually not associated with myalgia or tenderness. Symptoms of the condition can begin any time from days to months after therapy begins and its incidence and severity are related to steroid dose (24). The diagnosis is clinical, and muscle enzymes are typically normal (25). The condition is surprisingly common, with previous studies showing approximately 50% of patients on steroids after solid organ transplant developing symptoms (26). Treatment is supportive for pain control of the myalgia and removal of steroid with full resolution taking months after discontinuation. The neuropsychiatric side effects of corticosteroid therapy are well known. Initially, steroid use is associated with elevation in mood, a potential hypomanic state, and disruption of sleep. Symptoms associated with higher doses for longer duration include sleep disruption, restlessness and akathesia, depression (including increased risk of suicidality), cognitive impairment, and most rarely psychosis (27). The majority of these symptoms are reversible with withdrawal of the agent. Risk of neuropsychiatric side effects is increased with dose, duration of therapy, age of patient, and pre-morbid psychiatric disorder (28). Finally, there have been cases of

Idiopathic Intracranial Hypertension associated with long term administration of corticosteroid therapy, but these are rare and reversed with cessation of the agent (29,30).

Calcineurin inhibitors (CNIs)

The most commonly used CNIs for immunosuppression are cyclosporine and tacrolimus. The precise mechanism of CNI neurotoxicity is still unknown. Neurotoxicity associated with cyclosporine and tacrolimus can present in multiple ways ranging from more common mild symptoms to rare, but life-threatening, manifestations. Approximately half of patients will report at least one neurological symptom, with tremor, headache, and fatigue being among the most frequently observed (31). These symptoms are frequently associated with higher drug levels and typically resolve either with time, decrease in dose, or in some cases substitution of cyclosporine with tacrolimus or vice versa (32). Severe neurotoxicity with tacrolimus or cyclosporine is rare in renal transplant, but seizure (33), polyneuropathy (34,35), encephalopathy, visual disturbances, and coma have all been reported (36).

Both tacrolimus and cyclosporine are associated with development of Posterior Reversible Encephalopathy Syndrome (PRES) in renal transplant recipients (37-40). The exact mechanism of PRES is poorly understood but believed to be reversible subcortical brain edema caused by endothelial injury (41). Brain imaging studies reveal vasogenic edema typically (but not exclusively) of the bilateral parietal and occipital regions. Patients present initially with hypertension, headache, altered mental status, and visual disturbances, and may progress to seizures, stupor, and eventually coma. As the name of the condition suggests, most cases are reversible with supportive care including blood pressure control and discontinuation of responsible agents, but delay in diagnosis may lead to permanent deficits and death. Most cases of CNI-associated PRES presented within the first year after transplant, a majority of patients had CNI levels either elevated or high-normal, and a majority had hypertension. However, there have been cases of CNI-associated PRES with normotension, therapeutic levels of CNI, and after years of treatment (42). As such, the entity must remain on the differential for renal transplant patients on a CNI, regardless of the treatment being previously well tolerated.

A distinct pain syndrome has been reported with both tacrolimus and cyclosporine use (43). Termed Calcineurin Inhibitor Induced Pain Syndrome (CIPS), the entity is associated with bilateral, symmetric distal leg pain sparing hip areas and usually involving the feet, ankles, and knees. CIPS will affect some 2–15% of renal transplant patients on CNIs, and usually presents within the first year after kidney transplant (44). The pain is worsened with activity and improved with rest. Labs will show increased alkaline phosphatase and calcium, and imaging studies (MRI) reveal marrow edema in the regions of pain (45). CIPS is usually self-limited but can recur. Interestingly, it is associated with good long term prognosis of the graft. Treatment can be supportive for pain-management, removal of the CNI and replacement with non-CNI immunosuppression (46), or treatment with calcium channel blocking agents (47). There is one case report of rapid improvement in symptoms with one-time infusion of iloprost (48).

Other agents

Bortezomib is a small molecule proteasome inhibitor approved by the FDA for the treatment of multiple myeloma that is now finding increased usage as immunosuppressive therapy for renal transplant patients. Side effects in the renal transplant population are similar to multiple myeloma patients (49). The significant neurological side effect of bortezomib is a distal peripheral neuropathy and it is fairly common, affecting 20–40% of renal patients (50). Symptoms initially begin in a "stocking glove" distribution before spreading more proximally. The neuropathy is typically a painful, sensory polyneuropathy; motor neuropathy is rare (51). While reversible, neuropathy symptoms take a median of three months to resolve and may persist for longer (52). The most significant risk factor for development of neuropathy associated with bortezomib is pre-existing peripheral neuropathy (53). There are no established agents for treatment of bortezomib-induced polyneuropathy, and the mainstay of therapy is discontinuation or dose reduction of the offending agent. Some evidence exists suggesting reduction of incidence with concomitant dexamethasone dosing (54).

Acute neuropathy

While peripheral neuropathy after kidney transplant can present secondary to medications used for immunosuppression and antibiotic prophylaxis, acute neuropathy can also occur as a complication of surgery. Acute femoral neuropathy (AFN) is a relatively uncommon complication, with incidence ranging 2% to 4% (55,56).

The pathophysiology is believed to involve direct compression and ischemia of the nerve, possibly caused by steal phenomenon following anastomosis of the graft renal artery to the iliac artery. Method and duration of arterial anastomosis have both been correlated with increased incidence of neuropathy, with the highest risk occurring in surgeries with internal iliac ligation with external iliac anastomosis and prolonged anastomosis time greater than 40 minutes (57). Presentation of AFN can vary depending on where along the nerve's course the damage occurs. Motor complications are more common, with the majority of patients presenting with weakness of hip flexion and knee extension either immediately after surgery or in the days following. Atrophy of these muscles can occur in severe or prolonged cases. Sensory impairment occurs less frequently and presents as numbness and/or paresthesia of the anterior-medial thigh (58). EMG studies confirm a femoral neuropathy. Overall prognosis of AFN is good, and recovery of neurologic function is the most frequent outcome, but symptoms may last weeks to months. Treatment includes physical therapy and medications for neuropathic pain in cases of painful sensory neuropathy. Prevention can be achieved with careful positioning of retractors, avoiding anastomoses associated with increased risk, and careful surgery to prevent hematoma formation.

Seizure

Causes of seizure after renal transplant include drug toxicity, metabolic disorders (electrolyte disturbances), organ dysfunction, CNS infection, ischemic and hemorrhagic stroke, and PRES. Thankfully, the majority of seizures after renal transplant are isolated events and patients will not go on to develop a seizure disorder (59). Therapy is therefore focused on treating the underlying etiology. There is no role for primary seizure prophylaxis for all post-transplant patients, but patients who do have a seizure should be started on an anti-epileptic regimen. Levetiracetam is the drug of choice for seizure prevention, with lorazepam and fosphenytoin being used for status epilepticus. Levetiracetam is ideal due to its lack of interactions between it and the common immunosuppressive. As it is excreted renally, levetiracetam dosage must be adjusted according to renal function.

Stroke

Cerebrovascular disease is seen frequently in patients who have undergone kidney transplantation, with an incidence of stroke or TIA of 5% in the first year and 9.4% in the second year (60). A large proportion of the incidence can be explained by frequent comorbidities of renal transplant patients; diabetes, age, post-transplant kidney function, and previous stroke are all risk factors for ischemic stroke after transplant while diabetes, PKD, and hypertension are associated with hemorrhagic stroke (61). Renal patients also may develop post-transplant polycythemia and hypercoagulability which increase the risk of stroke. Prevention is aimed at control of risk factors (cholesterol, hyperglycemia, and hypertension) as well as prevention via antiplatelet agents such as aspirin. Control of cholesterol is especially important as some of the immunosuppressive regimens may cause hypercholesterolemia (62). Prophylactic anticoagulation is not a mainstay of therapy for all patients post-transplant.

Conclusions

As immunosuppression has improved, organ transplant has become more common and safer overall. As more patients experience improved survival, the total number of patients at risk for chronic complications increases as well. Neurological symptoms are a significant contributor to morbidity and mortality after kidney transplant. Serious neurological complications result in hospitalization, and therefore physicians must be aware of the conditions unique to this population.

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Footnote

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