Biomedical Research 2017; 28 (9): 3903-3906 *ISSN 0970-938X*
www.biomedres.info

Clinical characteristics of neurological complications after renal transplantation.

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Abstract

Background: To investigate the type and diagnostic criteria for the incidence of neurological complications after renal transplantation.
Material and methods: Clinical data of 1216 patients undergoing renal transplantation in the 309th Hospital of Chinese People's Liberation Army between September 2008 and December 2015 were retrospectively analysed. The pathogenesis, clinical characteristics and treatment of neurological complications following renal transplantation were investigated.
Results: Among 1216 cases, 58 patients presented with postoperative neurological complications, accounting for 4.8%. Specifically, 27 cases (46.6%) were diagnosed with encephalopathy, 12 (20.7%) with cerebrovascular diseases, 5 (8.6%) with epilepsy, 5 with central nervous system infection (8.6%) and 9 (15.5%) with peripheral neuropathy.
Conclusion: The pathogenesis of neurological complications after renal transplantation is complicated. Renal transplantation recipients are likely to present with diverse clinical symptoms, primarily characterized with encephalopathy and cerebrovascular events. Clinical diagnosis and treatment should be implemented as early as possible.

Keywords: Renal transplantation, Neurological complications, Diagnosis, Treatment.

Accepted on January 30, 2017

Introduction

Neurological complications are frequently identified in renal transplant recipients and largely contribute to relatively high morbidity and mortality [1]. Post-transplant neurological complications may be categorized into five areas including immunosuppressive medications, stroke, peripheral neuropathies, infection and malignant tumors. Multiple postoperative complications are directly caused by the neurotoxicity of immunosuppressive agents [2].

Calcineurin-inhibitors may cause slight symptoms, such as tremors and paresthesia, or even severe symptoms including disabling pain syndrome and leukoencephalopathy, etc. [3-5]. Severe neurological syndromes may also be caused by the monoclonal antibody OKT3. Stroke may occur in approximately 8% of renal transplantation recipients. It may be favoured by hypertension, diabetes mellitus, and accelerated atherosclerosis which is probably acquired during dialysis or after transplantation. Peripheral mononeuritis and polyneuritis may equally occur. An acute femoral neuropathy may occur in approximately 2% of patients due to postoperative nerve compression [6]. Guillain-Barr syndrome may also develop, triggered in some cases by cytomegalovirus or *Campylobacter jejuni* infection. Lymphoma is the most frequent type of brain tumor. They are usually associated with an Epstein Barr virus infection and are more frequently seen in patients who received an aggressive immunosuppressive therapy.

Infection represents the most frequent neurological complication. Acute meningitis usually caused by *Listeria monocytogenes*, sub-acute and chronic meningitis caused by *Cryptococcus neoformans*, focal brain infection caused by *Aspergillus fumigatus*, *Toxoplasma gondii* or *Nocardia asteroids*, and progressive dementia caused by polyoma J virus or other viruses are the most frequent types of neurological infections [7-9].

Therefore, clinical data of 1216 patients admitted to the 309th Hospital of Chinese People's Liberation Army between September 2008 and December 2015, who were complicated with neurological complications after renal transplantation were obtained. The incidence, diagnosis and treatment courses were retrospectively analysed.

Materials and Methods

Baseline data

In the 309th Hospital of Chinese People's Liberation Army, clinical data obtained from a total of 1216 patients who underwent allogeneic renal transplantation mainly from a deceased donor between September 2008 and December 2015 were retrospectively analysed for presence of neurologic

complications. All eligible subjects who were in accordance with operation indications were selected strictly according to preoperative discussion and evaluation. None of them reported a medical history of mental diseases. Male and female patients, 18 years of age or older, who had received a kidney transplant were qualified for inclusion in the study. After renal transplantation, 58 recipients, 27 male and 31 female, were diagnosed with evident neurological complications by experienced chief physicians. These patients were aged (38.5 ± 2.1) years on average, ranged from 25.0 to 62.0 years. Besides, 49 cases were found to have glomerulonephritis, 6 with diabetic nephropathy and 3 with interstitial nephritis. All patients were followed up ranging from 5 to 60 months.

Use of immunosuppressive agents after renal transplantation

After renal transplantation, a triple therapy consisting of cyclosporin (CsA)/tacrolimus (FK506) plus Mycophenolate Mofetil (MMF) plus Prednisone (Pred) was delivered. Informed consents were obtained from all participants. The study procedures were approved by the ethics committee of the 309th Hospital of Chinese People's Liberation Army.

Classification criteria of neurological complications

Based upon the clinical manifestations and imaging examinations, neurological complications were primarily categorized into encephalopathy (such as directional force, understanding and memory disorders, mental abnormality, delirium, dysphonia and urine incontinence), cerebrovascular events, epilepsy, central nervous system infection and peripheral neuropathy.

Results

Classification and incidence of neurological complications

We found that 58 (4.8%) cases in a total of 1216 patients presented with significant neurological complications following renal transplantation. Those 58 individuals experienced a total of 78 episodes of neurologic complications. The observed neurologic complications were classified as follows: encephalopathy in 27 cases (46.6%), cerebrovascular events in 12 (20.7%), epilepsy in 5 (8.6%), central nervous system infection in 5 (8.6%) and peripheral neuropathy in 9 patients (15.5%). Encephalopathy and peripheral neuropathy were the most common neurologic complications after renal transplantation.

Use of immunosuppressive agents and clinical treatment

Among 27 patients developing encephalopathy, 15 were administered with CsA and 12 with FK506. For 15 cases treated with CsA, 12 had normal CsA concentration, 2 with CsA concentration higher than normal range and 1 with CsA concentration lower than normal range. The FK506 concentration in all 12 patients was quantitatively detected within the normal range. Among a total of 27 patients, 6 cases presented with acute rejection responses after renal transplantation, 3 with infection and 2 with liver dysfunction. Corresponding interventions, such as dosage decrement or replacement of immunosuppressive agents were immediately implemented for those patients. Subsequently, 25 of 27 patients were recovered, whereas the remaining 2 cases died due to acute progression of severe complications.

Five patients developed the episode of epilepsy, and one of them had a medical history of chronic seizure and was untreated. Four cases were classified as complete episode of epilepsy and 1 as partial episode of epilepsy. Plain CT scan of the head detected no abnormality in 5 cases. MRI imaging revealed demyelinating lesions in the white matter of bilateral hemispheres. Five patients received the medication therapy of diazepam, phenobarbital or phenytoin sodium. After expectant treatment, 4 patients presented with no recurrent episodes and 1 case died.

In total, 12 patients developed cerebrovascular events after renal transplantation, 7 of whom were mainly induced by a medical history of chronic hypertension, 2 probably caused by a medical history of cerebral infarction, 1 by cerebral haemorrhage and 2 by diabetes mellitus. Upon episode, 6 cases presented with cerebral infarction, 1 with haemorrhagic infarction and 5 with cerebral haemorrhage (hemisphere haemorrhage in 3 cases and brain stem haemorrhage in 2). After corresponding therapies, 9 patients were significantly recovered and the remaining 3 died.

Nine patients developed peripheral neuropathy following renal transplantation. They were clinically manifested as body weakness, numbness, pain or decreased superficial reflex. Six patients were characterized with unilateral lower limb symptoms, 2 with asymmetry limb weakness and 1 with distal limb numbness and pain. However, all 9 cases had normal renal function after kidney transplantation. Clinical symptoms were significantly mitigated in 9 patients after receiving intramuscular administration of vitamin B12, vitamin B1 in combination with use of carbamazepine.

Five patients presented with central nervous system infection and clinically diagnosed with meningoencephalitis. However, the pathogenesis was not explicitly identified after cerebrospinal fluid bacterial culture and virological examination. Plain CT scan of the head revealed no evident abnormality. After 1 cycle of anti-bacteria, anti-tuberculosis and anti-fungus treatment, 3 cases were recovered and the remaining 2 died.

Discussion

Diverse characteristics of renal transplantation recipients make overall complication rates different from those of other organ transplant recipients. Neurologic complications are frequently observed with a reported incidence ranging from 6.8% to 14% in renal transplant recipients and may largely contribute to relatively a high morbidity and mortality [10]. Post-transplant

neurologic complications may be categorized as due to immunosuppressive medications, stroke, infection, neuropathies, and malignant tumors. However, among 1216 renal transplantation recipients in this research, merely 58 cases presented with neurological complications with an overall incidence rate of 4.8%. Such a lower incidence rate probably results from relatively short follow-up time in this investigation. A majority of patients presenting with mild symptoms in the early stage may be misdiagnosed. Hence, the actual incidence rate of neurological complications after renal transplantation may be higher.

Post-transplant headache is a recognized complication of organ transplant, both in the form of a de novo headache or worsening of a known migraine. Given their vasoactive properties, immunosuppressive agents like cyclosporine and tacrolimus are thought to play a role [11]. Nevertheless, the exact mechanism by which immunosuppressive agents induce or exacerbate the severity of headache remains elusive. In our study, encephalopathy was the most frequent neurologic complication occurring in 46.6% of 58 patients presenting with neurologic complications. Reversible Posterior Leukoencephalopathy Syndrome (RPLES) is commonly encountered in patients with hypertensive encephalopathy, eclampsia, kidney function failure and use of immunosuppressive agents [12]. RPLES is considered as a frequent complication induced by administration of CsA and FK506 in the population undergoing organ transplantation. The incidence rate of RPLES is reported as lower than 1% in patients receiving renal transplantation. RPLES patients are clinically characterized with headache, epilepsy, consciousness disorder and cortical blindness. CT scan or MRI of the head reveal a mass of abnormality involved with the white matter of bilateral occipital lobes. CT scan displays hypointense signal and MRI shows long T1 and T2 signals. RPLES-related symptoms and imaging abnormality can be alleviated by pressure-lowering, dehydration, dosage decrement or immunosuppressive agent replacement therapies, etc. Previous investigations have demonstrated that the incidence of RPLES is associated with the use of immunosuppressive agents [13]. Administration of immunosuppressive agents can significantly elevate blood pressure, which subsequently provokes cerebral vascular dysfunction, excessive brain perfusion, blood-brain barrier disorder and even petechial haemorrhage. Use of CsA, FK506 and alternative immunosuppressive agents can exert direct toxic effect upon the vascular endothelial cells, lead to vascular endothelial injury and constraction and eventually contribute to the blood vessel-derived oedema. In this study, 2 cases presented with severe cerebral oedema and cerebral hernia. To avoid the incidence of kidney function damage, clinical interventions, such as dehydration and immunosuppressive agent replacement therapies were not implemented. Eventually, these 2 patients died during subsequent follow-up.

Published reports [7-9] have demonstrated that the blood concentration of immunosuppressive agents is not correlated with the incidence and severity of encephalopathy. Therefore, much attention should be paid to the patients whose blood concentration of immunosuppressive agents is within normal range. The incidence of neurological complications should be diagnosed as early as possible.

In this study, 27 patients developed encephalopathy after renal transplantation due to viral infection, hypoxia and acute rejection responses of the renal graft, etc. In clinical practice, the occurrence of encephalopathy after renal transplantation is induced by complicated factors, which is a challenge to identify all the inducers and causes. Hence, postoperative clinical symptoms and signs of the patients should be intimately monitored following renal transplantation.

An array of stimuli may contribute to the episode of epilepsy including electrolyte disturbance (especially hypomagnesemia), bacterial infection, hypoxia, metabolic disorder (especially hypoglycaemia), acute rejection response of the graft and toxicity of immunosuppressive agents, etc. It has been reported that approximately 2% to 6% of patients receiving cyclosporin experience epilepsy, and approximately 5.6% to 11.6% of those administered with tacrolimus have epilepsy [14]. In present investigation, the incidence rate of epilepsy in patients was significantly enhanced when CsA was combined with use of MMF, FK506 and sirolimus. The episode of epilepsy is an isolated event after renal transplantation. Thus, long-term anti-convulsant treatment is not required. Use of phenytoin sodium and phenobarbital is an effective medication therapy for acute epilepsy. Nevertheless, these antiepileptic agents, as inducers of liver enzymes, can down-regulate the blood concentration of CsA and FK506. Therefore, the blood concentration of immunosuppressive agents should be closely monitored to avert the incidence of acute rejection responses after renal transplantation.

In this research, we observed that the incidence of acute stroke was relatively low. The incidence of ischemic stroke was higher compared with that of haemorrhagic stroke, whereas the mortality rate of patients with haemorrhagic stroke was higher than that of their counterparts developing ischemic stroke after renal transplantation, which is consistent with previous findings [13,14]. In this study, aging, hypertension, a medical history of cardiovascular disease and diabetes mellitus were the risk factors of acute stroke in renal transplantation recipients. However, this conclusion remains to be further validated by multi-center investigations. Previous research has demonstrated that atrial fibrillation and diabetes mellitus are independent factors for the prognosis of cerebrovascular events after renal transplantation. Pre-transplantation screening tests, such as carotid artery ultrasound or echocardiogram, contribute to estimating the risk of cerebrovascular events after renal transplantation [15]. For patients with a medical history of cardiovascular, cerebrovascular diseases or diabetes mellitus, the risk and benefit of renal transplantation should be explicitly evaluated before surgery. During perioperative period, the standard procedures of medical treatment and nursing care should be strictly implemented, aiming to reduce the incidence of acute stroke after renal transplantation.

In this study, the incidence of peripheral neuropathy in renal transplantation recipients was 9.8%, significantly higher

compared with 2.2% reported in previous findings [14,15]. Peripheral neuropathy was probably induced by intraoperative use of self-retaining retractor which led to femoral nerve injury and thigh nervous ischemia.

In this study, few recipients presented with central nervous system infection during the early stage after renal transplantation. However, clinical symptoms, physical signs and cerebrospinal fluid test results were severely interfered after administration of a large dose of steroid hormone and immunosuppressive agent therapy, which significantly increased the difficulty of clinical diagnosis and treatment. Recent investigations have demonstrated that a type of virus, known as lymphocytic choriomeningitis virus can be transferred from an organ donor to an organ transplantation recipient, which is likely to cause the incidence of meningitis and encephalitis with a high mortality rate. For these patients, decreased dosage of immunosuppressive agents and combined use of ribavirin are currently recommended.

Conclusion

Taken together, the early-stage incidence of neurological complications after renal transplantation was 4.8%, primarily consisting of encephalopathy, epilepsy and acute stroke. Postoperative cerebral haemorrhage is the most serious complication and cause of death. RPLES, epileptic state and central nervous system infection are the major causes of mortality. Previous findings hinted that the causes of early neurological complications after renal transplantation are complex. In this study, the incidence of neurological complications is associated with the use of immunosuppressive agents to certain extent.

Conflict of Interest

All authors declare no conflict of interests.

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