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Case Report

Improvement of a Post Pump Chorea After Switching to a Low Dose Tacrolimus Regimen in a Kidney Transplant Recipient: A Case Report

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Introduction

Kidney transplantation is the treatment of choice for end stage renal disease conferring for the patients the best survival and quality of life. Calcineurin Inhibitors (CNIs), cyclosporine A and tacrolimus have been used in renal transplantation for more than 20 years now and are considered as the cornerstone of immunosuppressive therapy in transplantation. Cyclosporine A was initially approved in 1983 by the U.S. Food and Drug Administration (FDA) for immunosuppression following organ transplantation. Tacrolimus received FDA approval in 1997 for renal transplantation [1,2]. More than 85 percent of renal transplant recipients are discharged from admission on tacrolimus as part of their maintenance immunosuppressive regimen [3]. This is largely because tacrolimus is more potent and associated with less rejection and nephrotoxicity than cyclosporine [4]. However; tacrolimus is also associated with more neurotoxicity and gastrointestinal side effects than cyclosporine [5]. Neurological complications of tacrolimus are usually mild (tremors, paresthesia and myalgia), but can be severe with encephalopathy, seizures and coma. Severe complications have been more frequently reported following liver and lung than with renal transplantation and typically occur with tacrolimus concentrations consistently above the therapeutic range of 15 ng/ml [6].

Case Report

We report the case of post pump chorea exacerbated after renal allograft transplantation with the use of a tacrolimus based immunosuppressive therapy. This is the case of a 21 years old girl, who had recurrent episodes of streptococcal infections during her infancy but with no regular follow up. In 2012 she was hospitalized for generalized edema with discovery of a massive mitral regurgitation and advanced renal failure necessitating the start of urgent dialysis, with partial recovery of her kidney function. She was operated of a mitral valve pasty in 2014 and continued chronic hemodialysis. She presented postoperatively a post pump chorea that was well controlled on risperidone. On the 13th of July 2017, the patient was operated of renal transplantation from living related donor, her mother. The immunosuppression protocol included an induction with Basiliximab with tacrolimus, mycophenolic acid and rapid tapering of steroids. The postoperative course was smooth with a nadir of creatinine of 0.8 mg/dl, normovolemia and good blood pressure control. The risperidone was continued throughout this period. Six weeks after transplantation, we started noting abnormal uncontrolled movements of the body, and the extremities mostly choreiform with some dystonic movements that would hamper her mobility and daily activities. She consulted her neurologist who increased the dose of risperidone to 0.5 mg twice daily, then to 4 times daily, that she did not tolerate because of increased sleepiness. The literature was reviewed for such tacrolimus side effects and none was found.

Since the patient's chorea was becoming worse; a switch of immunosuppression protocol was decided with introduction of everolimus at the 5th month after transplantation with progressive withdrawal of Myfortic and targeting lower trough level of tacrolimus (4-5 ng/ml). We did not consider using cyclosporine at this stage because of cosmetic issues and preferred to try a low dose tacrolimus based regimen with mTOR inhibitors. The patient started feeling better two weeks later, with a better control of her chorea and started going to school again after she stopped because of her chorea. The dose of risperidone was also decreased to 0.5 mg BID.

Discussion

In the peripheral immune system, calcineurin inhibitors bind a protein found in the cytosol of the lymphocyte: cyclophilin. This complex inhibits calcineurin activation, lowering the interleukin 2 production in the T-cell and thus inhibits the proliferation of T cells. Calcineurin is also expressed in several areas of the brain: cerebral

cortex, striatum, substantia nigra, cerebellum and hippocampus [7]. Calcineurin is the only calcium-activated phosphatase in the brain and a major regulator of key proteins essential for synaptic transmission and neuronal excitability, involved in memory and synaptic plasticity [8]. Multiple mechanisms have been proposed for calcineurin inhibitors neurotoxicity. Neurotoxicity may be related to endothelin, produced in excess in the presence of calcineurin inhibitors. If endothelial integrity is disrupted, cyclosporin and tacrolimus could gain access to astrocytes [9]. Endothelin could gain access to the cerebral vascular smooth muscle, resulting in vasoconstriction and vasospasm [10]. Elevated circulating endothelin could promote systemic hypertension. Under such conditions, local ischemia and consequent white matter edema could show typical transient alterations in the subcortical parietal and occipital lobes, as observed in cases of acute hypertensive encephalopathy [11] or in Posterior Reversible Encephalopathy (PRES). Subcortical edema that is present in PRES can be the result of a hyper-perfusion insult promoted by endothelial cell damage with breakthrough of autoregulation in the posterior circulation, which has paucity of sympathetic innervation.

Part of cyclosporine and tacrolimus toxicity may also arise from alterations in mitochondrial function [12] such as decrease of mitochondrial energy production and the subsequent activation of anaerobic glycolysis, impaired cellular calcium buffering, activation of proteases and phospholipases, activation of nitric oxide synthetase and generation of free radicals, leading to either apoptotic or necrotic cell death depending upon the severity of the insult [13]. It should be noted also that cyclosporine and tacrolimus are highly lipophilic and are bounded in plasma especially to Low-Density Lipoprotein (LDL). Low cholesterol concentrations lead to increased free concentrations of drugs but also lead to an increase in the amount of LDL receptors expressed on the cell membrane of astrocytes (at the blood-brain barrier); therefore, increased uptake of drugs can lead to damage of the blood-brain barrier as well as the white matter. Neurotoxic effects can manifest either in the central or in the peripheral nervous system. Early calcineurin inhibitor-induced neurotoxicity is considered when neurological symptoms occur within 4 weeks after transplantation [9]. Neurotoxicity can occur both at therapeutic and at high cyclosporine or tacrolimus levels. Sometimes, neurotoxicity can be only indirectly inferred from the resolution of the clinical symptoms when treatment is discontinued.

The major central neurotoxic effect of calcineurin inhibitors is Posterior Reversible Leukoencephalopathy Syndrome (PRES), typically distributed in the posterior regions of the white matter of the brain. Other major side effects include akinetic mutism, toxic encephalopathy, seizures. The minor central effects include insomnia, visual symptoms, headache, tremor, paresthesia and mood changes; they are more frequent than major effects, occurring in almost 40% of transplant patients. Major symptoms of neurotoxicity are treated by reducing the doses of immunosuppressive or by conversion from cyclosporine to tacrolimus and vice versa. Using a combination of drugs (calcineurin inhibitors plus mycophenolate mofetil or sirolimus) allows lower dosages of cyclosporine and tacrolimus without impairing the immunosuppression efficacy. Minor symptoms of neurotoxicity are easily managed with symptomatic treatment. We use common analgesics for headache, low doses of benzodiazepines for insomnia (clonazepam, midazolam), beta blockers for tremor (metoprolol, propranolol), antiepileptics for paresthesia (carbamazepine, gabapentin). Peripheral toxicity occurs weeks to months after starting immunosuppressive treatment. Both the nerve and the muscle may be involved [14]. Axonal and demyelinating neuropathy have also been reported. The more severe forms have been observed during tacrolimus therapy, such as multifocal demyelinating neuropathy Resembling Chronic Inflammatory Demyelinating Neuropathy (CIDP). Some patients may respond to intravenous immunoglobulins or plasma exchange.

Risk factors for the development of calcineurin inhibitors-related neurotoxicity are: age, the use of methylprednisolone, arterial hypertension, fluid overload, hypocholesterolemia because it increases brain uptake of immunosuppressant drugs and drug interactions [15] hypomagnesaemia, pre-existing brain disease, pre-existing blood-brain barrier alterations, hepatic encephalopathy, concomitant treatments (metoclopramide), surgical time >7 hours, and post-transplant hyponatremia [9]. To our knowledge this is the first case of exacerbation of chorea with tacrolimus, and improvement after targeting lower trough levels along with everolimus.

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