Posterior Reversible Encephalopathy Syndrome (PRES) as a Complication of Immunosuppressive Therapy in Renal Transplantation in Children

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ABSTRACT

Although kidney transplantation is by far the best method of renal replacement therapy, organ receiver is still not spared of eventual toxic consequences of drugs that are in charge of keeping the transplanted kidney functional. Both calcineurin inhibitors, of which tacrolimus more often, occasionally lead to neurotoxic side effects, mostly mild and reversible and dose-dependent in nature, but they can also be very severe or even fatal. It is very important to be aware of possible neurotoxic effects, to confirm them radiologically, and to prevent or reduce drug effects on nervous system. Sometimes the reduction of dose or substitution with another drug with similar mechanism effect is sufficient to terminate the neurotoxic effects of the drug and still not jeopardize the function of transplanted organ.

Keywords: Posterior reversible encephalopathy syndrome, kidney transplantation

1. 1. INTRODUCTION

Despite the constant improvement of conservative therapy for end-stage renal disease, kidney transplantation is the best treatment for children with terminal-stage renal failure. The risk of death among children which, after being diagnosed with end-stage renal disease, underwent renal transplantation, is more than four times lower than the risk of death in children treated with dialysis. Immunosuppressive therapy enables prolonged graft survival in transplantation, but it is also associated with adverse effects such as nephrotoxicity, hypertension, development of cardiovascular and metabolic disorders, susceptibility to infections and malignant cell proliferation, and neurotoxicity.

2. CASE REPORT

A fourteen year old girl was hemodialysis dependent for four months due to reflux nephropathy and dysplasia of native kidneys. Fifth postoperative day after living related renal transplantation (organ donor was her father) the girl suddenly felt severe, diffuse headache, she had a crisis of consciousness, psycho motor agitation, and tonic-clonic seizures. She did not involuntarily urinate nor there was any foam in the mouth or tongue biting. The attacks lasted for about ten minutes after which the girl was asleep for about an hour. As she gained full consciousness and woke up she had a partial and short-term amnesia. At the moment of the attack physical examination of the heart and lungs was normal, and basic laboratory tests (blood count, markers of inflammation, acid-base status, blood sugar, electrolyte status) taken at the time of the attack were within normal values. Her blood pressure during the attack was 140/85 mmHg, pulse 110/min. Three days after the first attack she had high blood pressure 190/115 mmHg, without any new attacks, but with headaches which required modification of anti hypertensive therapy. Clinical presentation after the first attack required a constant consultations of
pediatrician and neurologist who indicated further neuroradiological diagnostics that eventually showed multiple acute ischaemic changes in the light of posterior reversible encephalopathy syndrome (PRES), with lesions of the parietal and occipital lobes and cerebellum that progress to frontal and temporal lobes bilaterally (Figure 1 and Figure 2). Due to severe general condition, late developed hypertension, and delayed renal graft function with high values of renal function parameters, hemodialysis support was started. Even with all the measures being taken patients condition remains severe, and because of the potential neurotoxic effects of previous immunosuppressive therapy (corticosteroids, mycophenolate mofetil, tacrolimus) changes in calcineurin inhibitor therapy and drug dosage adjustment were made (tacrolimus–cyclosporin switch). The level of tacrolimus was adequate for post transplantation period and it was 13 ng / ml. We mainly suspected that it was a case of neurotoxic drug effects, tacrolimus in particular, based on clinical presentation and association of neurologic manifestations with delayed graft function which is also commonly caused by effects of calcineurin inhibitors. Prompt improvement in patients health after calcineurin inhibitors were replaced has further confirmed our assumptions. During in-hospital stay intensive monitoring and multidisciplinary approach were maintained, and patients condition was stabilized and improved, parameters of renal function were normalized so there was no realistic need for the hemodialysis support, whilst early repeated radiological examinations showed a discrete progression of ischaemic lesions. Control endocranial MRI findings after two months showed prevailing regression of previously visualized ischaemic brain lesion (Figure 3), and clinical laboratory tests showed good and preserved kidney graft function with normal values of serum creatinine. In her following, monthly check-up examinations the girl was without any neurological symptoms.

3. DISCUSSION
Neurotoxic effects of immunosuppressive therapy are well known and described in literature. Mild tremor is the most common neurological complication (almost 55%), and it is equally common with cyclosporin and tacrolimus[1,2]. Patients rarely develop more severe neurological symptoms such as severe headache, visual anomalies, and seizures of clonic-tonic or absans type. Neurological complications are mostly commonly related to hypertension, and they can mask hypertensive encephalopathy, with neuroradiological findings often describing reversible posterior leukoencephalopathy syndrome[3], in newer literature commonly described as Posterior reversible encephalopathy syndrome (PRES). Neurological adverse effects are mostly reversible and they retard to changing orally administered immunosuppressants, to dose reduction or exclusion of drug[4,13]. Adverse effects of tacrolimus include nephrotoxicity, hypertension, diabetes mellitus, neurotoxicity and increased susceptibility of severe infections. When using tacrolimus cases of akinetic mutism, encephalopathy, tonic-clonic seizures and focal neurologic events were described, and in most severe cases coma would occur. Studies that show frequency of neurological complications of cyclosporine compared to tacrolimus were contrary, but newer studies suggest that neurological side effects are more commonly seen in administration of tacrolimus. Neurological complications are also common in the use of sirolimus, cisplatin, bevacizumab and interferon therapy[5,6,7-12]. Although literature described it for significant period of time, PRES syndrome as isolated syndrome was described in year 1996 in series of cases[5]. It has been described as clinical syndrome of rapid onset of headache, confusion, decreased level of consciousness, visual changes, or tonic-clonic or absans attacks, which are associated with characteristic neuroradiological findings of posterior cerebral white matter edema. The pathogenesis of PRES is unclear, but it seems to be linked with the disorders of cerebral autoregulation and endothelial dysfunction. Neuroradiological findings are essential in diagnose of PRES. Typical findings are symmetrical white matter edema in the posterior cerebral hemispheres, especially in the parieto-occipital regions, but variations are also described. Repeated neuroradiological findings are a must for patient monitoring and confirmation of PRES syndrome[13,14,15]. With adequate therapy and treatment, full resolution of pathological findings could be expected in weeks.

4. CONCLUSIONS
Neurotoxic affects of immunosuppressive therapy are well known, but still insufficiently investigated. They are usually of reversible nature after the dosage has been adjusted or the drug has been excluded. Although tacrolimus is still the drug of choice in the prophylaxis of acute graft rejection, its neurotoxic effects are more common and do not depend on the length of treatment by drug, therefore the concentration of drug in the blood should be monitored, especially in the pediatric group of patients. PRES is a rare form of manifestation of calcineurin inhibitors neurotoxicity, and only if it is early detected and adequately treated the occurrence of irreversible changes is prevented.

CONFLICT OF INTEREST: NONE DECLARED
REFERENCES


