Published online: 31/05/2014
Published print: 06/2014

Med Arh. 2014 Jun; 68(3): 218-220
Received: April 12th 2014 | Accepted: May 25th 2014
© AVICENA 2014

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

Emir Hodzic¹, Majda Brcic¹, Mirza Atic¹, Alma Halilcevic¹, Amila Jasarevic¹, Mirna Aleckovic-Halilovic¹, Davor Trojak¹, Nedima Atic², Snezana Zulic², Zlatan Mehmedovic³, Ivana Iveljic¹

University Clinical Center Tuzla, Clinic for Internal Diseases, Tuzla, Bosnia and Herzegovina¹

University Clinical Center Tuzla, Clinic for Diseases of Children, Tuzla, Bosnia and Herzegovina²

University Clinical Center Tuzla, Clinic for Surgery, Tuzla, Bosnia and Herzegovina³

Corresponding author: Prof. Emir Hodzic, MD, PhD. Chief of Division for Transplantation. Department of Nephrology, Dialysis and Transplantation. Clinic for Internal Diseases. University Clinical Center Tuzla. Trnovac bb. Telephone(s): 035 303 392, 035 303 106. GMS: 061 193 660. Fax: 035 303 430. E-mail: emir.hodzic@ukctuzla.ba

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 antihypertensive therapy. Clinical presentation after the first attack required a constant consultations of

Figure 1. Primar neuroradiological MRI: blotchy melted lesions of high shadow intensity in parietal and occipital lobes

Figure 2. Primar neuroradiological MRI: blotchy melted lesions of high shadow intensity infratentorially in cerebellum

Figure 3 Regression of previously described lesions in cerebrum and cerebellum

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 to 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 most 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 retreat 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 comma 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^[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 know, 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

1. Randomised trial comparing tacrolimus (FK506) and cyclosporin in prevention of liver allograft rejection. European FK506 Multicentre Liver Study Group. *Lancet* 1994; 344:423.
2. A comparison of tacrolimus (FK 506) and cyclosporine for immunosuppression in liver transplantation. The U.S. Multicenter FK506 Liver Study Group. *N Engl J Med* 1994; 331:1110.
3. Schwartz RB, Bravo SM, Klufas RA, et al. Cyclosporine neurotoxicity and its relationship to hypertensive encephalopathy: CT and MR findings in 16 cases. *AJR Am J Roentgenol* 1995; 165:627
4. Wijdicks EF, Wiesner RH, Krom RA. Neurotoxicity in liver transplant recipients with cyclosporine immunosuppression. *Neurology* 1995; 45:1962.
5. Hinchey J, Chaves C, Appignani B, et al. A reversible posterior leukoencephalopathy syndrome. *N Engl J Med* 1996; 334:494.
6. Ito Y, Arahata Y, Goto Y, et al. Cisplatin neurotoxicity presenting as reversible posterior leukoencephalopathy syndrome. *AJNR Am J Neuroradiol* 1998; 19:415.
7. Ozcan C, Wong SJ, Hari P. Reversible posterior leukoencephalopathy syndrome and bevacizumab. *N Engl J Med* 2006; 354:980.
8. Allen JA, Adlakha A, Bergethon PR. Reversible posterior leukoencephalopathy syndrome after bevacizumab/FOLFIRI regimen for metastatic colon cancer. *Arch Neurol* 2006; 63:1475.
9. Bodkin CL, Eidelman BH. Sirolimus-induced posterior reversible encephalopathy. *Neurology* 2007; 68:2039.
10. Rajasekhar A, George TJ Jr. Gemcitabine-induced reversible posterior leukoencephalopathy syndrome: a case report and review of the literature. *Oncologist* 2007; 12:1332.
11. Junna MR, Rabinstein AA. Tacrolimus induced leukoencephalopathy presenting with status epilepticus and prolonged coma. *J Neurol Neurosurg Psychiatry* 2007; 78:1410.
12. Kozak OS, Wijdicks EF, Manno EM, et al. Status epilepticus as initial manifestation of posterior reversible encephalopathy syndrome. *Neurology* 2007; 69:894.
13. Fugate JE, Claassen DO, Cloft HJ, et al. Posterior reversible encephalopathy syndrome: associated clinical and radiologic findings. *Mayo Clin Proc* 2010; 85:427.
14. Lamy C, Oppenheim C, Méder JF, Mas JL. Neuroimaging in posterior reversible encephalopathy syndrome. *J Neuroimaging* 2004; 14:89.
15. Fugate JE, Claassen DO, Cloft HJ, et al. Posterior reversible encephalopathy syndrome: associated clinical and radiologic findings. *Mayo Clin Proc* 2010; 85:427.
16. Ellis D. Clinical use of tacrolimus (FK-506) in infants and children with renal transplants. *Pediatr Nephrol* 1995; 9:487.
17. Ciancio G, Siquijor AP, Burke GW, et al. Post-transplant lymphoproliferative disease in kidney transplant patients in the new immunosuppressive era. *Clin Transplant* 1997; 11:243.
18. Dharnidharka VR, Ho PL, Stablein DM, et al. Mycophenolate, tacrolimus and post-transplant lymphoproliferative disorder: a report of the North American Pediatric Renal Transplant Cooperative Study. *Pediatr Transplant* 2002; 6:396.
19. Hodzic E. et al. Voljeti bubregom: Informacije i uputstva za pacijente sa transplantirananim bubregom. Soreli Tuzla 2012.

European Association of Science Editors

EASE

Username * Password *

[Request new password](#)

The European Association of Science Editors (EASE) is an internationally oriented community of individuals from diverse backgrounds, linguistic traditions and professional experience who share an interest in science communication and editing.

[Home](#) [About Us](#) [Membership](#) [Publications](#) [Services](#) [EASE Events](#) [Other Events](#) [Web Shop](#)

Welcome to EASE

12th EASE General Assembly and Conference, Split, Croatia, 13–15 June 2014

The complex world of science editing

Please note that Prof. Rosenberg (Danish Medical Journal) is no longer able to join us to present the plenary lecture on the afternoon of Saturday, 14th June. Liz Wagner (Publications Consultant) has kindly agreed to step in and **plenary and parallel session abstracts** are now available.

An updated (May 2014) version of the **programme** can be downloaded (pdf). **Poster abstracts are now available** together with details of the **optional workshops** (including prices), **accommodation**, meals and **general information about Split, including transport**.

On-site registration in Split will begin at 2.15 pm on Friday with the Opening Ceremony at 4.00 pm. The conference ends on Sunday at 1.45 pm. Please note that there are optional courses running before and after the opening and closing ceremonies. It is possible to attend the optional workshops without coming to the conference.

EASE/KCSE Travel Bursaries

We are delighted to announce the recipients of the first KCSE/EASE Bursary Awards. Dr Isaac Katano teaches at Uganda Christian University and is Associate Dean of the Business Faculty and Dr Jibril Habuleh is a sponsored member of EASE from Somaliland. [Find out more.](#)

Forthcoming events

EuroScience Open Forum 2014
Saturday, 21 June, 2014
Denmark

In the Spotlight

Armen Yuri Gasparyan
United Kingdom

Dr. Armen Yuri Gasparyan has been involved in clinical research on cardiovascular issues in inflammatory rheumatic disorders since 1994, and got his PhD degree in 2002. He was a trainer of English-speaking medical students (2003-2008) and got an academic title of Associate Professor of Medicine.

[Read more](#)

Editorial Services

Editorial service at Somaliland medical journal
Somaliland Medical Association