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Cyclosporin A Induced Neurotoxicty After Heart Transplantation

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Abstract: Cyclosporine-A(CsA) can cause a wide range of adverse effect on both the Central Nervous System(CNS) and Peripheral Nervous System(PNS). Side effects of CsA on CNS have been reported to occur in up to 42% of patients. However the majority of these reports has been obtained from studies in bone marrow and liver transplantation recipients. There are few reports about CsA induced neurotoxicity after heart transplantation. A 65-year-old female patient who underwent heart transplantation for cardiomyopathy, received azathioprine, prednisolone, CsA in the postoperative period. She was administered CsA at 3 mg kg day and blood CsA (Co) levels ranged between 250-350 ng mL^{-1}. CsA induced neurotoxicity occured at postoperative 6th month. Neurotoxicity of CsA generally occurs with intravenous administration of high levels , in the presence of a predisposing factor and early treatment period which is reversible. In our patient CsA induced neurotoxicity occured with normal levels of CsA, oral CsA treatment and in late treatment period. Although all the symptoms due to neurotoxicity were reversible, ptosis remained as an irreversible sequela. For this reason clinicians must be aware of the neurotoxic side effects from the begining to the end of the therapy.

Key words : Heart transplantation, neurotoxicity, cyclosporin

INTRODUCTION

Cyclosporin A (CsA) has many side effects including nephrotoxicity, hypertension, hyperkalemia, hypomagnesemia, increased risk of certain cancers and oppurtinistic infections, gum hyperplasia, hypertrichosis, hepatotoxicity and neurotoxicity are also observed[1,2]. Neurotoxicity is a less known toxic effect and presents with a wide range of clinical symptoms. Moreover these side effects were reported to occur in up to 42 % of patients. These side effects have particularly been reported after liver, bone marrow, kidney and rarely after heart transplantation[2]. Here we present a case of neurotoxicity with CsA following heart transplantation with normal range of blood CsA (Co) measurements.

Case report: A 55-year old female patient had been accepted as a cardiac transplant recipient with diagnosis of dilated cardiomyopathy following routine evaluations. She was scheduled for heart transplantation. One year later, surgery was performed. She had an unevenful surgery and early postoperative period. She was followed by CsA (3 mg kg^{-1} per day), azathioprine(2 mg kg per day), prednisolone (0.5-mg kg^{-1} per day) therapy for 6 months. Blood CsA levels (Co) were measured between 250-350 ng mL^{-1} on monthly visits. She was doing well and her routine laboratory measures pertaining to heart transplantation including coronary angiography were normal.

On 7th month of her follow-up, she developed a severe headache and vomitting. Physical examination revealed confusion, somnolance, hemiparesia, negative light reflex, pupil dilatation and pithosis on left eye. Other vital signs were in natural values. She had a tonic-clonic seizure while she was awaiting for further laboratory assesments. During the event, the blood CsA levels (Co) were 254 ng mL^{-1}, with normal serum levels of cholesterol, triacylglycerol and magnesium. Also liver and renal functions were normal. The patient did not exhibit arterial hypertension. Emergency Electroencephalography (EEG) showed epileptiform activity which any causitive reason could not be explained. Heterogenous hypodense lesions that extended the subcortical areas located in the parietal and temporal white matter bilaterally were detected by Computarized Tomograpyh (CT) of brain. Magnetic Resonance Imaging (MRI) indicated decreased signals along subcortical white matter on frontotemporoparietal region of left and temporoparietal region of right hemispheres. Those signal differences were free from contrast infiltration (Fig. 1).

Cerebrospinal fluid examinations and serologic tests including herpes simplex, ebstein-barr, cytomegalo virus, cryptococcus and toxoplasmosis were found to be negative. Echocardiography and cardiac biopsy were also detected as normal.

Since all neurologic and clinical evaluations were not associated with either infection or a intracranial mass, we concluded that these syptomps were releated to CsA

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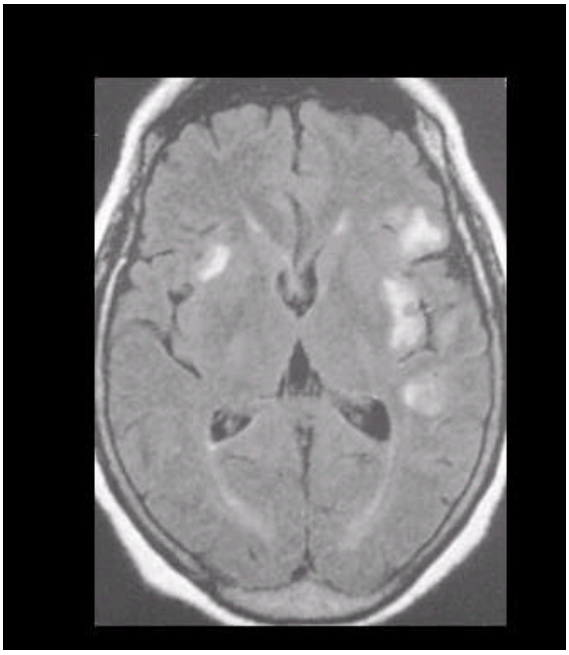

Fig. 1: The patient's MR images at 7th month

intoxicity although CsA levels (Co) were in normal values (175-250 ng mL^{-1}). Hence, all neurologic symptomps disappeared after lowering the dose of CsA except 3rd nevre paralysis.

She discharged on the following immunosuppresive regimen: Low dose CsA (2 mg kg per day), azathiopurin (2 mg kg per day) and prednisolone (0.5 mg kg^{-1} per day). MRI didn't performed 6 weeks later, because she was die after sever head trauma.

DISCUSSION

CsA can cause a wide range of adverse effect on both the Central Nervous System (CNS) and Peripheral Nervous System (PNS)[1].

CsA induced toxicity by separating three categories as a grade 1,2 and 3. Grade 1 neurotoxicity includes mental status changes, tremor, headache; grade 2 includes visual disturbance, cortichal blindness; grade 3 includes seizures and coma[2]. We initially observed grade 1 neurotoxicity in our patient, but symptoms progressed to grade 3 according to this scale.

Few postmortem examinations have been carried out in patients who died with presumed CsA-related neurotoxicity. No specific histological substrate is known[3-5]. One report described diffuse myelin and axonal loss throughout the entire spinal cord sparing the anterior horn cells in a patient who died with paraplegia. The brain was normal[3]. Terrovitis I.V. et al. present a case history of symmetric polyneuropathy with flaccid paraplegia, neurological complication of CsA administration[6]. We observed hemiparesia in our patient.

CsA induced neurotoxicity has been suggested that intravenous administration and high levels of CsA contribute to the drug-associated neurotoxicity. Howewer, neurotoxicity can also be observed after oral CsA therapy with normal blood CsA levels[2]. There were no notewothy differences between the mean CsA concentrations and clinical data in those with or without CNS lesions[7]. Our patient was also showed neurotoxicity after oral CsA therapy. Significant correlation between neurotoxicity and hypocholesterolemia has been shown. When total cholesterol or LDL levels are low, up-regulation of the LDL receptor occurs. Since intracellular transport of cyclosporine is also via these LDL receptors, upregulation of these receptors lead to the increased tissue levels of CsA[1,6].

Large series reported an incidence of CsA-related seizures of 1.5-6%. Seizures are also frequent in PLE[1]. Generalized tonic-clonic seizures often occur with high CsA levels[8]. In our case, we observed tonic-clonic seizure, all neurologic symptomps disappeared after lowering the dose of CsA except 3rd nevre paralysis.

Hyponatremia hypocalcemia, aluminium overload, magnesium defiency and hypoglycemia are frequently observed and are considered to contribute to development of seizures. Infections, graft rejection and its treatment with steroids and pretransplant (hepatic) encephalopathy are cofactors in CsA- associated seizures. The increse of neurotoxic substances, such as bilirubin, Blood Urea Nitrogen (BUN), or ammonia, has also been thought to correlate with CNS toxicity[1,2]. In our case, we observed neither electrolyte disturbances nor infection. In addition, graft rejection and elevation of neurotoxic substances, such as bilirubin, BUN, or ammonia were not observed.

A reversible Posterior Leukoencephalopathy Syndrome (PLE) is the most serius CsA-associated neurological side effect. This syndrome is characterized by headache, altered mental functioning, seizures and cortical blindness associated with multifocal, bilateral white matter abnormalites on imaging studies indicating leukoencephalopathy predominantly in the posterior regions (parietooccipital and temporal lobes) of the cerebral hemispheres and also pons, thalamus and cerebellum. Most of the patients this syndrome are hypertensive and in more than half CsA levels are high. Low cholesterol and magnesium levels are found in over 50% of patients. Neurological signs have regressed after the treatment of hypertension or reduction or withdrawal of CsA[1,2]. In our patient, clinical findings were similar to PLE although hypertension, high CsA levels, hypocholesterolemia and hypomagnesemia were

absent. White matter abnormalites on MRI was similar to the affected areas in PLE. Therefore, neurological findings of our patient could be PLE.

After 582 allogeneic bone marrow transplants, Openshaw H. et al. have encountered four patients who developed transient unilateral or bilateral 6th nerve palsies. Three of the four patients also had bilateral ptosis[9]. We observed 3rd nevre paralysis in our patient.

CT and particularly MRI are both useful techniques in patients with CsA neurotoxicity[2]. On CT non-enhancing areas of hypodensity are seen predominantly in the white matter of the occipital regions. MRI is more sensitive and demonstrates decreased signals in the same areas. However, extension into the parietal areas is common. White matter lesions in the temporal and frontal lobes or in the cerebellum and pons are less frequent[1]. These pathological findings are rapidly dissappear with cessation of CsA therapy. In our case, the pathological findings were located in temporal and parietal white matter bilaterally, which were demonstrated by both CT and MRI. MRI didn't performed 6 weeks later, because the patient was die after sever head trauma.

Many studies reported CsA-related neurotoxicity in early treatment period[1]. Another interesting finding in our patient was neurotoxicity developed after 7 months of medication. It seems that the neurologic symptoms are not associated with therapy duration.

More clinical observations and studies are needed to understand the mechanisms of CsA -releated neurotoxicity.

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