Cyclosporin A Induced Neurotoxicity After Heart Transplantation

Irfan Tasoglu, Yildirim Imren, Mehmet Gungor Kaya, Dilek Erer, Erkan Iriz and Mehmet Emin Ozdogan

Department of CVS, Department of Cardiology Medical Faculty, Gazi University

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\(^{-1}\) 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 beginning 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 opportunistic 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\(^{[3]}\). 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 uneventful surgery and early postoperative period. She was followed by CsA (3 mg kg\(^{-1}\) per day), azathioprine (2 mg kg\(^{-1}\) 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 vomiting. Physical examination revealed confusion, somnolance, hemiparesia, negative light reflex, pupil dilatation and ptosis on left eye. Other vital signs were in natural values. She had a tonic-clonic seizure while she was awaiting for further laboratory assessment. 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 Tomography (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, cryptoccocus 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 sympotms were releated to CsA...
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neurotoxicity after oral CsA therapy. Significant

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

toxicity although CsA levels (Co) were in normal

intoxicity values (175-250 ng mL\(^{-1}\)). Hence, all neurologic

symptoms disappeared after lowering the dose of CsA

except 3rd nerve paralysis.

She discharged on the following immunosuppressive

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, cortical 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\(^{[6]}\). 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. However,

neurotoxicity can also be observed after oral CsA therapy with normal blood CsA levels\(^{[2]}\). There

were no noteworthy 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\(^{[5]}\).

Large series reported an incidence of CsA-related

seizures of 1.5-6%. Seizures are also frequent in PLE\(^{[3]}\).

Generalized tonic-clonic seizures often occur with high

CsA levels\(^{[8]}\). In our case, we observed tonic-clonic

seizure, all neurological symptoms disappeared after

lowering the dose of CsA except 3rd nerve paralysis.

Hyponatremia hypocalcaemia, 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\(^{[4,5]}\). 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 serious 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\(^{[2]}\). In our patient, clinical findings

were similar to PLE although hypertension, high CsA

levels, hypocholesterolemia and hypomagnesemia were
absent. White matter abnormalities 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\(^3\). We observed 3rd nerve 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 disappear 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-related neurotoxicity.

REFERENCES