Cyclosporine-Associated Leukoencephalopathy in Organ Transplant Recipients: Experience of Three Clinical Cases

R. Muñoz, M. Espinoza, O. Espinoza, A. Andrade, E. Bravo, and F. González

ABSTRACT

Leukoencephalopathy is a structural alteration of cerebral white matter mainly involving damage to myelin. Several reports have linked cyclosporine (CsA) with this alteration. The clinical features vary from qualitative alterations of consciousness to neurological deficits. Magnetic resonance imaging (MRI) of the brain demonstrates the damage to the white matter, which is essential for the differential diagnosis. We describe three clinical cases of leukoencephalopathy. The first case is a 43-year-old man received a cadaveric kidney transplant using immunosuppression with of mycophenolate mofetil, prednisone, and CsA. Four months later he developed meningism and bilateral sixth nerve palsy. The second case is a 50-year-old man with a cadaveric kidney transplant received immunosuppressive treatment with azathioprine and prednisone. As a result of gouty arthritis of the ankle, azathioprine was replaced with CsA to allow addition of allopurinol. Two weeks later he developed confusion and personality changes. The third case is a 16-year-old man received a orthotopic liver transplant. Postoperatively he suffered generalized tonic-clonic seizures. In all patients the CsA levels were toxic and signs of neurological alterations were present on MRI. All patients recovered rapidly after CsA withdrawal.

THE INTRODUCTION of the calcineurin inhibitors (CNI)—cyclosporine (CsA) and tacrolimus—revolutionized posttransplantation immunosuppressive therapy in the 1980s. These drugs effectively prevented acute rejection episodes significantly prolonging graft survival. However, 1% to 6% of organ transplant recipients may develop toxic leukoencephalopathy characterized mainly by altered mental status, visual abnormalities, and seizures.[1,2] The pathogenesis of neurotoxicity is not fully understood. The use of magnetic resonance imaging (MRI) has led to a greater appreciation of the damage that CNI can inflict on white matter.[3] This picture may be completely reversible upon withdrawal of the drug before the the appearance of white matter necrosis. Herein we have described three clinical cases with this alteration.

CASE REPORTS

Case 1

A 43-year old man with an antecedent history of chronic renal insufficiency of unknown etiology received a cadaveric kidney transplant in 2004. His immunosuppressive treatment was antithymocyte-globulin induction with mycophenolate mofetil (MMF), CsA, and prednisone. Four months later, he was hospitalized due to pneumonia, and received fluorquinolones for 14 days. During the stay, the blood CsA (C0) level was 659 ng/mL. Ten days after discharge, he experienced headache, meningism and bilateral sixth nerve palsy. Cerebrospinal fluid showed a clear liquid with 270 cells including 60% polymorphonuclears and 40% mononuclear cells and a glucose of 54 mg/dL. Gram stain, culture IFI-CMV, PCR-TBC, and india ink were all negative. We began empiric treatment with ceftriaxone, vancomycin, ampicillin, and ganciclovir. MRI showed many foci of hypersignal in the subcortical white matter, particularly in the broadcoast crown and semioval centers (Fig 1). CsA was withdrawn with complete clinical improvement.

Case 2

A 50-year-old man with previous end-stage renal disease due to mesangiocapillary glomerulonephritis received a cadaveric kidney transplant in 1987. His immunosuppressive treatment was azathioprine and prednisone. Because of gouty arthritis of the ankle, azathioprine was replaced by CsA to initiate treatment with

From the Department of Nephrology (R.M., M.E, O.E., F.G.), Hospital del Salvador, Santiago, Chile; Faculty of Medicine (R.M., F.G.), Universidad de Chile, Santiago, Chile; Department of Infectology (A.A.), Hospital del Salvador, Santiago, Chile; and Department of Neuroradiology (E.B.), Instituto de Neurocirugía Asenjo, Santiago, Chile.

Address reprint requests to Rodrigo Muñoz, Department of Nephrology Hospital del Salvador, Av Salvador 364, Providencia, Santiago, Chile. E-mail: romunoz@msn.com.

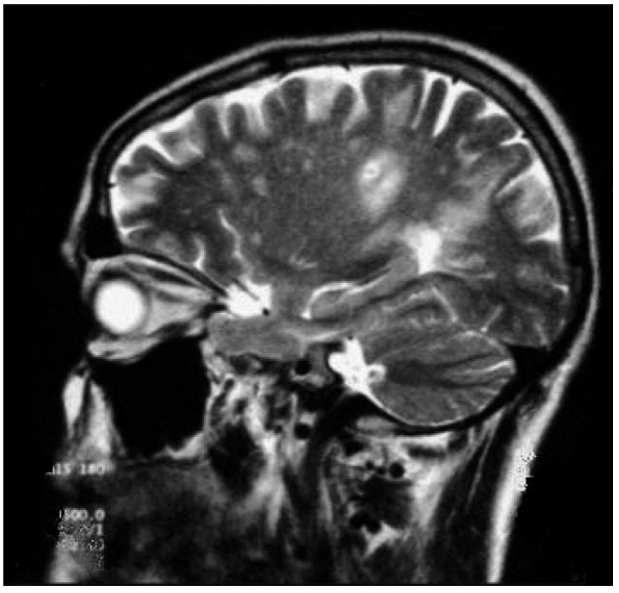

Fig 1. FLAIR-weighted sagattal MRI. Many foci or hypersignal in the white substance subcortical of preference in broadcast crown and semioval centers.

allopurinol. Two weeks later the patient evolved to confusion, irritability, and personality changes. Blood CsA (C0) level was 547 ng/mL. The MRI showed alterations compatible with leukoencephalopathy (Fig 2). A fast recovery was achieved by replacing CsA with MMF.

Case 3

A 16-year-old man with liver cirrhosis due to chronic autoimmune hepatitis received a cadaveric orthotopic liver transplant in March 2003. Immunosuppressive treatment included prednisone, CsA, and MMF. In the postoperative period, he developed generalized tonic-clonic seizures. Blood pressure was normal. Electroencephalogram was inconclusive. Blood cholesterol was 250 mg/dL. Cerebrospinal fluid showed a clear liquid with 25 cells, protein of 198 mg/dL, and glucose of 60 mg/dL. Culture was negative. Blood CsA C0 level was 405 ng/mL. The MRI revealed alterations compatible with reversible posterior leukoencephalopathy (Fig 3). CsA was replaced with tacrolimus and the patient recovered.

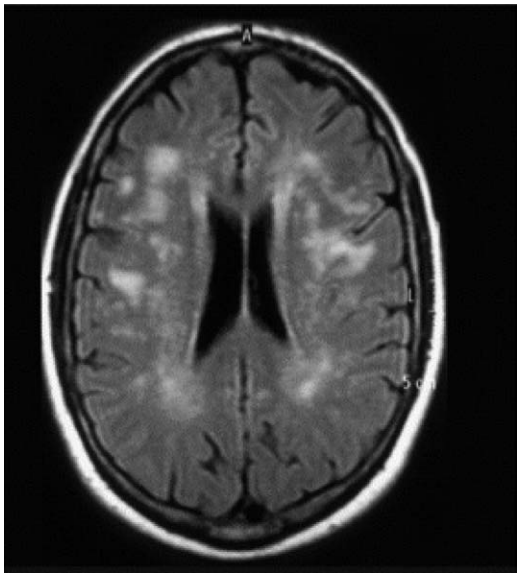

Fig 2. T2-weighted axial MRI. Zones of hypersignal in the periventricular and parietal subcortical white matter.

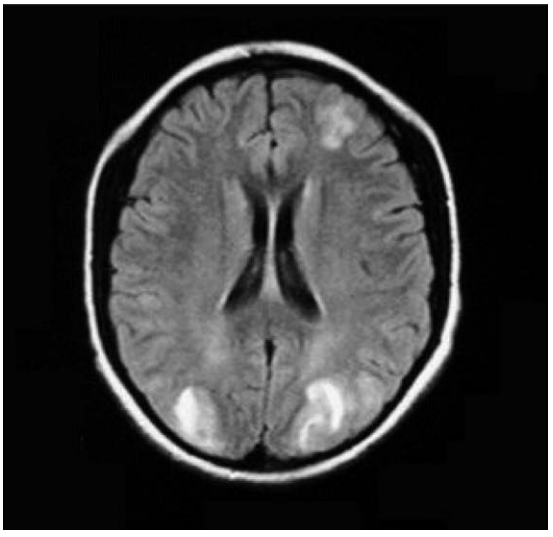

Fig 3. T2-weighted axial MRI. Zones of corticosubcortical hypersignal at occipital and left frontal level.

DISCUSSION

The main features of toxic leukoencephalopathy in our series included mental changes, qualitative alterations of consciousness, seizures, meningismus, and bilateral sixth nerve palsy. The leukoencephalopathy particularly involves white-matter tracts devoted to higher cerebral functions, causing clinical features that range from inattention and forgetfulness to changes in personality.[3] Seizures have been the only clinical manifestation of CNI in 30% of patients.[4] Liver transplant recipients seem to developed these lesions earlier after transplantation than other organ transplant recipients. Their median time to onset was 9 days versus 28 days in renal transplant recipients.[4] The respective times of onset in our cohort were 10 and 14 days, respectively. There is a report in which the sixth nerve palsy resolved at 24 to 48 hours after CsA withdrawal.[5] It is conceivable that metabolic abnormalities caused by transplantation and alteration of the blood-brain barrier may render liver transplant recipients more vulnerable to leukoencephalopathy in the early posttransplant period.[4] The mechanisms and pathophysiology of the lesions have not been precisely defined. Nevertheless, a number of factors have been proposed to be causally associated with leukoencephalopathy: abnormal CsA metabolism due to hepatic dysfunction or hypocholesterolemia, which may lead to an increased free, unbound fraction of CsA and, therefore, greater availability of this highly lipophilic drug to the brain.[6] Some workers have

postulated that endothelial damage plays a role; the release of endothelin may lead to labile blood pressure and vasospasm.[7] In addition, thrombotic microangiopathy may lead to microvascular damage.[8] Hypertension, which has been suggested as a primary cause of the brain changes, has been associated with increased sympathetic neural activation.[9] A direct neurotoxic effect of CsA on astrocytes has also been described.[10]

Increased CsA or tacrolimus levels have been reported in 61% of patients with leukoencephalopathy, although in about 50% of cases this disorder is seen despite therapeutic drug levels.[4] Cerebrospinal fluid examination may demonstrate increased protein in approximately one fourth of cases.[4]

T2-weighted MRI is the diagnostic procedure of choice, because of its superior ability to display white matter.[3] Subcortical and deep white matter changes have been the most commonly described alterations. The lesions of CsA toxicity predominate in four major regions of the cerebral hemispheres: occipital poles (posterior reversible leukoencephalopathy); parietal region; frontoparietal junction; and inferior temporo-occipital junction. This pattern corresponds to the wathershed zones between main branches of cerebral arteries.[11] The watershed distribution suggests that local brain-blood flow is reduced; a blood vessel or arterial process renders the boundary zones between major arterial territories most vulnerable.

Two entities deserve particular mention in the differential diagnosis. Progressive multifocal leukoencephalopathy associated with papovavirus infection is a late occurring lesion that follows a relentlessly progresive course, resulting in death within several months of the onset of disease. On MRI it often appears as asymmetric lesions in the parieto-occipital white matter producing a mass effect.[12] The other entity is herpes virus 6 (HHV-6). encephalitis. Although we did not perform serology in our cases, usually these patients generally have extraneural evidence of HHV-6 infection.[13] Management of leukoencephalopathy can be achieved by CNI dose reduction or replacement with rapamycin or everolimus.[14]

In conclusion, a transplanted patient receiving CNIs who displays neurological alterations must be primarily considered in the differential diagnosis to have drug toxicity besides ruling out a infectious etiology. An essential tool is the MRI. Herein we have also demonstrated the remarkable reversibility of symptoms upon withdrawal of change in the drug.

REFERENCES

1. Cilio MR, Danhaive O, Gadisseux JF, Otte JB, Sokal EM, et al: Unusual cyclosporin related neurological complications in recipients of liver transplantation. Arch Dis Child 68:405, 1993

2. Bonham CA, Dominguez EA, Fukui MB, et al: Central nervous system lesions in liver transplant recipients: prospective assessment of indications for biopsy and implications for management. Transplantation 66:1596, 1998

3. Filley CM, Kleinschmidt-DeMasters BK: Toxic leukoencephalopathy. N Engl J Med 345:425, 2001

4. Singh N, Bonham A, Fukui M: Immunosuppressive associated leukoencephalopathy in organ transplant recipients. Transplantation 69:467, 2000

5. Openshaw H, Slatkin NE, Smith E: Eye movement disorders in bone marrow transplant patients on cyclosporin and ganciclovir. Bone Marrow Transplant 19:503, 1997

6. De Groen PC, Aksamit AJ, Rakela J, et al: Central nervous system toxicity liver transplantation: the role of cyclosporin and cholesterol. N Engl J Med 317:861, 1987

7. Zoja C, Furci L, Ghilardi F, et al: Cyclosporine-induced endothelial cell injury. Lab Invest 55:455, 1986

8. Bartynski WS, Grabb BC, Zeigler Z, et al: Watershed imaging features and clinical vascular injury in cyclosporin-A neurotoxicity. J Comput Assist Tomogr 21:872, 1997

9. Mark AL: Cyclosporine, sympathetic activity and hypertension. N Engl J Med 323:673, 1990

10. Reyes J, Gayowski T, Fung J, et al: Expressive dysphasia possibly related to FK-506 in two liver transplant recipients Transplantation 50:1043, 1990

11. Bartynski W, Zeigler Z, Spearman P, et al: Etiology of cortical and white matter lesions in cyclosporin-A and FK-506 neurotoxicity. AJNR Am J Neuroradiol 22:1901, 2001

12. Bronster DJ, Lidov MW, Wolfe D, et al: Progressive multifocal leukoencephalopathy after orthotopic liver transplantation. Liver Transpl Surg 6:371, 1995

13. Paterson DL, Singh N: Can a herpes virus infection mimic tacrolimus associated neurotoxicity recipients? Ann Neurol 41:270, 1997

14. Forgacs B, Merhav HJ, Lappin J, et al: Successful conversion to rapamycin for calcineurin inhibitor-related neurotoxicity following liver transplantation. Transplant Proc 37:1912, 2005