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 who received a cadaveric kidney transplant using immunosuppression with 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 who received a cadaveric kidney transplant with CsA and prednisone. As a result of gouty arthritis of the ankle, azathioprine was replaced with CsA to allow the addition of allopurinol. Two weeks later he developed confusion and personality changes. The third case is a 16-year-old man who received an 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 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 a 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 fluoroquinolones 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...
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.

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 develop 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 vaso-
spasm. In addition, thrombotic microangiopathy may lead to microvascular damage. Hypertension, which has been 
suggested as a primary cause of the brain changes, has been 
associated with increased sympathetic neural activation. A 
direct neurotoxic effect of CsA on astrocytes has also been 
described.

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. Cerebrospinal fluid examination may demonstrate 
increased protein in approximately one fourth of cases.

T2-weighted MRI is the diagnostic procedure of choice, 
because of its superior ability to display white matter.

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 leukoen-
cephalopathy); parietal region; frontoparietal junction; and 
inferior temporo-occipital junction. This pattern corresponds 
to the watershed zones between main branches of cerebral 
arteries. 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 differen-
tial diagnosis. Progressive multifocal leukoencephalopathy 
associated with papovavirus infection is a late occurring 
lesion that follows a relentlessly progressive 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. 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.

Management of leukoencephalopathy can be achieved by 
CNI dose reduction or replacement with rapamycin or 
everolimus.

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

REFERENCES

cipients of liver transplantation. Arch Dis Child 68:405, 1993
nervous system lesions in liver transplant recipients: prospective 
assessment of indications for biopsy and implications for manage-
ment. Transplantation 66:1596, 1998
3. Filley CM, Kleinschmidt-DeMasters BK: Toxic leukoenceph-
4. Singh N, Bonham A, Fukui M: Immunosuppressive associ-
ated leukoencephalopathy in organ transplant recipients. Trans-
plantation 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
system toxicity liver transplantation: the role of cyclosporin and 
endothelial cell injury. Lab Invest 55:455, 1986
features and clinical vascular injury in cyclosporin-A neurotoxicity. 
J Comput Assist Tomogr 21:872, 1997
9. Mark AL: Cyclosporine, sympathetic activity and hyperten-
possibly related to FK-506 in two liver transplant recipients. Trans-
plantation 50:1043, 1990
cortical and white matter lesions in cyclosporin-A and FK-506 
focal leukoencephalopathy after orthotopic liver transplantation. 
13. Paterson DL, Singh N: Can a herpes virus infection mimic 
tacrolimus associated neurotoxicity recipients? Ann Neurol 41:270, 
1997
to rapamycin for calcineurin inhibitor-related neurotoxicity follow-
ing liver transplantation. Transplant Proc 37:1912, 2005