

## Brief Report

# Severe Central Nervous System Toxicity After Chronic Treatment with Cyclosporine

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**Summary:** Severe neurologic complications following treatment with cyclosporine are uncommon. They tend to occur during the first month of treatment and disappear after withdrawal or reduction of the dose of the drug. We report the case of a man who underwent a liver transplantation and subsequently developed severe central nervous system toxicity. After two years receiving cyclosporine, he presented with a brachial monoparesis and a complex visual disturbance. Symptoms slowly worsened during four months. On admission, he had confusion and seizures. Multiple areas of T2 prolongation, located in cerebral white matter, were seen on magnetic resonance imaging (MRI). Symptoms partially improved after cyclosporine withdrawal, but brain lesions shown on MRI persisted in serial imaging studies after two years of follow-up. We discuss the mechanisms that have been proposed to explain this clinical picture. Severe cyclosporine-associated neurotoxicity can also occur after chronic administration, even with serum levels in therapeutic range. **Key Words:** Cyclosporine—Nervous system diseases, chemically induced—Liver transplantation—Magnetic resonance imaging

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Cyclosporine (CsA) is a potent immunosuppressive drug. At present, it is mainly used following bone marrow and organ transplantation, and its administration is considered to be one of the most important factors accounting for the increasing survival in these patients (1). Occasionally, CsA therapy is limited by adverse side-effects. High blood pressure and renal and hepatic toxicity are the most frequent (2). Neurologic complications are less common, occurring in 10–25% of patients (3,4). Although also described following renal (5), cardiac (6,7), and bone marrow (3,8) transplantation, neurologic side-effects seem to be more frequent following liver transplantation (1,2,4–6,9–11). Tremor and seizures are the commonest features (12). Generally, neurotoxicity appears during the first

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month of treatment and diminishes upon CsA withdrawal or reduction of the dose (6). We report the case of a man with severe central nervous system (CNS) toxicity following two years of treatment with CsA and subsequently a partial improvement after withdrawal of the drug.

#### CASE REPORT

A 53-year-old caucasian man, with a history of diabetes mellitus and primary hepatocarcinoma on a cirrhotic postnecrotic liver, underwent a liver transplantation in 1988. He never had any signs of neurologic disturbance prior to liver transplantation. On admission, immunosuppressive therapy included an oral daily dose of 40 mg of prednisone, 100 mg of azathioprine, and 60 mg of CsA. He was admitted to our hospital in November 1990 because of two generalized seizures with focal onset. During the previous four months he had developed a brachial monoparesis that slowly progressed up to the admission date. Simultaneously, he developed a fluctuating complex visual disturbance that included loss of visual acuity, visual field defects, hallucinations, and difficulty with the recognition of relatives' faces and personal objects. General physical examination did not disclose any abnormality. Blood pressure was 130/70 and temperature 36°C. The patient was somnolent with temporospatial disorientation. He had a severe left pyramidal brachial monoparesis. The seizures were treated with standard doses of i.v. phenytoin followed by an oral daily dose of 300 mg.

Blood count and determination of serum electrolytes, creatinine, total protein, albumin, triglycerides, cholesterol, phosphorus, uric acid, and total bilirubin were normal. (plasmatic osmolarity 282 mmol/L, serum glutamic-oxaloacetic transaminase (SGOT) 65 UI/L, serum glutamic-pyruvic transaminase (SGPT) 68 UI/L, alkaline phosphatase 157 UI/L, blood glucose 7.10 mmol/L). Chest x-ray, electrocardiogram (ECG), and abdominal ultrasonographic examination were normal. Serum CsA was 365 ng/ml, as determined by radioimmunoassay (normal range 250–600 ng/ml). Cerebrospinal fluid (CSF) examination was normal. CSF cultures for bacteria, fungi, and viruses and CSF detection of antibodies against common viruses were negative. Computed tomography (CT) revealed a nonenhancing area of hypoattenuation in the right occipital white matter. A visual field examination with Goldman perimetry the following day revealed an extensive defect that preserved only both right lower quadrants. Visual acuity was 20/200 in both eyes. An electroencephalogram (EEG) showed a diffuse background slowing pattern, predominantly over the right posterior regions, that improved with alerting. An MRI performed after three days showed areas of T2 prolongation in the white matter of both cerebellar hemispheres, right frontal, and occipital lobes bilaterally, predominantly over the right one (Fig. 1).

CsA was withdrawn because the clinical picture and the imaging findings suggested CsA neurotoxicity. After 48 h, mental status was normal and hallucinations had disappeared. The visual disturbance slowly improved; six months later the visual acuity was 20/40 in both eyes without any visual field defect. The brachial monoparesis also improved, but to date a slight distal weakness remains. Two months later, brainstem auditory-evoked potentials revealed an alteration of the

FIG. 1. Axial spin-echo T<sub>2</sub>-weighted MR images (TR 2000, TE 100), 3 days after admission, show high signal intensity in occipital white matter.



morphology and latency of waves III and IV. Visual-evoked potentials showed a severe reduction of the amplitude of the evoked response and a slight pathologic prolongation of the wave latency, indicating a postchiasmal pathology. Four serial MRI performed during a two-year follow-up period did not reveal any change in the lesions.

#### DISCUSSION

Leucoencephalopathy (2-4,6-8,10) is the most severe neurologic complication associated with CsA. The pathogenesis of the cerebral white matter changes is unclear. De Groen et al. (4) have found a correlation with low serum level of cholesterol. As CsA is a lipophilic drug, hypocholesterolemia can increase serum level of CsA. It has also been proposed that the neurotoxicity could be caused by CsA metabolites (13). Walker and Brochstein (12) have defined two different clinical syndromes. One includes tremor and ataxia as the main features along with other symptoms like paraparesis, quadriparesis, confusion, or depression. These episodes tend to appear subacutely after prolonged CsA therapy with a mean of two months (3,8). The other syndrome consists of confusion and cortical blindness, with seizures and focal symptoms as other possible features. Temporal onset is more acutely within the first weeks of CsA therapy (2,4,6,7,10). Cranial CT usually reveals disseminated areas of hypoattenuation in the white matter which appear as T2 prolonged areas. The occipital region is the most frequently affected one, and therefore visual disturbance is a common component of this syndrome (6). Cerebral edema with axonal swelling or transient ischemia may be likely mechanisms because many of the cerebral lesions are reversible (4,6). Alternatively, some pathological studies have revealed CNS demyelination (10).

However, other postmortem findings have been nonspecific, with reactive astrogliosis affecting white matter and occasionally extending into overlying cortex with associated neuronal loss (11).

Clinical and radiologic differential diagnosis of the case we report includes several possibilities. Infectious disease and metastatic or primary tumor in an immunosuppressed patient can be excluded with the complementary studies and the clinical evolution of the patient. A vascular origin can also be excluded because the illness took several months with a progressive course to fully develop and the lesions shown on MRI do not correspond to a vascular territory. It is unlikely that this symptomatology could be explained as the first attack of Multiple Sclerosis or a progressive multifocal leukoencephalopathy because of patient age, temporal onset, and stability in the cerebral changes without any new lesions during two years of follow-up. In our opinion, the most likely etiology is a CsA toxic damage of CNS white matter. The clinical picture is very similar to cases described previously (2,4,6,7). The withdrawal of CsA was followed by a nearly complete recovery of the neurologic disfunction. However, this case has some peculiarities. The symptomatology began after a two-year treatment period. To our knowledge, this is the longest period reported between the onset of CsA therapy and the beginning of a toxic CsA leukoencephalopathy of these characteristics. Moreover, the CsA level was in the therapeutic range and the CsA dose had not been modified previously. Although most of the patients reported with this neurologic picture have high serum levels of CsA (2,5), other cases do not present this correlation (7). Chronic exposure to CsA or its metabolites of a previously injured CNS could be a reasonable explanation. Because of the satisfactory evolution of the neurologic symptoms and of the liver transplantation we did not perform a pathological study nor did we reintroduce CsA.

We conclude that severe CNS toxicity associated with CsA may appear after chronic use of the drug, even with normal serum CsA level. Early recognition of this complication is of paramount importance because brain damage may be permanent.

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