Irreversible Dementia following Ciclosporin Therapy in a Renal Transplant Patient

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Dear Sir,

Ciclosporin A (CS) associated central nervous system toxicity was first described in 1982 [1]. Since then, reports have increased to such an extent that convulsions are considered to be present in 1.5% of recipients of renal transplants who were treated with this drug [2]. The clinical picture of this neurotoxicity varies greatly and includes convulsions, paresthesia, motor spinal cord syndrome, cerebellar-like syndrome, tremors, aphasia, depression, and other signs of mental disturbance. These symptoms may be severe and may be a cause of death [3]. While all the cases described to date recovered completely following CS withdrawal, symptoms reappeared after its reintroduction [4].

We report on a case of dementia following an episode of convulsions in a renal transplant under CS which still persists 26 months after discontinuation of the drug. This 31-year-old man had a history of poliomyelitis at the age of 3 years, with residual paralysis of the lower limbs. In 1978, although no clinical symptoms were present, an EEG was performed for medicolegal reasons which showed reduced organization of cerebral waves in the left parieto-occipital zone. After 6 months the patient became uremic because of unknown nephropathy and was placed on maintenance hemodialysis.

The patient subsequently developed severe osteomalacia, characterized by bone radiotransparency, crushing of the vertebral bodies, and several spontaneous fractures. Alkaline phosphatase and parathormone levels were only slightly elevated, while calcium levels were normal. Aluminum hydroxide (8 g/day) was prescribed to control the phosphoremia. The patient underwent renal transplantation in September 1985. Because of an acute tubular necrosis, immunosuppression initially consisted in the administration of steroids and azathioprine. After recovery from ischemic damage after 3 weeks the patient was switched from azathioprine to CS. Blood levels ranged from 270 to 720 ng/ml. The patient was discharged after 5 weeks with normal graft function. Seventy days after transplantation he became confused, and 1 day later he developed seizures. The EEG showed signs of widespread damage with epileptogenic characters in the anterior projection. A Brain CT scan did not disclose any densitometric alterations; the cerebrospinal fluid was sterile with normal pressure and contained 0.5 g/l glucose, 0.3 g/l protein, and 1 cell/mm3. The patient was incapable of judging time, space, and personal relationships. He presented echolalia, rapid mood swings, and loss of sphincter control. CS levels in the cerebrospinal fluid were below the sensitivity limits of
the assay (62.5 ng/ml). The drug was substituted by azathioprine. However, only a slight improvement was obtained, mainly concerning control of diuresis and defecation. To date, the patient is still demented. Subsequent EEG and brain CT have not revealed any further changes. Hypomagnesemia has been reported to be associated with CS neurotoxicity [5], but in our patient serum and urinary magnesium levels following renal transplantation were in the normal range. Other authors have found that CS-related seizures occur most frequently in patients with an aluminum overload [6]. The most severe from of aluminum intoxication, diagnosed as dialysis dementia,

... can itself cause seizures, and this mechanism may worsen CS neurotoxicity. In addition, aluminum increases the permeability of the blood-brain barrier for neuropeptides and for some non-peptide substances and also enhances the mechanism by which a substance normally penetrates this barrier [7]. Therefore, aluminum could promote the passage of CS or its toxic metabolites into the cerebrospinal fluid. Unfortunately, we do not know the pretransplant blood aluminum levels of this patient. However, the presence of a diffuse osteomalacia with slightly increased alkaline phosphatase levels and normal calcium levels led us to suspect that an aluminum-induced bone disease may have existed. Eight months after successful renal transplantation plasma aluminum levels were within the normal range (42 µg/l), but the urinary excretion rate was still high (135 µg/day).

It is difficult to understand why CNS symptoms persisted in our patient after withdrawal of CS. However, the preexistence of minimal changes in EEG together with an aluminum overload may have enhanced the neurotoxic side-effect of CS creating a seemingly irreversible lesion.

References
