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Cyclosporine-induced parkinsonism

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Sirs: Cyclosporine A (CyA) is an immunosuppressant used to prevent rejection of solid organ transplantation as well as in the treatment of autoimmune disorders. It works by selectively inhibiting transcription of interleukin-2 (IL-2) and several other cytokines, mainly in T-helper lymphocytes.

The main side effects of CyA are nephrotoxicity and neurotoxicity. Manifestations of neurological involvement include tremor, seizures, headache, psychosis and sleep disturbances. Posterior reversible leukoencephalopathy, characterized by headache, visual disturbances, seizures, elevated blood pressure and MRI abnormalities, is also associated with CyA use [1].

Parkinsonism can develop during treatment with many drugs, but CyA is not recognized as a known precipitant. To date, only three other cases have been reported in the literature [2, 3]. We sought to describe a case of a patient who underwent bone marrow transplantation and developed parkinsonism after CyA use.

A 51-year-old male with acute lymphocytic leukemia underwent allogeneic stem cell transplantation in 2005. CyA 3 mg/kg/d was started for graft-versus-host disease prophylaxis. Two months later, he developed rest tremor and reduced facial expression followed by dysarthria, bradykinesia, rigidity, and reduced arm swing. There was no history of movement disorders nor was the patient taking any other drug associated with parkinsonism (amlodpine, omeprazol, ganciclovir, folinic acid and trimethoprim/sulfamethoxazole). The serum CyA levels were within the therapeutic range. A brain MRI showed small bilateral chronic subdural hematomas in the frontal region that were known previously and had been managed conservatively (Fig. 1). CyA was discontinued and levodopa/carbidopa 250/25 mg TID was started. Two months later, the parkinsonian signs had completely disappeared and levodopa/carbidopa was discontinued. He was started on mycophenolate mofetil 1 g/y for immunosuppression, but died 22 months after the bone marrow transplantation from recurrence of lymphocytic leukemia. During follow-up, parkinsonian features never recurred. No post mortem studies were performed.

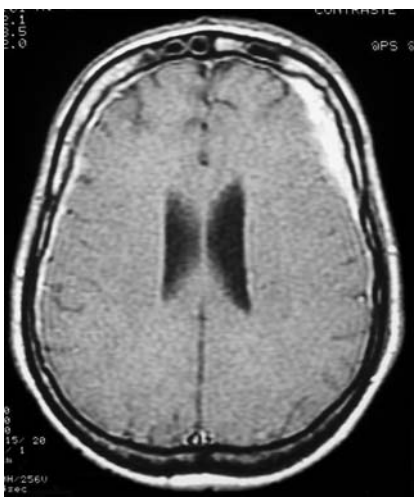

Fig. 1 T1-weighted magnetic resonance imaging showing bilateral frontal subdural hematomas

The mechanisms of CyA neurotoxicity are not completely clear. The drug is hydrophobic and would be expected to cross the blood-brain barrier (BBB), but the permeability is poor over an intact BBB. Breakdown of the barrier seems to be necessary for CyA to exert its effects in the central nervous system.

There is evidence of a functional rather than a structural effect of CyA in the basal ganglia since no lesions were observed in one autopsied case described by Wasserstein [2]. In addition, in all but one case, no basal ganglia abnormalities were observed on MRI. Possible mechanisms are a reversible drug-induced brain microangiopathy or a direct effect of CyA on neurotransmitter function. Interestingly, the development of parkinsonism does not seem to be dependent of increased serum CyA levels, since in the case described by Kim et al. [3] and ours, the levels were within the normal range.

Similar to the other cases described, our patient had a great improvement after discontinuation of CyA and low dose levodopa/carbidopa. No recurrence of parkinsonian symptoms/signs was observed during the follow-up. This suggests that the CyA-induced parkinsonism has a reversible and monophasic course and the drug does not anticipate or trigger the development of Parkinson's disease in predisposed individuals.

Previous reports of CyA-induced parkinsonism includes only one kidney [3] and two bone marrow transplant patients [2]. Munhoz et al. described an additional bone marrow transplant patient with rest tremor, bradykinesia and rigidity while on CyA therapy, but the authors could not establish a

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causal effect [4]. Parkinsonism is uncommon in the post-transplant period. Besides CyA, additional causes include antiemetics and amphotericin B [5], manganese toxicity [6, 7], demyelinating leukoencephalopathy [8] and West Nile meningoencephalitis [9].

This case should alert neurologists involved in the care of transplant patients that reversible parkinsonism is a rare side effect of CyA use. Discontinuation of the offending drug and low dose levodopa/carbidopa therapy provide neurological improvement.

Conflict of interest The authors declare no conflict of interest.

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