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CASE REPORT

CENTRAL NERVOUS SYSTEM TOXICITY OF CYCLOSPORIN A TREATMENT IN RHEUMATOID ARTHRITIS

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SUMMARY

A 35-yr-old woman with rheumatoid arthritis, receiving cyclosporin A, presented with diplopia, ptosis, loss of horizontal and vertical eye movements, dysarthria, nasal regurgitation. After differential diagnosis, cyclosporin A neurotoxicity was suspected and the treatment stopped. All side-effects were reversed with the discontinuation of the drug. Central nervous system neurotoxicity with low-dose cyclosporin A treatment was discussed.

KEY WORDS: Rheumatoid arthritis, Cyclosporin A, Neurotoxicity.

FOR many years, cyclosporin A (CsA) has been used successfully in transplantation medicine. More recently, CsA has also entered the therapeutic field of immune-mediated disorders. Multiple trials have demonstrated the efficacy of CsA in the treatment of active rheumatoid arthritis (RA) [1, 2]. Despite its well-known beneficial effects, CsA administration is associated with a number of systemic complications: nephrotoxicity, hepatotoxicity, hypertension, gum hyperplasia, hypertrichosis and neurotoxicity.

Neurotoxicity described in CsA administration is generally mild, most commonly consisting of involuntary fine tremors, headache, tinnitus and nervousness that respond to dose reduction [3]. However, more complex types of neurotoxicity, including motor and cerebellar syndromes, seizures, cortical blindness and coma, have rarely been described in bone marrow, renal and liver transplant patients [4–6].

In this case report, our aim is to emphasize awareness of possible severe neurotoxicity of CsA treatment in RA.

CASE REPORT

A 35-yr-old woman with RA for 4 yr was admitted with severe headache, tinnitus, diplopia, ptosis, reduced visual acuity, inability to walk due to loss of balance, palmar and plantar burning, and paraesthesiae, nausea, vomiting and nasal regurgitation of fluids. Her family members noted that she was unable to remember the events of previous days. With the above-mentioned symptoms, she was hospitalized for differential diagnosis of central nervous system (CNS) infection, vasculitis and CsA neurotoxicity.

In her history, she had a combination of conventional second-line drugs (i.m. gold sodium thiomalate and sulphasalazine). Because of failure of this treatment and fulminant erosive progression of the disease, CsA treatment was initiated following a 3 month wash-out period. She had been on methylprednisolone (2.5 mg/day) and CsA (150 mg/day) treatment for the last 4 months. She had no NSAID treatment in this period. During CsA treatment, hypertrichosis and gum hyperplasia were noticed. There was no clinical and laboratory evidence of nephrotoxicity and hypertension. CsA dosage was increased to 175 mg/day a week before the initiation of the above mentioned symptoms. There was no history of recent viral or bacterial infections. Physical examination showed blood pressure 130/75 mmHg, pulse rate 80/min, body temperature 37°C and weight 50 kg. She had typical hand and foot deformities of RA. Her locomotor examination revealed acute arthritis of the bilateral knee and right shoulder joints. Neurological examination revealed bilateral ptosis, loss of horizontal and vertical eye movements, dysarthria, loss of balance, and inability to stand and walk without help (Figs 1 and 2). Fundoscopic findings were normal. She was unable to remember objects when asked to recall them at 5 min. Strength, reflexes and sensory examinations were normal.

Laboratory findings were white blood cell count 6.8×10^3/l, haemoglobin 9.8 g/dl, haematocrit 30.3%, erythrocyte sedimentation rate 55 mm/h, blood iron level 43 μg/dl (60–150), total iron binding capacity 244 μg/dl (245–400). Serum ferritin levels could not be studied. Serum vitamin B_{12} and folate levels were normal. Her biochemical analysis including serum electrolytes, lipids, transaminases, serum magnesium level, creatinine, creatinine clearance and BUN were all in normal ranges. CRP: 116 mg/l (0–5), RF: 485 IU/ml (0–20), IgG: 20.13 g/l (6.5–16), IgM: 3.92 g/l (0.6–3.7). Other immunological parameters (ANA, anti-ds DNA, C_3, C_4) were normal. ANCA were not studied. The blood CsA level was measured as 36 ng/ml (50–300). Lumbar puncture revealed normal cerebrospinal fluid (CSF) pressure (100 mm CSF). Glucose and protein levels of CSF were normal, and contained two mononuclear cells/mm^3. The oligoclonal band test was found to be negative in CSF. Cultures of urine, blood and CSF were sterile. Also serological studies of serum and CSF were negative for viral and bacterial infections. Cranial computed tomography (CT) and brain stem magnetic resonance imaging (MRI) were normal. The electromyographic and nerve conduction studies were normal. The visual evoked potentials (VEP) showed long latency. In the brain stem auditory evoked potential study (BAEP), the first current was absent bilaterally. EEG was normal.

After her neurological consultation and the above-mentioned laboratory tests, CsA neurotoxicity was suspected and CsA treatment was stopped. Six days after discontinuation of CsA, she improved with regard to nausea, vomiting and fluid regurgitation. Ptosis, horizontal and vertical eye

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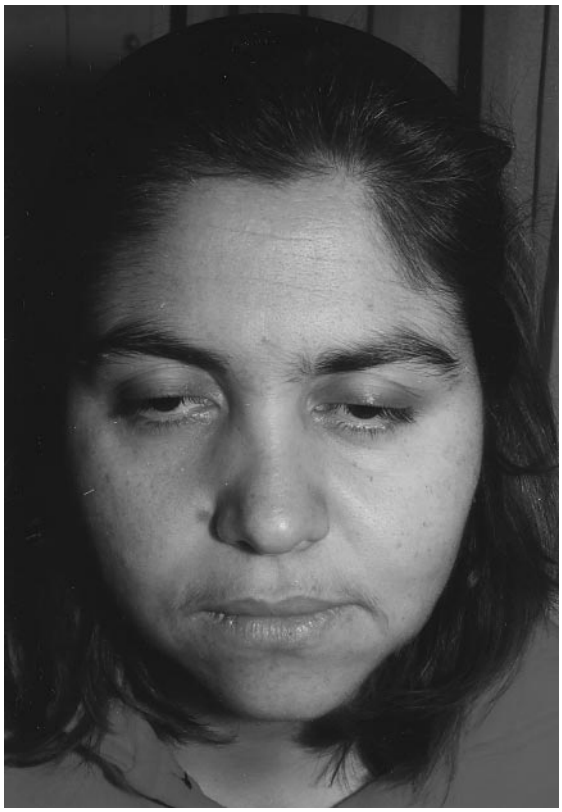

FIG. 1.—Front view of the patient with bilateral ptosis.

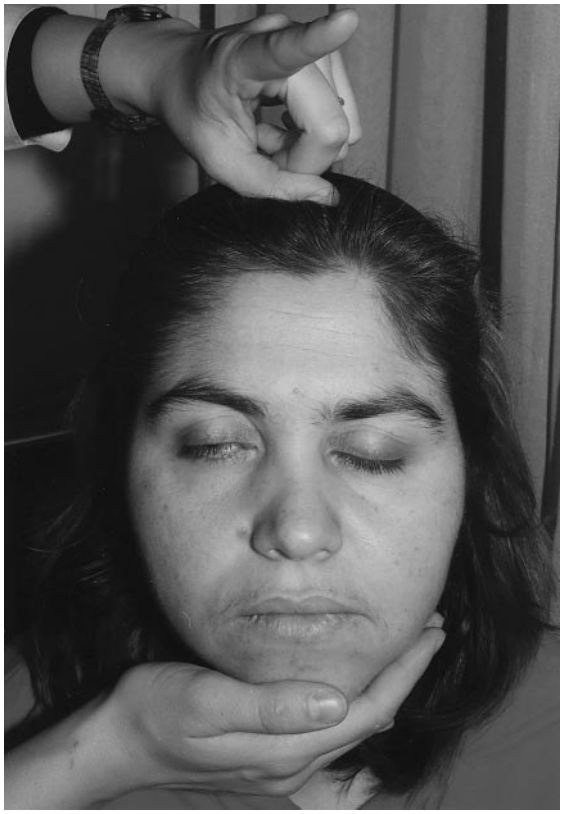

FIG. 2.—The loss of vertical eye movements.

movements resolved after 20 days. She was discharged on the 35th day with no further recurrence of mental and neurological abnormalities. Two months later, her control cranial CT and BAEP studies were normal, but her VEP study was still abnormal.

Even though CsA is not believed to cross the intact blood–brain barrier, neurological side-effects occur [7]. These side-effects are generally mild, consisting of tremor, headache, tinnitus, and rarely seizure activity [3, 5, 8–10]. More severe neurotoxicity has been reported in kidney, bone marrow, liver, lung and heart transplant patients, and one case with uveitis [4–6, 11–13]. Serious complications include encephalopathy, seizures, motor disturbances, visual disorders (cortical blindness, complex visual hallucinations), cerebellar oedema and brain stem compression. The mechanism of CsA toxicity in the CNS is unclear. Dose dependency of treatment of CsA neurotoxicity is controversial. CNS side-effects are more frequently seen in patients with high levels of CsA in plasma [6]. However, Palmer and Toto [5] reported severe neurological toxicity due to CsA with low therapeutic levels. The association of CsA neurotoxicity with concurrent high-dose methylprednisolone treatment, hypertension, hypomagnesaemia and low cholesterol levels has been presented. In CNS toxicity, white matter abnormalities have been shown on CT and MRI. In our patient, the form of clinical presentation and the exclusion of other CNS disorders, including those of inflammatory and infectious aetiology, support the CsA neurotoxicity. None of the predisposing factors (low magnesium and cholesterol levels, high-dose methylprednisolone therapy, hypertension and high blood levels of CsA >300 ng/ml) were noticed in our patient. The role of the anaemia, as in our patient, in CsA neurotoxicity is as yet unknown. Groen *et al*. [6] have found no correlation between anaemia and CsA neurotoxicity in their cases. Although white matter changes in MRS have been described occasionally, CsA neurotoxicity with normal MRS, as in our case, has also been reported [14]. In our patient, VEP and BAEP studies indicated the involvement of cranial nerves II and VIII. In the literature, vestibular and cochlear toxicity have been described with CsA levels. Yocum *et al*. [3] reported neurotoxicity (hyperaesthesiae, tingling, nervousness, tinnitus and tremor) that led to the withdrawal of the two patients with RA receiving low-dose CsA therapy. Total improvement of clinical status following the withdrawal of CsA treatment suggested CsA CNS neurotoxicity in our patient with RA.

In conclusion, greater awareness of severe and complex CNS neurotoxicity, even with low-dose CsA treatment, in RA is of the utmost importance.

REFERENCES

1. Weinblatt M, Helgott S, Coblyn J *et al*. The effects of cyclosporin A on Eicosanoid excretion in patients with rheumatoid arthritis. Arthritis Rheum 1991;34:481–5.
2. Tugwell P, Bombardier C, Gent M *et al*. Low dose Cyclosporin versus placebo in patients with rheumatoid arthritis. Lancet 1990;335:1051–5.
3. Yocum DE, Klippel HJ, Wilder RL *et al*. Cyclosporin A treatment in severe refractory rheumatoid arthritis. Ann Intern Med 1988;109:863–9.
4. Nussbaum ES, Maxwell RE, Bitterman PB *et al*. Cyclosporine A toxicity with acute cerebellar edema

and brainstem compression. J Neurosurg 1995;82: 1068–70.
5. Palmer BF, Toto RD. Severe neurologic toxicity induced by Cyclosporine A in three renal transplant patients. Am J Kidney Dis 1991;XVIII:116–21.
6. Groen PC, Aksamit AJ, Rakela J *et al*. Central nervous system toxicity after liver transplantation. N Engl J Med 1987;317:861–6.
7. Kahan BD. Cyclosporine. N Engl J Med 1989;321:1725–38.
8. European Multicentre Trial Group. Cyclosporin in cadaveric renal transplantation: one year follow up of a multicentre trial. Lancet 1983;2:986–9.
9. Rubin AM, Kang H. Cerebral blindness and encephalopathy with Cyclosporin A toxicity. Neurology 1987;37: 1072–6.
10. Atkinson K, Biggs J, Darveniza P *et al*. Spinal cord and cerebellar like syndromes associated with use of Cyclosporine in human recipients of allogeneic marrow transplants. Transplant Proc 1985;17:1673–5.
11. Hughes RL. Cyclosporine-related central nervous system toxicity in cardiac transplantation. N Engl J Med 1990;323:420–1.
12. Noll RB, Kulkarni R. Complex visual hallucinations and Cyclosporine. Arch Neurol 1984;41:329–30.
13. Monteiro I, Pinto AJ, Rocha N *et al*. Case report: Cyclosporin A-induced neurotoxicity. Br J Radiol 1993;66:271–2.
14. Atkinson K, Biggs J, Darveniza P *et al*. Cyclosporin-associated central nervous system toxicity after allogeneic bone marrow transplantation. Transplantation 1984;38:34–7.