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Dysarthria and cerebellar ataxia: late occurrence of severe neurotoxicity in a liver transplant recipient

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Abstract. Neurological complications of cyclosporin (CyA) therapy are frequent, usually occurring within the 1st month after transplantation. Though leukoencephalopathy is one of them, it is rarely documented. Here we report the case of an anti-HCV-positive patient with cirrhosis who underwent liver transplantation and developed cyclosporin-induced leukoencephalopathy. The presenting symptoms were dysarthria, difficulty walking, and dysphagia. They were first noted 6 months after transplantation in association with an episode of recurrent HCV acute hepatitis. White matter abnormalities were evident on computed tomography (CT) scanning and magnetic resonance (MR) imaging. This condition improved to some degree after cyclosporin withdrawal. To our knowledge this is the second reported case of CyA neurotoxicity occurring late after liver transplantation. Moreover, the association with acute hepatitis suggests the possibility of graft dysfunction as a contributing and triggering factor.

Key words: Neurotoxicity, liver transplantation, cyclosporin – Liver transplantation, neurotoxicity, cyclosporin – Cyclosporin, neurotoxicity, liver transplantation

Introduction

Leukoencephalopathy is a rarely documented neurological manifestation of cyclosporin toxicity characterized by scattered white matter changes and various presenting symptoms such as confusion, cortical blindness, visual hallucinations, and para- and quadriparesis, usually occurring early after transplantation [6]. We report here on a case of CyA-related leukoencephalopathy that appeared late after liver transplantation and with an unusual clinical picture.

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Case report

A 52-year-old man with hepatitis C virus (HCV)-related cirrhosis underwent orthotopic liver transplantation in November 1990 on account of a small, unresectable hepatocellular carcinoma. The cirrhosis was relatively well compensated (Child-Pugh A 6), and the patient had been working until the day before the operation. He had signs of severe portal hypertension, with prominent esophageal varices that had bled once and marked splenomegaly.

The postoperative course was remarkably smooth and the patient was discharged 19 days after the operation in good health and with a normal biochemistry. In accordance with our immunosuppressive protocol, the patient was treated with 1 g methylprednisolone endovenously (ev) given intraoperatively. Postoperatively, he received 200 mg methylprednisolone on day 1, tapered to 20 mg after 1 week. He was converted to oral prednisone as soon as food intake was possible (day 6), and this was tapered to 0 mg over a 3-month period. Rabbit antithymocyte globulin (RATG Fresenius), 3 mg/kg per day, was given for the first 5 postoperative days in addition to azathioprine, 2 mg/kg per day, for the 1st month. CyA was started on day 3 (1 mg/kg per day ev) and converted to oral intake on day 8. Blood cyclosporin levels (RIA monokit) ranged between 80 and 230 ng/ml throughout the follow-up period.

Five months after the transplantation, liver enzymes started to rise with alanine transferase (ALT) peaking at 260 U/l. A liver biopsy was performed on day 190 that showed lymphocytic infiltrate in the portal tracts and sparse periportal acidophilic bodies. These histological abnormalities were attributed to recurrent HCV infection. In our experience nearly 50% of HCV ELISA 2-positive recipients develop post-transplantation hepatitis.

At that time a mild dysarthria was noted. A brain CT scan and Doppler ultrasound were normal. The cyclosporin level was 170 ng/ml. No changes in CyA pharmacokinetics occurred in conjunction with recurrent HCV disease and CyA levels had never been above 200 ng/ml in the preceding 4 weeks. Serum cholesterol was 214 mg/100 ml (normal values 160–220 mg/100 ml). The magnesium level was within normal limits. Serum creatinine was 1.5 mg/100 ml (Table 1). No additional medication that could have helped induce CyA neurotoxicity was used. Further outcome was characterized by progressive deterioration of dysarthria, difficulty walking and dysphagia.

On day 225 a second CT scan showed slight hypodense changes in the white matter. Magnetic resonance (MR) imaging of the head revealed hyperintensities on DP and T2 and hypointensities in T1 weighted images in the white matter that were particularly evident in the cerebellar area (Fig. 1). Other investigations performed at that

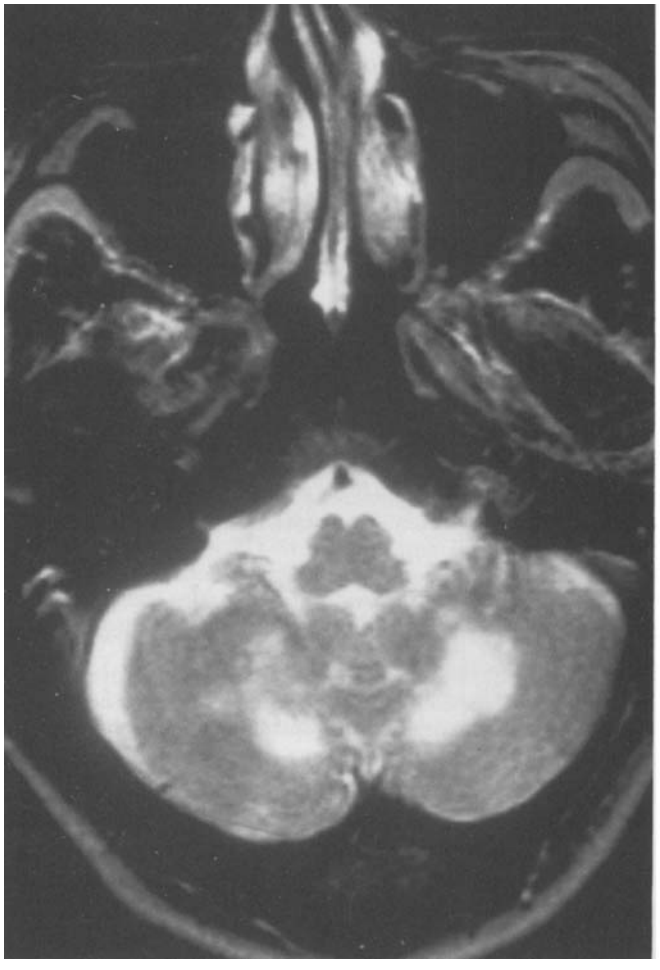

Fig. 1. Magnetic resonance imaging (MRI) T_2 weighted sequences (day 225). Hyperintensities of white matter are evident in the cerebellar area

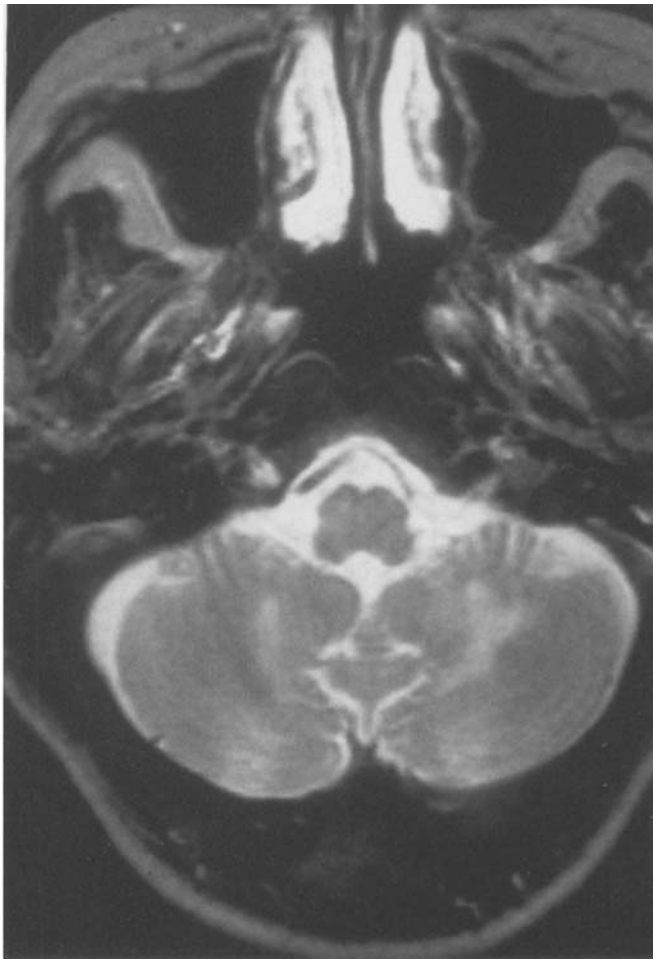

Fig. 2. Magnetic resonance imaging (MRI) T_2 weighted sequences (day 255) 4 weeks after CyA withdrawal. Hyperintensities of the white matter are dramatically reduced

time included examination of cerebrospinal fluid, which was normal, and electroencephalography, which showed diffuse slowing.

Because of the persistence of neurological symptoms, CyA was discontinued (day 220) and the patient returned to an immunosuppressive regimen consisting of prednisone, 0.5 mg/kg per day, and azathioprine, 2 mg/kg per day.

During the following 4 weeks a slow neurological amelioration was noted: the patient's speech became much less affected and the ataxic gait less evident, while dysphagia completely disappeared. A second MR performed at this time documented a marked amelioration, particularly of the cerebellar lesions (Fig. 2).

On day 290 the patient had to be readmitted because of weakness and jaundice. Hepatic function tests were abnormally elevated (ALT 250 U/l, AST 160 U/l, bilirubin 8 mg/100 ml). A second liver biopsy was consistent with the diagnosis of acute hepatitis and was interpreted as ongoing recurrent HCV.

As hepatocellular cholestasis progressed over the following weeks to an extent that seemed disproportionate to the severity of hepatitic histologic appearance (bilirubin 15 mg/100 ml), a possible toxic effect induced by azathioprine was suspected. This suspicion was largely based upon clinical judgment. Azathioprine was then withdrawn and the patient resumed taking CyA at a low dosage (50–100 ng/ml) starting on day 320. Unfortunately, neurological symptoms worsened over the following 2 weeks, with no improvement shown by liver function tests. The patient returned to the previous regimen on day 340. Readministration of azathioprine, 1.5 mg/kg per day, did not affect liver biochemistry. In the following 2 weeks a retrograde cholangiography and a CT scan of the abdomen showed a bile collection compressing the common bile duct. The collection was drained and bilirubin was reduced to 5 mg/100 ml.

Discussion

Although neurological manifestations of CyA have been recognized for several years, the exact role of CyA neurotoxicity is still not well defined [1–3, 5, 7, 8, 11]. Other conditions such as hypertension, graft dysfunction, high-dose steroids and other comedications, are often present as well, and each of these may affect the transplant recipient as well. It has also been reported that hypomagnesemia and hypocholesterolemia are often associated with CyA and may thus represent important cofactors in its neurotoxicity [5, 9].

Other authors [6, 10] have observed that CyA toxicity in the central nervous system is much more common among recipients of liver transplants than among recipients of other organs. Tollemar et al. [10] report that 35 % of their liver transplant patients had central nervous system effects in varying degrees after transplantation, a proportion similar to that reported by others. Compare this to 0.5 % for renal, bone marrow, or pancreatic recipients. It

Table 1. Biochemistry at the time of neurological complications

	Day 190 (first episode)	Day 320 (second episode)
CyA (WBTL ng/ml)	170	70
Creatinine (mg/dl)	1.5	1.2
Magnesium (mmol/l)	1	1
Glycemia (mg/dl)	80	90
Natremia (mmol/l)	135	140
Prothrombin time (control 12–14 sec)	12	15
Bilirubin (mg/dl)	1	15
SGOT (U/l)	260	320
SGPT (U/l)	120	180

has been suggested that poor liver function before transplantation may damage the brain-blood barrier and facilitate CyA neurotoxicity.

With regard to the clinical aspects, the presenting symptoms of encephalopathy are extremely variable, being related to the different areas of the white matter that have been affected. In nearly all cases, these symptoms appear early after transplantation. Our patient had none of the aforementioned symptoms. Cirrhosis was well compensated. He had a very smooth postoperative course. He did not suffer from hypertension. CyA levels were always found to be within normal limits (150–250 ng/ml). Nor was he receiving any other medication at the time.

Neurological symptoms appeared 6 months after transplantation and 3 months after steroid withdrawal. To our knowledge, only one other case of severe CyA neurotoxicity appearing late after transplantation [4] has been reported. Neurological symptoms in our patient partially regressed after CyA withdrawal. Resumption of CyA at a low dosage was associated with a rapid, recurrent neurotoxicity. Finally, it is worth noting that neurological symptoms were first observed in association with an episode of hepatitis. It can be postulated that graft dysfunction may have been a contributing and triggering factor.

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