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Speech disorder related to tacrolimus-induced pontine myelinolysis after orthotopic liver transplantation

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Dear Editors:

Speech disorders may occur after orthotopic liver transplantation (OLT) due to the neurotoxicity of immunosuppressive drugs [1, 2, 3, 4, 5, 6, 7, 8]. The clinical picture may vary, ranging from mild dysarthria to mutism, and there is no clear anatomo-clinical relationship. Most cases show no evidence of lesions upon cerebral magnetic resonance imaging (MRI). Cyclosporine-induced speech disorders associated with cerebral lesions were found in only two cases in which MRI revealed a lesion in the pons displaying the characteristics of central pontine myelinolysis (CPM) [2, 3]. Tacrolimus-induced speech disorders have been reported less frequently [4, 5, 6] and in these cases no evidence of cerebral lesions were found at MRI. We describe a liver transplant patient exhibiting a speech disorder associated with high levels of tacrolimus and pontine demyelinating lesions at MRI.

A 54-year-old male weighing 70 kg underwent OLT on May 18, 2001 for end-stage cirrhosis secondary to alcohol abuse, complicated by the development of a hepatocellular carcinoma. He had diabetes mellitus type II and a congenital atrophic left kidney. Two months before OLT, neurological assessment showed mild bradykinesia, the electroencephalogram (EEG) was generally slow and disorganized, and cerebral MRI was normal. The patient had no history of variceal bleeding, spontaneous bacterial peritonitis, surgical procedures, or blood transfusions. At entry, the patient had Child score C10, the creatinine level was 2.3 mg/dl, and the sodium level was normal (140 mEq/l). Liver transplantation was performed via piggy-back technique; during the operation the patient was hemodynamically stable and there was no electrolyte imbalance.

The donor was an 82-year-old female, the ischemic time was less than 6 h, and after transplantation the graft started to produce bile immediately. The immunosuppressive protocol was as follows: 0.5 g methylprednisolone was administered intravenously during reperfusion of the graft, and daclizumab, a monoclonal antibody against the IL-2 receptor, was administered at 2 mg/kg after hepatectomy. Tacrolimus was started nearly 5 h after the surgical procedure at a dosage of 0.075 mg/kg. It was given orally through the nasogastric tube, and the dosage was adjusted with the purpose of maintaining a serum tacrolimus level (STL) of between 10 and 20 ng/ml. On day 7, daclizumab was repeated at a dosage of 1 mg/kg and the T-tube was closed after normal colangiography performed through the tube. The STL was within the normal range until day 5, when, without any change in

therapy, high levels (28–30 ng/ml) were found. The daily dose was reduced, resulting in a normalization of STL. During the first 10 days no general and neurological complications occurred, and the liver function tests improved progressively. On May 31 the patient developed severe dysarthria, mild dysphagia, and mild ataxia, with a STL of 19 ng/ml.

Cerebral MRI showed irregular lesions of the pontine region, with a hyperintense signal in T2-weighted images and a hypointense signal in T1-weighted image (Fig. 1). No electrolytic abnormalities were found, in particular no changes in natremia. Hypothesizing tacrolimus neurotoxicity, the immunosuppressive protocol was switched to cyclosporine microemulsion (Neoral) and steroids.

Within the following days, the neurological picture improved progressively with the disappearance of dysphagia and a remarkable reduction of speech impairment and ataxia. One month after OLT, cerebral MRI was unchanged. Ten months later, the patient exhibited only slight dysarthria and no MRI abnormalities (Fig. 2).

This patient experienced severe dysarthria after OLT, associated with mild dysphagia and ataxia. The neurological picture can reasonably be attributed to tacrolimus toxicity for several reasons: (1) the finding of high serum levels of tacrolimus just before the onset of neurological symptoms, (2) the prompt improvement of clinical symptoms after discontinuation of the drug, and (3) the lack of any other potential causes. The choice of Neoral as alternative to tacrolimus was based on its availability at our transplant center and on the fact that our experience and previous studies (for a review see [9]) suggest conversion from tacrolimus to a cyclosporine-based regimen to be associated with an improvement in tacrolimus-related symptoms in recipients of various transplanted organs, without the appearance of adverse effects. In our patient, MRI disclosed damage at the center of the basis pontis large enough to affect descending motor pathways on both sides, justifying symptoms of pseudobulbar palsy.

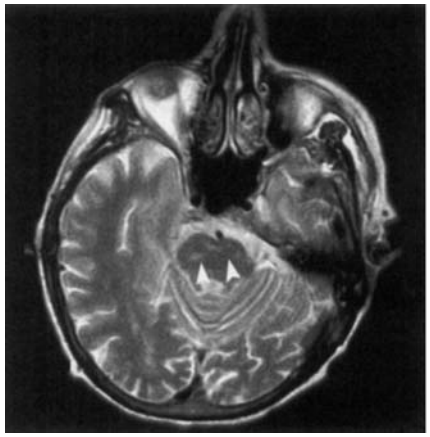

Fig. 1 Cerebral magnetic resonance imaging: irregular lesions of the pontine region with hyperintense signal in T2-weighted images and hypointense signal in T1-weighted image (see *white arrows*)

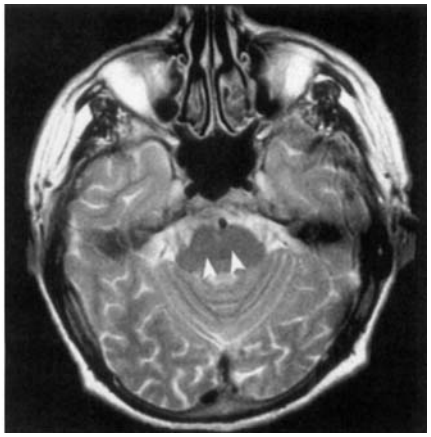

Fig. 2 Cerebral magnetic resonance imaging: normal (see *white arrows*)

Speech disorders are a known complication of immunosuppressive agents in liver transplant patients, especially during cyclosporine therapy, but the anatomo-clinical relationship remains unclear. Usually, the radiological appearance of cyclosporine and tacrolimus neurotoxicity is that of extra-pontine demyelination. However, in some patients with cyclosporine-induced speech disorders, a radiological picture of typical CPM was found [1, 2, 3]. In the few reported patients exhibiting speech disorders related to tacrolimus, no consistent lesions were found at MRI. Our case represents the first example of a speech disorder related to tacrolimus-induced pontine myelinolysis. It is probable that prompt withdrawal of tacrolimus prevented the occurrence of a more severe neurological feature of CPM in our patient such as, for example, locked-in syndrome.

This observation reinforces the idea that demyelinating pontine lesions may be seen in liver transplant patients in the absence of sodium changes and that immunosuppression may be involved in their pathogenesis [10]. The mechanisms of immunosuppressant neurotoxicity are far from clear, but perfusional transient cerebral damage could play a role [11]. This may explain the usual reversibility of both clinical symptoms and neuroradiological abnormalities.

In conclusion, our observation provides information on possible anatomo-clinical correlations in speech disorders occurring after liver transplantation, suggesting a crucial role of pontine region damage in their genesis by means of interruption of cortico-bulbar fibers. Early recognition of such disorders and prompt withdrawal of the immunosuppressive agent may reverse the neurological picture.

References

1. Guarino M, Stracciari A. Speech disorders in transplant recipients taking cyclosporine. Neurology 2000; 54: A412
2. Rodriguez J, Benito-Leon J, Molina JA, Ramos A, Bermejo F. Central pontine myelinolysis associated with cyclosporin in liver transplantation. Neurologia 1998; 13: 437
3. Bird GL, Meadows J, Goka J, Polson R, Williams R. Cyclosporin-associated akinetic mutism and extrapyramidal syndrome after liver transplantation. J Neurol Neurosurg Psychiatry 1990; 53: 1068
4. Bronster DJ, Gurkan A, Buchsbaum MS, Emre S. Tacrolimus-associated mutism after orthotopic liver transplantation. Transplantation 2000; 70: 979
5. Boeve BF, Kimmel DW, Aronson AE, de Groen PC. Dysarthria and apraxia of speech associated with FK-506 (tacrolimus). Mayo Clin Proc 1996; 71: 969
6. Reyes J, Gayowski T, Fung J, Todo S, Alessiani M, Starzl TE. Expressive dysphasia possibly related to FK506 in two liver transplant recipients. Transplantation 1990; 50: 1043
7. Bronster DJ, Boccagni P, O'Rourke M, Emre S, Schwartz M, Miller C. Loss of speech after orthotopic liver transplantation. Transpl Int 1995; 8: 234
8. Valldeoriola F, Graus F, Rimola A, et al. Cyclosporine-associated mutism in liver transplant patients. Neurology 1996; 46: 252
9. Abouljoud MS, Anil Kumar MS, Brayman KL, Emre S, Bynon JS. Neoral rescue therapy in transplant patients with intolerance to tacrolimus. OLN-452 Study Group. Clin Transplant 2002; 16: 168
10. Fryer JP, Fortier MV, Metrakos P, et al. Central pontine myelinolysis and cyclosporine neurotoxicity following liver transplantation. Transplantation 1996; 61: 658
11. Beresford TP. Neuropsychiatric complications of liver and other solid organ transplantation. Liver Transpl 2001; 7: S36