



Abnormal Cerebral Blood Flow Findings in Transplant Patients With Posttransplant Apraxia of Speech

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NEUROLOGICAL COMPLICATIONS of transplantation medicine are increasingly being recognized. Higher doses of the immunosuppressants cyclosporin A and tacrolimus have been associated with the occurrence of neurological complications, such as tremor, headache, or encephalopathy.¹⁻³ Rarely, a characteristic speech or language disorder, which may be described as cortical dysarthria or speech apraxia, can occur in transplant patients. The pathophysiology of this rare but disabling complication remains unknown.

CASE REPORTS

Case 1

A 63-year-old Caucasian female was admitted with hepatic encephalopathy. She was confused but was able to communicate. Speech was fluent. She underwent orthotopic liver transplantation. The postoperative course was complicated by acute rejection of the transplanted liver. She was treated with OKT-3 and FK-506. Following extubation, she was unable to speak, and unable to move tongue and lips to commands (orobuccolingual apraxia). She was noted to have some involuntary movements involving her tongue and lips. Verbal comprehension was intact. FK-506 level was elevated at 36.6 (normal range 5 to 20 units). FK-506 was then replaced by cyclosporin A. Brain MRI did not show significant changes except for nonspecific small vessel ischemic changes. Cerebral blood flow (CBF) SPECT imaging using 25 mCi of Tc-99m ECD (Neurolite[®]) demonstrated marked asymmetry in subcortical perfusion (decreased left basal ganglia and thalamus), but there was no major cortical hemispheric asymmetry. Patient expired secondary to aspiration pneumonia 3 weeks after brain SPECT imaging. Autopsy was performed. Gross examination of the brain was within normal limits. Routine histologic sections were taken for microscopic review. The entire brain demonstrated a diffuse microgliosis and astrogliosis. Deep white matter was most severely involved, followed by deep gray matter and cerebral cortex. Immunocytochemical stain for glial fibrillary acidic protein demonstrated prominent astrogliosis in the basal ganglia (Fig 1). The basal ganglia and pons showed small foci of necrosis with swollen axons and macrophage infiltration. There was no evidence of neuronal loss in these regions. Bilateral watershed infarcts were present. Immunohistochemistry for CMV and VZV was negative.

Case 2

This 64-year-old male underwent orthotopic heart transplantation complicated by postoperative course of inability to communicate while being treated with mycophenolate and FK-506. FK-506 was discontinued and cyclosporin A was started. Apraxia of speech

improved on cyclosporin. Cerebrospinal fluid analysis was unremarkable except for mild elevation of protein at 68. Fungal, bacterial, and viral cultures were negative. MR imaging showed nonspecific small vessel ischemic changes. No focal abnormalities were identified. CBF SPECT imaging using 25 mCi of Tc-99m ECD demonstrated asymmetric subcortical perfusion (decreased left basal ganglia and thalamus). There was also mild hemispheric asymmetry in blood flow with slightly reduced perfusion to the left parietal and frontal cortices (Fig 2). FK-506 level was elevated at 27.5 (normal range 5 to 20 units).

DISCUSSION

Neurological complications of organ transplantation have commonly been associated with immunosuppressive therapy. These complications include cerebrovascular disorders, tremors, seizures, primary central nervous system lymphoma, encephalopathies, and posttransplant lymphoproliferative disorder.¹⁻³ Immunosuppression in these patients included FK-506 and cyclosporin A. FK-506-related neurotoxic symptoms have been reported to improve with administration of lower doses.¹

There are few reports of speech apraxia in transplant patients.⁴⁻⁶ In one study,⁴ the incidence of speech apraxia was reported as 1%. These patients developed speech or language problems in the first 2 weeks of transplantation. The complication was reversible in most patients with readjustment of dosage or switching the medication to other immunosuppressant agents. In our cases, this neurological toxicity was associated with higher levels of tacrolimus. In one of our patients, the symptoms improved once the medication was changed to cyclosporin.

Different mechanisms underlying peri- or posttransplant apraxia of speech include direct toxic effects of immunosuppressant agents, pretransplant basal ganglia disease, or an interaction between these two. There are no reported major structural brain abnormalities on CT or MRI imaging in these patients. There is one single report of CBF SPECT imaging in one patient with apraxia of speech⁴ showing decreased cortical perfusion in the left temporoparietal

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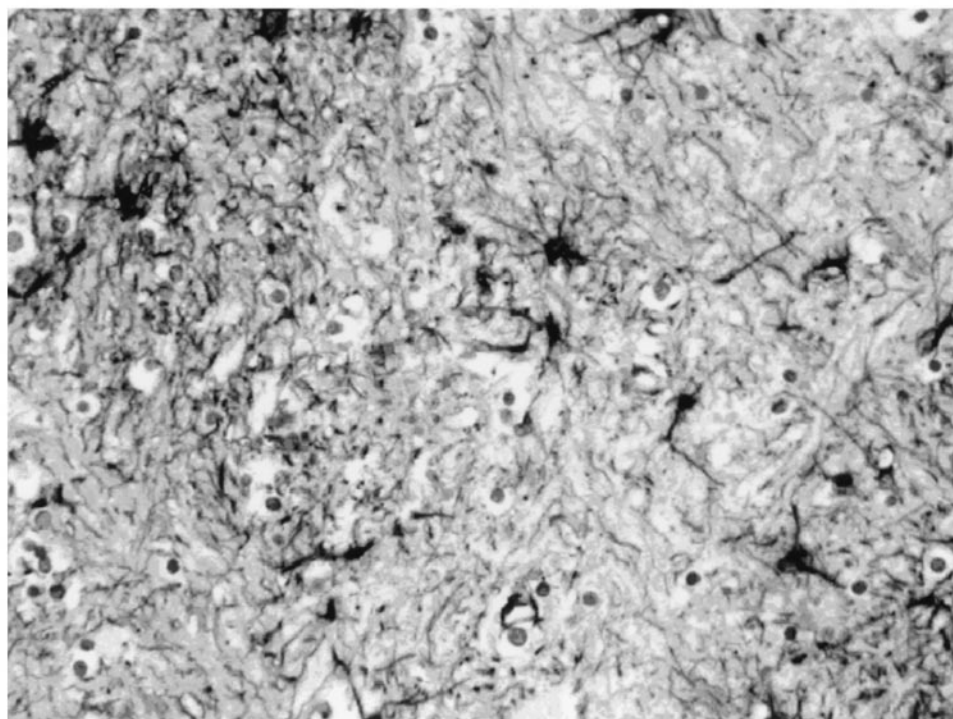


Fig 1. Immunocytochemical stains for glial fibrillary acidic protein demonstrated prominent gliosis in deep gray and white matter. Radial cytoplasmic processes of astrocytes stained dark brown with diaminobenzidine.

cortices. No neuropathological or postmortem data have been reported in patients with apraxia of speech after transplantation.

SPECT scans in our patients showed asymmetrical blood flow in basal ganglia and thalamus without corresponding abnormalities on MR imaging. Our second patient also had reduced left-sided parietal and frontal cortical blood flow. It



Fig 2. Coronal SPECT image of patient 2 showing asymmetric perfusion to the basal ganglia (decreased on the left).

is possible that these blood flow findings are related to neurotoxic side effects of FK-506. The postmortem findings of bilateral gliosis in the basal ganglia in our first patient are nonspecific. It is unclear whether this neuropathological finding is suggestive of some previous inflammation resulting in gliosis or is related to metabolic abnormalities secondary to hepatic disease.

CBF studies in patients with hepatic encephalopathy have demonstrated abnormally increased flow to the basal ganglia.^{7,8} It has been suggested that abnormal blood flow to the basal ganglia will disrupt basal ganglia thalamocortical pathways, which are important for motor and behavioral function.⁸ However, preexistent hepatic basal ganglia disease cannot explain the basal ganglia perfusion changes in our second patient who had normal liver functions.

Many areas of the brain have been known to be associated with speech production from ideation to articulation. A lesion-based analysis in patients with and without apraxia of speech resulting from stroke has shown that left anterior insula is necessary for articulation.⁹ This is important as the left basal ganglia have been found to be dominant for speech production in right-handed individuals.¹⁰ Therefore, it is plausible that basal ganglia dysfunction may interrupt basal ganglia-thalamo-cortical connections, including the insula.

In conclusion, these findings suggest that posttransplant apraxia of speech may be related to asymmetry in cerebral

blood flow particularly affecting the basal ganglia and thalamus of the dominant hemisphere. Further studies will be needed to investigate the role of basal ganglia in speech motor and language functions.

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