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BRIEF REPORT

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Loss of speech after orthotopic liver transplantation

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Abstract Alteration of speech is a rare but distressing complication of orthotopic liver transplantation (OLT). We describe a characteristic speech disorder identified in a large series of consecutive patients undergoing OLT. Between 1988 and 1993, 525 adults underwent OLT. For all recipients with neurologic complications, we reviewed clinical findings, imaging and electrophysiologic test results, and perioperative laboratory data. Five patients (ages 23–52; UNOS status 3–4) exhibited a characteristic pattern of stuttering dysarthria, leading to complete loss of speech production, occasionally with elements of aphasia. In four of the five patients, right-sided focal seizures were subsequently noted. All cases presented within the first 10 postoperative days and improved within 1 month of cessation of cyclosporin (CyA), although halting, monotonous speech was evident to some degree in all five for up to 1 year. There was no correlation between onset of symptoms and CyA levels. None of the patients had clinical or radiologic findings suggestive of central pontine myelinolysis or akinetic mutism. EEGs and Spect scan results were consistent with dysfunction in the left frontotemporoparietal regions of the brain. A characteristic speech disorder, which may be described as cortical dysarthria or speech apraxia, occurs in approximately 1 % of adults undergoing OLT. Prompt recognition of this syndrome and temporary cessation of CyA therapy may favorably affect the course.

Key words Liver transplantation, aphasia · Aphasia, liver transplantation · Cortical dysarthria, liver transplantation

Introduction

Neurologic complications have been reported in as many as one-third of all patients undergoing orthotopic liver transplantation (OLT) [1]. Among the most dramatic and debilitating are alterations in speech and language, which may be related to the use of immunosuppressive drugs, including cyclosporin (CyA) [5] and FK 506 [6]. Such abnormalities have been variously described as receptive aphasia [5] and mutism with akinesia [4]. Stein et al. [9] described a "cerebrocerebellar" syndrome in four patients with aphasia and dysarthria, associated with ataxia, quadriparesis, seizures, and organic mental syndrome.

We report on five liver transplant recipients who developed a characteristic picture of language dysfunction, and we examine the incidence, time course, localization, and outcome.

Patients and methods

Of 525 adult patients who underwent OLT between 1988 and 1993, 121 developed neurologic complications. Five of the 121 patients

Table 1 Clinical and radiographic findings in patients with post-transplant loss of speech

Patient number	Onset post-OLT	Seizure	Studies	Associated neurologic findings	Improvement
1	POD 3	POD 17, R arm focal POD 19, R arm focal	CT(−)x3; EEGx3 (1. Bitemporal slowing; 2. L frontotemporal epileptiform activity; 3. L frontotemporal slowing); Spect scan (hypoperfusion, L temporoparietal)	R arm weakness	POD 33
2	POD 4	POD 10, R arm focal	CT(−); MRI (L periatrial increased signal)	R arm weakness gait ataxia	POD 26
3	POD 4	POD 9, R arm and face, focal	CT(−); MRI(−); EEG(−)	None	POD 22
4	POD 8	POD 15 multifocal	CT(−); MRI(−); EEG(diffuse cerebral dysfunction)	Diffuse weakness	POD 27
5	POD 9	None	CT(−); MRI(small hyperintensity signal-lateral pons); EEG(−)	Diffuse weakness	POD 21

(two female and 3 male), aged 23–52 years (mean age 40 years), experienced a distinct speech disorder. One of the five had undergone retransplantation for primary nonfunction.

Standard immunosuppression consisted of CyA (< 4 mg/kg per day IV, and then 10 mg/kg per day p.o. divided doses when oral fluids were tolerated, adjusted to maintain trough levels between 800 and 1000 ng/ml by polyclonal TDx assay); azathioprine, 1–2 mg/kg per day; and methylprednisolone (at an initial dose of 200 mg/day IV, decreased by 40 mg/day over 5 days), followed by prednisone, 20 mg/day for maintenance. This standard regimen was employed in all but the one retransplanted patient, who also received a 3-day induction course of OKT3.

Clinical findings and perioperative laboratory data [e.g., electrolytes, blood urea nitrogen (BUN), creatinine, albumin, bilirubin, and CyA levels] were reviewed. Each patient's HLA phenotype was noted. CT scan and MRI of the brain, and electroencephalography (EEG) were obtained as indicated.

Results

Five of 525 consecutively transplanted patients (1 %) were found to have a characteristic speech disorder. Findings are summarized in Table 1. All five patients were UNOS status 3–4; none had acute fulminant hepatic failure. All of the patients were on CyA and all had uneventful surgery lasting an average of 6.30 h (range 4.45–9.0 h). In three cases, venovenous bypass was used. Perioperative serum electrolytes were normal, with no significant fluctuations before the onset of the speech disorder. In one patient, a low serum Mg level (1.3 mg/dl) was noted.

None of the patients had intra- or postoperative hypotension. One patient had transient elevation of BUN and creatinine, with a return to normal renal function within 2 weeks post-OLT.

Analysis of the HLA-DR phenotype of these patients failed to reveal any characteristic genetic pattern.

When an alteration in speech production occurred, CyA levels were above the therapeutic range (1100 ng/ml) in two patients. In the one patient receiving OKT3 induction, neurologic symptoms appeared after the first oral dose of CyA. Thereafter, this patient received low-dose CyA IV (1.2 mg/kg per day), despite the presence of speech alteration. In the other four patients, CyA had been administered at a maximum dose of 2–4 mg/kg per day IV for a mean of 3.5 days (range 2–6 days) before the onset of speech disorders. In two of these patients, CyA was discontinued and replaced by OKT3. In the other two patients, the oral dose of CyA was reduced and given in conjunction with an increased dose of azathioprine but was discontinued at the onset of seizure activity. CyA was withheld in all five cases for a mean of 9 days (range 3–16 days). During the period of CyA reduction/withdrawal, all patients experienced at least one episode of rejection, despite the addition of OKT3 or increase in azathioprine.

In all cases, language dysfunction appeared within the first 10 postoperative days (range 3–9 days), presenting as halting dysarthric speech, usually with stuttering, and progressing to anarthria. In some, elements of true aphasia, including writing and comprehension deficits, especially with reading, were noted later in the course. Four patients developed seizure activity (usually right-sided, focal, tonic-clonic), and two had postictal right arm weakness. In two patients, seizure activity occurred before cessation of CyA; seizures occurred in the third patient after CyA was restarted and in the remaining patient while on OKT3 alone. Two patients

had more than one episode of seizure. In all instances, seizures were successfully controlled by administration of phenytoin.

All associated neurologic complications appeared within 2 weeks of the onset of loss of speech (range 3–15 days). Two patients were diffusely weak, two had focal right arm weakness, and one had gait ataxia, although in two, gait could not be tested initially due to the general debility. None, however, had a spastic quadriparesis.

CT scans were normal in all five patients. MRI showed a small "questionable" left periatrial hyperintensity signal in one patient, a hyperintensity signal in the lateral, dorsal pons in another patient, and was normal in two others. EEG was normal in two patients and was abnormal in two others, showing left frontotemporal abnormalities (patient no. 1) or diffuse cerebral dysfunction (patient no. 4).

In all patients, speech dysfunction improved significantly within 1 month of onset. Although all patients ultimately improved, and in no case did focal weakness or seizures persist, all were left with varying degrees of a peculiar, monotonous, "robotic" speech. This speech pattern continued to improve but persisted the course of over 1 year. The extent of remaining deficit was not related to the severity or duration of the initial episode.

Two cases will now be briefly described.

Patient no. 1 was noted 3 days after transplantation to be having language difficulty, characterized by word searching and stuttering. CyA was decreased and finally discontinued. A CT scan of the brain was normal and an EEG showed bitemporal slowing. The patient became anarthric by postoperative day (POD) 8. She was able to read without errors but was unable to write and appeared to be emotionally labile. Gait, power, and coordination were normal. Speech began to return slowly with apparent apraxia, the patient being unable to produce the desired sounds either with the tongue or lips but still able to swallow without difficulty. Speech was monosyllabic and monotonous, and comprehension was grossly normal.

CyA was reinstituted. On PODs 17 and 19, the patient had focal, right arm, tonic-clonic seizures that were treated with phenytoin. Magnesium levels were 1.6 mg/dl and 1.4 mg/dl, respectively. EEG now showed left frontotemporal epileptiform activity. CT scans were again negative but Spect scan of the brain showed hypoperfusion of the left temporoparietal region. She developed right arm weakness postictally that persisted for 2 weeks. CyA was again discontinued and the patient was converted to FK 506. By POD 33, she had improved dramatically and was able to read, write, and comprehend. Speech was still mildly dysarthric, with a hesitant, monotonous, and monosyllabic pattern, but was faster and easier to understand. One year after OLT, she remains mildly impaired with a similar, but less pronounced, speech disorder.

Patient no. 3 was noted on POD 4 to have stuttering and difficulty producing sounds. Comprehension and writing were normal and she could read correctly but had difficulty enunciating. She became anarthric after several days. CyA was decreased and finally discontinued, but on the 9th postoperative day she had a focal seizure of the right face and arm. CT scan, MRI, and EEG were normal. Comprehension and writing remained normal, and gait, power and coordination, sensory and swallowing and respiratory function were normal throughout the course. The patient made slow improvement over several weeks, and by the 22nd postoperative day she was dramatically better. One year after transplantation, slightly monotonous, choppy speech and rare word searching persist.

Discussion

These five patients exhibit a discrete syndrome of early postoperative speech disorder. It appeared in all in the first 10 days, progressed from stuttering to anarthria, with varying degrees of dysphasia in some, and largely improved within 1 month.

Our reported incidence of 1 % may, in fact, underrepresent the true occurrence of this disorder, which could not be detected in patients who were intubated for long periods postoperatively. Likewise, the disorder may not have been recognized in patients with mild dysarthria.

Previously described language disorders associated with CyA have categorized the patterns as aphasia, dysarthria, or mutism associated with akinesia, but there has been little description of the deficits, and localization in the nervous system has been unclear.

The type of language abnormality seen in our cases suggests a dominant hemisphere location, possibly the left premotor cortex and underlying white matter. The primary deficit was a "pure word mutism" (aphemia), a slow, halting, dysrhythmic, dysarticulatory speech, with preservation of comprehension, often with complete loss of speech production. This is sometimes referred to as "cortical dysarthria" and usually results from lesions of the frontal lobe [2]. Our patients' inability to produce coordinated and comprehensible speech might also be described as "apraxia" (i.e., the inability to perform the previously learned motor act of talking), resulting in a dysarticulatory, awkward pattern, often seen with aphasia [3]. Whether there is a difference between such motor speech disorders as cortical dysarthria and apraxia is debatable [8].

The "acquired" stuttering so characteristic of our patients' speech has been described with aphasias, localizing to the dominant hemisphere [2].

In no case did the CT or MRI show the expected features of CyA toxicity (i.e., biparieto-occipital white

matter abnormalities) [5]. The EEG and Spect scan findings and the right arm seizures and paresis suggest a left cerebral dysfunction.

In summary, all of the speech and motor dysfunction seen in these patients points primarily to the left hemisphere, particularly the frontal lobe, although bilateral cerebral dysfunction may have been transiently present in some.

Some of the cases of "cerebrocerebellar syndrome" described by Stein et al. [9] probably represent the same clinicopathologic entity. Their report emphasized the cerebellar picture of limb and speech ataxia. Several of their cases also had notable lethargy, and one was reduced to a state of "vigilant unresponsiveness" [9]. In contrast, cerebellar findings were rare in our patients, and none had alteration of consciousness.

Central pontine myelinolysis (CPM) may also present with quadriparesis and dysarthria and even seizures and may not be appreciated on CT scan. CPM has been documented in up to 29% of patients dying after OLT [11]. In our series, however, the clinical and laboratory studies indicated a primarily left cerebral event.

In patient no. 5, MRI did demonstrate abnormalities in the pons. These, however, were lateral and dorsal to the basis pontis, a finding not consistent with CPM. Although lateral pontine myelinolysis has been described on pathology [7], these focal hyperintensities were outside the basis pontis. The clinical findings in this one patient differed from the others in that he had no seizures or focal weakness. There was no hyperreflexia or Babinski sign to suggest quadriparesis from pontine myelinolysis, the anarthria appeared 9 days after transplantation, and his rapid recovery of speech after cessation of CyA suggests that both the MRI lesions and clinical picture were due to CyA toxicity.

We were impressed with the rapid response to dexamethasone in one patient; however, further experience suggested that stopping CyA was the more important intervention and that reinstitution of CyA, while well tolerated in some patients, caused progression of this syndrome in others. In one such case (patient no. 1), FK 506 was substituted without deleterious effect. FK 506 has also been described as causing aphasia, dysarthria, and seizures [6], and three patients were recently reported with transient mutism, speech apraxia, and seizures [10].

The left cerebral hemisphere may be uniquely prone to the neurotoxic effects of CyA, but the complexities of language production might simply make for a more obvious manifestation of such toxicity. Although precise localization is not possible in this series, the distribution of neurologic deficit suggests a more anterior lesion (frontal lobe) than that usually seen in patients with CyA toxicity on neuroimaging studies (parietooccipital) [5]. No laboratory or historical data in our series could explain why these five patients developed such a discrete left cerebral syndrome, while other patients on CyA have akinetic mutism, cortical blindness, or coma.

The pathophysiology of this unique disorder remains unknown. It is evident, however, that rapid recognition of this syndrome is important, as discontinuation of CyA, where possible, might prevent progression and lead to earlier and more complete resolution. At the present time, it is unclear whether FK 506 represents an alternative therapy for patients with this dramatic and disturbing syndrome after successful liver transplantation.

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