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Improvement in Chronic Hepatocerebral Degeneration Following Liver Transplantation

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Abstract

Chronic progressive hepatocerebral degeneration with spastic paraparesis, dementia, dysarthria, ataxia, tremor, and neuropsychiatric symptoms follows long-standing portal-systemic shunting, is associated with structural changes in the central nervous system, and does not respond to conventional therapy for hepatic encephalopathy. A case of advanced chronic liver disease with severe, progressive hepatocerebral degeneration after 23 yr of portal-systemic shunting is reported in whom there was significant objective improvement in intellectual function and in the chronic neurological signs 3 mo after orthotopic liver transplantation and further improvement 12 mo after transplantation.

Abbreviations used in this paper:

CT, computed tomographic; EEG, electroencephalogram; HE, hepatic encephalopathy; OLT, orthotopic liver transplantation.

Hepatic encephalopathy (HE) complicating chronic liver disease is characterized by episodes of acute neuropsychiatric dysfunction often with a precipitating factor, superimposed on a background of chronic neurological disease. Acute HE is a potentially reversible encephalopathy due to a metabolic disturbance, probably causing widespread alteration in cerebral neurotransmission (1). This should be distinguished from the less-common chronic progressive encephalopathies such as "acquired hepatocerebral degeneration" (2) and the persistent neuropsychiatric syndromes associated with cirrhosis (3). Chronic progressive encephalopathy is characterized by dementia, dysarthria, ataxia, tremor, extrapyramidal signs, and spastic paraparesis (2,4). It is more common in patients with large portal-systemic shunts, and usually does not respond to therapy for HE. Structural changes in the central nervous system have been reported in association with this rare, more persistent neuropsychiatric syndrome (2,3). Liver transplantation provides an opportunity to study the extent to which the chronic neuropsychiatric syndrome is reversible.

A patient is reported with advanced chronic liver disease and 23 yr of portal-systemic shunting in whom severe long-standing neuropsychiatric dysfunction was a major manifestation of illness. Following successful orthotopic liver transplantation (OLT), there was a significant objective improvement in cerebral function and in the long-standing neurological signs.

Case Report

A 44-yr-old woman was referred in April 1988 for consideration for OLT. Splenomegaly was first noted at 19 yr of age. Two years later she had massive upper gastrointestinal

hemorrhage secondary to bleeding esophageal varices, and after stabilization, an end-to-side portacaval anastomosis was performed. A liver biopsy performed during the laparotomy showed "post necrotic scarring with regenerative nodules." Her splenomegaly subsequently resolved, and she had no further hematemeses. She had no history of risk factors for liver disease, specifically no blood transfusions before the initial presentation, no prescription or illegal drug use, and no relevant family history. She did not drink alcohol and had no symptoms suggestive of connective tissue disease. At 37 yr of age, she had her first episode of clinical hepatic encephalopathy, although her family de scribed episodes of intermittent confusion and abnormal behaviour for the previous 5 yr. She had several subsequent hospital admissions with ascites, peripheral edema, and recurrent chest infections.

On admission in April 1988, she complained of lethargy and an inability to perform simple household duties. She was unable to shop or manage her finances and was cared for at home by her daughters. They had noted progressive deterioration in speech and memory and an altered gait over the 2 yr before admission. During this time, she had become more jaundiced, her pruritus had worsened, easy bruising had occurred, and she had lost 13 kg in weight.

Physical examination showed a thin pigmented woman with scleral icterus who looked much older than her stated years. The liver and spleen were not palpable. She had thin skin with a few spider nevi, but no other peripheral signs of chronic liver disease. Examination of the higher functions was conducted with the Mayo Clinic short test of mental status (5) and with assessment by a speech therapist. Her orientation was correct for all items except the state. She was able to repeat up to 6 numbers forwards. She could repeat the names of 4 objects on the second attempt, but could not recall any of these names after 5 min. Arithmetic calculation was correct for 3 items of 4 but was very slow. For paired items in which she was required to name an abstract feature common to both items, she obtained 1 correct response from 3 pairs. On information testing, she obtained 2 correct responses from 4 items. She was able to construct a clock showing the time as 11:15, but was unable to copy a cube. Her total score was 23 of a possible 38 (5). Serial 2's and 7's were performed slowly, with 4 errors out of 14 calculations and 3 errors from 7 calculations, respectively. In naming the months of the year backwards, she omitted 2 months. She deleted 3 letters from the alphabet. A Reitan's number connection test with 25 points took 180 s to complete.

Assessment by a speech therapist showed that she had delayed and poor auditory comprehension and recall of a paragraph. She was unable to accurately complete tasks requiring reading of whole paragraphs, and had mild word-finding difficulty. She was unable to write her name and address without making spelling errors and was unable to complete a dictation task. A mild ataxic dysarthria was present. The glabellar tap test was positive. A coarse and irregular tremor was present in the outstretched arms when the wrists and fingers were extended. Clasp-knife rigidity was present in the lower limbs, with nonsustained ankle clonus. Bradykinesia and symmetrical mild weakness were present in the upper and lower limbs. The deep tendon reflexes were symmetrically increased. The right plantar response was equivocal, and the left was flexor. Her gait was slow and ataxic. Joint position sense was reduced in the toes bilaterally. The remainder of the sensory examination was normal.

Laboratory investigations showed the following concentrations: serum total bilirubin, 165 μM(3-20); conjugated bilirubin, 96 μM(0-7); albumin, 20 g/L (35-50); globulin, 45 g/L (21-41); alkaline phosphatase, 242 μ/L (30-115); aspartate amino transferase, 89 μ/L (5-40), γ glutamyl transferase, 18 μ/L (5-65); and prothrombin time was 42 s (12-16). An abdominal ultrasound examination revealed a small echo-genic liver with marked splenomegaly and a patent porta-caval shunt. Results of other investigations, including iron and copper studies, α fetoprotein, human immunodeficiency virus and hepatitis serology, α-1 antitrypsin, and antinuclear antibody tests were normal. Her

electroencephalogram (EEG) showed an α rhythm of 8-9 Hz and was otherwise normal. A computed tomographic (CT) brain scan showed generalized cerebral atrophy of similar degree to that present on a CT scan performed in 1983.

Orthotopic liver transplantation was performed on May 1, 1988. The operation was uncomplicated. Histological study of her liver revealed micronodular cirrhosis with no evidence of cholestasis, Mallory's hyaline, α-1 antitrypsin globules, copper-associated protein, hepatitis B surface antigen, iron-storage disease, or malignancy. She had no postoperative complications, and was discharged from the hospital 18 days after surgery on a normal diet and a standard immunosuppressive regimen (6). This consisted of initial therapy preoperatively and perioperatively with methylprednisolone (1 g i.v.), azathioprine (2 mg/kg i.v.) and the introduction of cyclosporin A (6 mg/kg), with appropriate adjustment of doses according to response and blood levels of cyclosporin. Azathioprine was ceased 3 mo after OLT, and cyclosporin and prednisolone were continued indefinitely in low doses (cyclosporin 17.5 mg/kg, adjusted by blood levels and prednisolone, 5-10 mg/day). She remains well and has had normal biochemical parameters since OLT (Table 1).

Table 1. Biochemical Parameters Before and After Liver Transplantation

		After OLT	
Biochemical parameter	Before OLT	3 mo	12 mo
STB	(3-20) 165 μM	5	5
CB	(0-7) 96 μM		
S Alb	(35-50) 20 μ/L	37	41
S Glob	(21-41) 45 μ/L		
SAP	(30-115) 242 μ/L	120	100
AST	(5-40) 89 μ/L	22	15
GGT	(5-65) 18 μ/L	67	18

STB, serum total bilirubin; CB, conjugated bilirubin; S Alb, serum albumin; S Glob, serum globulin; SAP, serum alkaline phosphatase; AST, serum aspartate aminotransferase; GGT, γ-glutamyl transferase. Reference ranges given in parentheses.

A detailed neurological assessment was performed 3 mo and again 12 mo after OLT. At 3 mo, the score of the Mayo Clinic short test of mental status had improved from 23 to 29. Her orientation, attention, and immediate recall were unchanged. Arithmetic calculation was again correct for 3 of 4 items; however, she performed calculations much faster. Tests for abstraction were now all performed normally. Information testing improved from 2 to 3 items. She was now able to copy a cube correctly. She could not recall any of 4 objects after 5 min. Serial 2's and 7's were performed much faster, with no errors from 14 calculations and 3 errors from 7 calculations, respectively. She named the months of the year backwards and the letters of the alphabet correctly. The Reitan's test took 100 s to complete. Assessment by the same speech therapist showed improvement in auditory comprehension and recall of a paragraph. Reading comprehension was normal. Improvements in naming, verbal explanation, and verbal reasoning abilities were present. The dysarthria was still present but had improved in comparison with an audio recording of her speech before transplantation. Results of the glabellar tap test remained positive. The postural tremor was reduced in amplitude. The tone in the limbs was normal. The bradykinesia had improved considerably, but the mild weakness in the upper and lower limbs remained. The deep tendon reflexes remained increased. The right plantar response was extensor and the left was flexor. Joint position sense was normal in the lower limbs. Her gait had improved markedly, but on tandem walking she continued to fall to either side. The EEG showed an α rhythm of 11 Hz. The findings are summarized in Table 2.

Twelve months after OLT, she was fully independent in all aspects of daily living, e.g., managing her finances, running the household, and shopping in a normal manner. Although formal assessment showed some abnormalities in intellectual and motor function, her family regarded her as functioning in a completely normal way. On examination, the improvement noted at 3 mo had been sustained, and there had been additional improvement. Her score on the Mayo Clinic short test of mental status had improved further to 32. In particular, her short-term memory had improved: she was now able to recall 3 of 4 items after 5 min. The time to complete the Reitan's test had improved further to 47 s. The dysarthria was unchanged from 3 mo after OLT, but the glabellar tap test was now only weakly positive. The postural tremor had completely resolved. There was mild weakness of hip flexion and knee flexion, but muscle strength was otherwise normal. There was mild bilateral slowing of rapid alternating movements. The deep tendon reflexes including the jaw jerk remained increased, but the plantar responses were flexor. Gait and tandem gait were normal. There was mild impairment in proprioception in the toes, but sensation was otherwise normal. A CT scan showed no change in the cerebral atrophy from that observed preoperatively. The findings are summarized in Table 2.

Table 2. Response of Neurological Features to Liver Transplantation

Neurological feature	3 mo after OLT	12 mo after OLT
Short-term memory	U	I
Arithmetic ability	I	I
Abstract reasoning	N	N
Language skills	I	I
Number connection	I	N
Constructional ability	N	N
Bradyphrenia	I	I
Bradykinesia	I	I
Glabellar Tap	U	I
Dysarthria	I	I
Postural tremor	I	N
Clasp-knife rigidity	N	N
Deep tendon reflexes	U	U
Plantar reflexes	U	N
Gait	I	N
EEG	N	N
CT brain scan	U	U

U, unchanged compared with before OLT; I, improved compared with before OLT; N, improved to normal.

Discussion

This report documents significant objective improvement both in cerebral function and neurological signs following successful orthotopic liver transplantation in a patient with severe long-standing neuropsychiatric dysfunction and cirrhosis. The neurological symptoms and signs manifested by this patient comprise the syndrome of the acquired type of chronic hepatocerebral degeneration as described by Victor *et al* (2). Earlier reports by Parkes *et al.* (7) and Chu *et al.* (8) have described electroencephalographic and somatosensory-evoked potential changes following OLT. Parkes *et al* (7) describe improvement in confusional state, depression, intelligence quotient, and a motor disorder following OLT in a cirrhotic patient with a 5-yr history of encephalopathy following a

portacaval anastomosis. The current patient is similar but differs in that the duration of both the portal-systemic shunting (23 yr) and the history of neuropsychiatric disturbance (12 yr) were significantly longer. The slow deterioration in cerebral function was punctuated by episodes of acute HE that responded to standard medical therapy. Other common causes of dementia, such as hypothyroidism and vitamin B_{12} deficiency, were excluded.

In this patient, there was objective evidence of improvement in arithmetic ability, abstract reasoning, language skills, constructional ability, Reitan's number test, and dysarthria. Her short-term memory, however, remained impaired at 3 mo, but had significantly improved 12 mo after transplantation. The clasp-knife rigidity in the lower limbs resolved completely. Although the reflexes remained brisk, ankle clonus disappeared and both plantar responses became normal. The bradyphrenia improved considerably, but not completely. The postural tremor was reduced in amplitude at 3 mo and had completely resolved at 12 mo. The positive glabellar tap test result remained weakly positive. The gait returned, over many months, to normal. The increase in the frequency of the α rhythm on the EEG after OLT provided further evidence of improvement of cerebral function.

The degree of improvement in neurological manifestations of chronic hepatocerebral degeneration in this patient following successful OLT and while ingesting a normal daily protein intake is of interest, and is not known to have been previously documented in a patient with such long-standing portal-systemic shunting. Acute HE is reversed by dietary protein restriction, lactulose, and neomycin, and is worsened by hypokalemia, constipation, and drugs that increase γ-aminobutyric acid-ergic activity (9,10). However, the chronic neuropsychiatric syndromes and chronic hepatocerebral degeneration have been regarded as largely irreversible and caused mostly by organic structural changes in the brain and spinal cord (2). It is noteworthy that significant improvement in the neuropsychiatric syndrome has been defined following prolonged lactulose usage and by Freund *et al.* (11) using a branched chain-enriched amino acid diet. The neuropathological changes observed in non-Wilsonian hepatocerebral degeneration include diffuse astrocytic hyperplasia, microcavitation and zonal necrosis of the deeper parts of the cerebral cortex and of the lenticular nuclei, loss of nerve cells in the cerebral cortex, putamen, thalamus, cerebellar cortex, and dentate nuclei, and loss of axons in the corticospinal tracts in the spinal cord with fibrous gliosis (2,4,12). In the current patient, in whom a portal-systemic shunt had been present for 23 yr, significant neurological improvement had occurred by 3 mo after OLT, and this continued. Although ongoing neurological improvement was observed in most aspects, late recovery was most obvious in the abnormal motor signs. Thus, whereas the tremor, gait disturbance, and upper motor neuron signs showed some early improvement, by 12 mo, tremor had disappeared, gait was normal, and the other abnormal motor findings were substantially improved. It is unlikely that the immunosuppressive regimen contributed to the neurological improvement; there has been progressive improvement despite reduction of doses to low maintenance levels, as has been discussed.

This case illustrates that even after 23 yr of portal-systemic shunting and 12 yr of symptoms of chronic HE, a significant degree of reversibility of symptoms and signs may be observed. Thus, chronic neuropsychiatric syndromes and chronic progressive hepatocerebral degeneration should not be regarded as a contraindication to liver transplantation.

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