Transient Improvement of Acquired Hepatocerebral Degeneration With Parkinsonian Symptoms After Failed Liver Transplant: Case Report and Literature Review

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Abstract

Objectives: **Acquired (non-Wilsonian) hepatocerebral degeneration is an infrequent neurologic disorder in patients with liver dysfunction and long-standing portal-systemic shunting. The clinical manifestations include dysarthria, ataxia, tremor, and cognitive dysfunction. Typically, patients with acquired hepatocerebral degeneration respond poorly to medical therapy as the underlying end-stage liver disease remains. Information regarding the effect of orthotopic liver transplant on acquired hepatocerebral degeneration, however, is limited and conflicting.**

Materials and Methods: **We conducted a review of literature via a PubMed search to summarize the effect of orthotopic liver transplant on acquired hepatocerebral degeneration.**

Results: **We present a 56-year-old man with compensated hepatitis C cirrhosis who developed acquired hepatocerebral degeneration with Parkinsonian symptoms refractory to conventional Parkinson medical therapy. Orthotopic liver transplant led to marked clinical improvement of the acquired hepatocerebral degeneration. However, the patient developed recurrence of acquired hepatocerebral degeneration 6-week postorthotopic liver transplant as he developed graft failure from aggressive progressive hepatitis C recurrence. Our review found a heterogeneous group of case series, suggesting that the experience with orthotopic liver transplant is variable.**

Conclusions: **Our experience demonstrates that orthotopic liver transplant may lead to resolution of acquired hepatocerebral degeneration; however, acquired hepatocerebral degeneration may return with recurrent liver disease. Future studies with long-term follow-up are needed.**

Key words: *Portal-systemic shunting, Hepatitis C, Cirrhosis, Organ transplant, Movement disorder*

Introduction

Acquired (non-Wilsonian) hepatocerebral degeneration (AHCD) is an uncommon neurologic disorder that has been described in patients with severe liver disease, especially in those with surgically or spontaneously induced portal-systemic shunts. The cerebral deposition of heavy metals, especially manganese, may play a role in the pathogenesis of AHCD.[1] Acquired hepatocerebral degeneration involves the brain's cortical area and the basal ganglia, especially the globus pallidus and cerebellum. Microscopically, neuronal loss, Alzheimer type II astrocytes, and cytoplasmic glycogen granules in basal ganglia are characteristic.[2, 3, 4] The clinical features of AHCD include neuropsychiatric (apathy, lethargy, excessive somnolence, secondary dementia), or extra-pyramidal symptoms (ataxia, dysarthria, rigidity, tremor, choreoathetosis, parkinsonism, myoclonus and dystonia), or both.[1, 3, 5, 6, 7]

Despite its recognition as a sequelae of end-stage liver disease, AHCD remains a condition that lacks well-defined clinical features and is of low prevalence. No medications have been reported to ameliorate the progression of AHCD, and the data

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regarding dopamine replacement therapy in patients with Parkinsonism related to AHCD are conflicting.[1, 3, 8-14] Recent studies suggest that liver transplant may be an effective therapy for AHCD. However, the reported clinical outcome after liver transplant in cirrhotic patients with AHCD is inconsistent and limited.[7, 8, 13, 15-28] This is concerning given the disparity between organ donor need and its availability. If AHCD fails to improve or worsens post-OLT, then it may be considered a relative contraindication; conversely, if AHCD improves post-OLT, then patients with AHCD should be given priority for transplant, similar to other extrahepatic sequelae, such as hepatopulmonary syndrome and hepatorenal syndrome.

Here, we report a man with AHCD secondary to hepatitis C cirrhosis who experienced a dramatic near-complete resolution in neurologic symptoms post-OLT that proved to be transient, as his neurologic symptoms recurred when his allograft began to fail.

Case report

A 57-year-old white man developed symptoms of intermittent postural tremor, diminished facial expression, bradykinesia, and diminished coordination 3 years pre-transplant. This affected his fine motor skills such as handwriting and shoe tying. He denied any cognitive changes, hypnophobia, hypersalivation, micrographia, or swallowing difficulties. His Parkinsonism features were initially diagnosed as idiopathic Parkinson's disease in the setting of well-compensated cirrhosis and portal hypertension.

Clinically, this patient had biopsy confirmed liver cirrhosis secondary to chronic hepatitis C (genotype 1), Child-Pugh Score of 5 (class A: normal liver biochemistry, no ascites, and a lack of clinical features consistent with classic hepatic encephalopathy), Model for End Stage Liver Disease (MELD) score of 9, and portal hypertension (ultrasound confirmed splenomegaly, and mild-to-moderate esophageal varices). The hepatitis C was not treated with pegylated interferon and ribavirin because of the risk of sudden decompensation. Over the next 3 years, his liver disease remained relatively well-compensated with MELD score of 10.5 and Child-Pugh score of 7 (class B).

The diagnosis of acquired hepatocerebral degeneration became apparent based on clinical, laboratory, and imaging data. Neurologic examination revealed significant hypomimia, mild hypophonia, facial masking, bilateral postural tremor (which later became resting tremor), bilateral bradykinesia, bilaterally decreased arm swing, stooped posture, postural instability, cogwheeling, and mild rigidity bilaterally. The reminder of the results of his neurologic examination was normal. His Montreal cognitive assessment (MoCA) score[29] was 30/30. Slit lamp examination for Kaiser-Fleischer rings was negative. Spider nevi and gynecomastia were noted. Cardiovascular and pulmonary examinations were unremarkable.

Results of his laboratory studies are presented in Table 1. His serum manganese was mildly elevated. His serum ceruloplasmin was mildly depressed, with a normal serum and 24-hour urine copper. Serology for HIV and hepatitis B were negative. Magnetic resonance imaging of his brain shows symmetric high T1 signal in the globus pallidi bilaterally (Figure 1A). The results of the corresponding T2-weighted image were normal (Figure 1B). The results of his electroencephalogram were unremarkable.

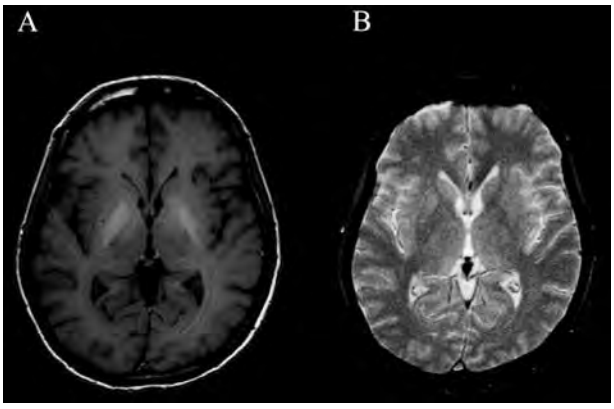

Figure 1. A. An axial T1-weighted magnetic resonance imaging showing bilateral symmetric hyperintensities in the globus pallidi at the initial presentation. **B.** T2-weighted axial magnetic resonance imaging shows normal signal intensity in the globus pallidi.

The patient was treated with levodopa-benserazide; however, despite this, his Parkinsonism symptoms became progressively worse. One month pre-transplant, he was admitted to hospital because of decreased balance and increased falls that significantly impaired his ambulations and left him bed-ridden. His debilitating Parkinsonism symptoms remained refractory to anti-Parkinson medications, and a decision was made to proceed with a liver

transplant. The post-transplant period was complicated by an episode of mild acute rejection with rejection activity index of 4/9, requiring methylprednisolone pulse therapy. Immuno - suppression was consisted of tacrolimus, mycophenolate, and prednisone. Other post-transplant medications included valganciclovir (for *cytomegalovirus* prophylaxis), rabeprazole, propranolol, and carbidopa-levodopa (25/100 mg 1.5 tablets 4 times/d, and sustained release 50/200 mg 1 tablet at night) post-transplant. His overall clinical condition improved dramatically following transplant. Patient reported he was "99%" better for approximately 6 weeks. His mobility was excellent, and tremor and bradykinesia were markedly diminished. He was able to dress himself independently, which was not possible before OLT.

After OLT, his liver chemistry was initially stable but began to raise 5 weeks after OLT and peaked at 10 weeks (Table 1). Liver biopsy at 5 weeks after OLT revealed aggressive recurrence of hepatitis C with fibrosing cholestatic hepatitis. Recurrence of hepatitis C was confirmed with the presence of hepatitis C virus RNA in the serum. Neurologically, his Parkinsonian symptoms gradually reappeared 6 weeks after OLT, which was coincidental with the onset of his graft dysfunction. He developed tremor, bradykinesia, and difficulty moving his limbs. He had no dyskinesia, dystonia, or falling, and his cognition and memory remained normal. Neurologic evaluation revealed mild hypophonia, facial masking, bradykinesia, bilateral cogwheeling, occasional resting tremor, bilaterally reduced arm swing, and mildly stooped gait. Motor strength was normal, except mildly weak hip flexors. Finger-to-nose, sensory, and reflexes were normal and symmetric. The dose of carbidopa-levodopa was increased (25/100 mg 2 tablets 4 times/d, and sustained release 50/200 1 tablet at night).

In an attempt to salvage graft function, the hepatitis C virus-associated fibrosing cholestatic hepatitis was treated with pegylated interferon and ribavirin combination therapy and a change from tacrolimus to cyclosporine. His liver biochemistry was essentially normalized 12 weeks after pegylated interferon and ribavirin treatment (23 weeks after OLT, Table 1), although his viral load did not significantly decrease. At 29 weeks after OLT, his cyclosporine was discontinued owing to gum hyperplasia. At 34 weeks after OLT, his liver biochemistry again became marked elevated (Table 1), and cyclosporine was restarted at a lower dose. Liver biopsy revealed acute graft rejection (rejection activity index of 6/9). He did not respond to pulse methylprednisolone and rejection activity index continued to increase to 8/9. The steroid refractory graft rejection was treated with antithymocyte globulin therapy with slight improvement in liver biochemistry (Table 1). He was readmitted 41 weeks after OLT with pancreatitis in the context of recurrence of hepatitis C and transplant rejection (Table 1). Five days later, he was transferred to the intensive care unit for encephalopathy, hypernatremia, and diabetic ketoacidosis. After discharge from the intensive care unit, his care became palliative, and he died 43 weeks after OLT.

Table 1. Laboratory data before and after liver transplant.

Biochemical parameters	Normal values	Before OLT	Day 0	5 weeks after OLT	10 weeks after OLT	23 weeks after OLT (12 weeks after peginterferon-ribavirin treatment)	34 weeks after OLT	37 weeks after OLT	41 weeks after OLT
Hemoglobin (g/L)	135-170	127	111	130	135	62	101	98	117
WBC (109/L)	4-11	2.8	11.6	6.9	2.2	2.2	4.1	3.6	10.0
Platelets (109/L)	150-400	70	102	161	121	95	148	115	173
aPTT (Seconds)	24-40	34	30	30	27	31	30	29	36
INR	0.9-1.2	1.1	1.2	1.0	1.1	1.1	1.0	1.1	1.2
Creatinine (μmol/L)	70-120	78	101	71	73	107	78	88	112
Albumin (g/L)	35-50	28	31	35	23	35	33	24	19
Total bilirubin (μmol/L)	0-18	19	18	19	278	24	55	294	528
Direct bilirubin (μmol/L)	0-5	9	9	9	212	18	41	227	458
AST (U/L)	10-38	140	432	181	221	22	128	294	202
ALT (U/L)	25-80	61	201	220	116	7	25	305	30
Alkaline phosphatase (U/L)	35-120	83	59	116	188	62	701	357	314
GGT (U/L)	10-58	128	114	336	4206	103	1332	2351	3521

Abbreviations: ALT, alanine aminotransferase; aPTT, activated partial thromboplastin time; AST, aspartate aminotransferase; GGT, gamma glutamyl transferase; INR, international normalized ratio; WBC, white blood cells

Table 2. Patient characteristics of reported cases of patients with AHD who received OLT.

ID	Paper	Age at transplant	Sex	Cirrhosis cause	Clinical status before LT	Clinical status after LT	Follow-up
1	Powell et al.[15]	44	F	N/A	AHCD	Intellectual function and neurologic signs resolved completely.	12 mo
2	Pool et al.[16]	N/A	N/A	N/A	Hepatic encephalopathy	5 patients had bradykinesia and cognitive deterioration that improved.	10-20 mo
3	Counsel and Warlow[17]	52	M	Alcohol	HM	No improvement of hepatic myelopathy (lower limbs spasticity, pyramidal weakness, brisk reflexes).	18 mo
4	Trois et al.[18]	60	F	Hepatitis C virus	HM	Hepatic myelopathy (spastic weakness, tremor, sensory impairment) improved, able to walk with a cane.	1.5 y
5	Lewis et al.[31]	45	M	Congenital hepatic fibrosis	AHCD/HM	Pt died from infection 2 weeks post-transplant.	N/A
6	Spar et al.[19]	N/A	N/A	N/A	HE	Parkinsonism improved in all 3 patients.	4 mo
7	Layrargues[7]	60	F	Primary biliary cirrhosis (PBC)	HE/AHCD	Asterixis, bucco-linguo-facial dyskinesia resolved completely.	2 mo
8	Stracciari et al.[20]	59	M	Alcohol and hepatitis C virus	AHCD	Movement disorder (hypomimia, dysarthria, bradykinesia, oral dyskinesia, bilateral hand tremor) and cognitive disorder resolved completely.	12 mo
9	Lazeyras et al.[21]	Mean 55 (44-69)	4 M/4F	N/A	MHE	Parkinsonism improves, but mild parkinsonism persisted.	4 mo
10	Shulman et al.[13]	70	M	N/A	AHCD	Movement disorder (tremor, gait imbalance, cogwheel rigidity, bilateral absence of arm swing) resolved.	6 mo
11	Weissenborn, et al.[22]	35	M	Hepatitis B virus, Hepatitis C virus	HM	Hepatic myelopathy improved (able to walk 1-2 km with a walking stick).	13 y
		40	M	Hepatitis C virus	HM	Hepatic myelopathy improved (able to walk several km with a walking stick).	2.5 y
		42	M	Hepatitis B virus, Hepatitis D virus	HM	Hepatic myelopathy improved (able to walk a few meters with a walking stick).	9 mo
12	Mattarozzi et al.[23]	51.9 (mean)	23 patients in total	N/A	MHE	Selective attention and verbal short-term memory improved.	6 and 18 mo
13	Papapetropoulos and Singer[24]	63	F	Hepatitis C virus	AHCD	Oro-bucco-lingual dyskinesias resolved post-transplant but reappeared 3 months after LT.	
14	Klos et al.[8]	52	M	Primary sclerosing cholangitis (PSC)	Cirrhotic patient with basal ganglia T1 hyperintensity	Parkinsonism persisted.	1 y
		43	F	Primary biliary cirrhosis (PBC)	Cirrhotic patient with basal ganglia T1 hyperintensity	Cognitive impairment resolved.	1 wk
15	Servin-Abad et al.[25]	47	F	Hepatitis C virus	AHCD	Confusion, dysarthria, gait instability, choreoathetotic movement of torso and extremities completely resolved for 11 months post LT and completely resolved after retransplant.	N/A
16	Nardone et al.[26]	Mean 51 (39-64)	3M/2F	PBC, Hepatitis B virus, alcohol	HM	2 patients with mild hepatic myelopathy improved, whereas 3 patients with more advanced disease did not improve.	6 mo
17	Pinarbasi et al.[27]	50	M	Hepatitis D virus	AHCD	AHCD (Confusion, dysarthria, bilateral lamb and gait ataxia) essentially resolved.	6 mo
		48	M	Hepatitis B virus	HM	HM improved (Able to walk independently 8 months).	8 mo
18	Fernandez-Rodriguez et al.[28]	68	M	Viral	AHCD	No improvement in neurologic disorder.	3-24 mo
		74	F	Viral	AHCD		(mean
		46	M	Hemochromatosis	AHCD		13 mo)

Abbreviations: AHCD, acquired hepatocerebral degeneration; F, female; HE, hepatic encephalopathy; HM, hepatic myelopathy; M, male; MHE, minimal hepatic encephalopathy; N/A, not applicable; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis

Discussion

Acquired (non-Wilsonian) hepatocerebral degeneration is an uncommon neurologic disorder that often occurs in patients with decompensated liver disease, especially those with extensive porto-systemic shunts. Since its first description by Van Woerkem in 1914,[30] this neurologic condition has

been well described. The clinical manifestations of AHCD are heterogeneous including (1) neuropsychiatric changes, such as delirium, apathy, lethargy, somnolence, and emotional instability; (2) movement disorder, such as tremor, Parkinsonism, akinesia, choreoathetosis, myoclonus, ataxia, asterixis, dystonia, and pyramidal signs; (3) myelopathy.[1, 3-5, 31, 32]

The exact prevalence of AHCD is not known, but it is estimated to be in the range of 1% to 2%. [27, 28] Acquired (non-Wilsonian) hepatocerebral degeneration typically affects adult in the fifth to sixth decade of life [1, 5, 8, 27]; however, it has been shown to affect children. [33]

Histologically, AHCD is characterized by diffuse brain atrophy and translucent discoloration within the cortex and basal ganglia.[2, 5] Small vacuoles (polymicro- cavitation) corresponding to the translucent lesions are observed on light microscopy. Polymicro-cavitation originates in the deep cortical layers and basal ganglia and characteristically extends into adjacent white matter tracts.[4] Alzheimer type II abnormalities of astrocytes are abundant in the regions of vacuolization.[5, 12] Neuroradiologically, patients with AHCD present with generalized mild-to-moderate atrophy and hyperintense T1-weighted signal in the pallidum, mesencephalon, and putamen, suggesting deposition of a paramagnetic substance, probably manganese, within the brain.[3, 11, 34-36]

To date, the pathogenesis of AHCD remains unclear. The presence of porto-systemic shunting may predispose patients to AHCD by allowing neurotoxic substances contained within the portal circulation to enter and deposit to the brain via the systemic circulation. Candidates for neurotoxins include ammonia, aromatic amino acids, and heavy metals, particularly manganese.[3, 12, 35-41] Approximately 3% of ingested manganese is absorbed, of which 98% undergoes biliary excretion.[42] In patients with liver disease, however, manganese may enter the systemic circulation and brain. Manganese is neurotoxic and affects both neuronal and astrocytic integrity.[43] Its accumulation in the basal ganglia and various parts of the cortex may account for abnormal movement disorders, the neuropsychiatric manifestations as well as the hyperintensities signal on T1-weighted images.[3]

Acquired hepatocerebral degeneration-related Parkinsonism, similar to idiopathic Parkinson's disease, is characterized by tremor, bradykinesia, rigidity, postural instability, and shuffling gait.[1] Information regarding the effect of dopamine replacement therapy for Parkinsonism symptoms is inconsistent. Some patients with AHCD-related Parkinsonism responded to levodopa and dopamine agonists,[1, 3, 8-10] whereas other data suggest patients with AHCD-related Parkinsonism respond poorly to conventional medications.[8, 11-14]

Acquired hepatocerebral degeneration was once thought to be irreversible; however, it has been suggested that liver transplant may improve, and possibly reverse AHCD. Therefore, a systematic literature search was performed of PubMed including the search terms: "acquired hepatocerebral degeneration," and "liver transplant." Additional papers and reports were identified through a manual review of the reference lists of identified case report and review articles. The literature search is summarized in Table 2.

Our review found a heterogeneous group of case series reported in 18 papers, suggesting that the experience with OLT is variable, although the reported experience with AHCD-associated Parkinsonian symptoms, and generalizable to our patient, is limited. Many patients improved or had complete resolution of AHCD after transplant. The improvement include Parkinsonism,[13, 15, 16, 20, 21] hyperkinetic movement disorder,[7, 20, 24, 25] ataxia,[25, 27] myelopathy,[18, 22, 26, 27] and cognitive dysfunction.[8, 20, 23, 27] Similar to our patient, 2 patients eventually developed recurrence of neurologic deficits post-transplant. [24, 25] As well, several patients did not improve their neurologic deficits or neuroimaging abnormalities post-transplant,[8, 17, 26, 28] and 1 patient had perioperative complications.[31]

Given the limited experience with AHCD outcomes post-transplant, especially in the case of Parkinsonian manifestations of AHCD, our experience may be clinically valuable. Our patient, who had Parkinsonian symptoms, had otherwise well-compensated cirrhosis and the intent of the liver transplant was to ameliorate his neurologic symptoms (ie, treatment of extrahepatic manifestations of cirrhosis as opposed to overt liver failure). Although our patient experienced complete resolution of his neurologic manifestations after OLT, this improvement lasted for approximately 6 weeks and was followed by a gradual recurrence that was

temporally associated with graft dysfunction, suggesting that AHCD was reversed with reversal of liver failure, only to recur when the transplanted liver failed. Similar to our experience, Servin-Abad and associates[25] reported a case of complete resolution followed by subsequent recurrence of AHCD owing to recurrent hepatitis C virus and chronic rejection that led to cirrhosis at 11 months after OLT. In that patient, another OLT resulted in complete resolution. In our situation, the cause of graft loss was, for the most part, hepatitis C-associated fibrosing cholestatic hepatitis, which is a contraindication for retransplant without successful eradication of the virus.

In summary, we report a patient with a 6-week period of near-complete resolution of neurologic symptoms of AHCD after OLT, and subsequent recurrence with graft failure. Our experience suggests that OLT is a possible effective therapy for AHCD-related Parkinsonism.

References

1. Burkhard PR, Delavelle J, Du Pasquier R, Spahr L. Chronic parkinsonism associated with cirrhosis: a distinct subset of acquired hepatocerebral degeneration. *Arch Neurol.* 2003;60(4):521-528.
2. Finlayson MH, Superville B. Distribution of cerebral lesions in acquired hepatocerebral degeneration. *Brain.* 1981;104(Pt 1):79-95.
3. Jog MS, Lang AE. Chronic acquired hepatocerebral degeneration: case reports and new insights. *Mov Disord.* 1995;10(6):714-722.
4. Ferrara J, Jankovic J. Acquired hepatocerebral degeneration. *J Neurol.* 2009;256(3):320-332.
5. Victor M, Adams RD, Cole M. The acquired (non-Wilsonian) type of chronic hepatocerebral degeneration. *Medicine (Baltimore).* 1965;44(5):345-396.
6. Mendez MF. Hepatic dementia or acquired hepatocerebral degeneration. *J Am Geriatr Soc.* 1989;37(3):259-260.
7. Layrargues GP. Movement dysfunction and hepatic encephalopathy. *Metab Brain Dis.* 2001;16(1-2):27-35.
8. Klos KJ, Ahlskog JE, Josephs KA, Fealey RD, Cowl CT, Kumar N. Neurologic spectrum of chronic liver failure and basal ganglia T1 hyperintensity on magnetic resonance imaging: probable manganese neurotoxicity. *Arch Neurol.* 2005;62(9):1385-1390.
9. Lunzer M, James IM, Weinman J, Sherlock S. Treatment of chronic hepatic encephalopathy with levodopa. *Gut.* 1974;15(7):555-561.
10. Morgan MY, Jakobovits AW, James IM, Sherlock S. Successful use of bromocriptine in the treatment of chronic hepatic encephalopathy. *Gastroenterology.* 1980;78(4):663-670.
11. Aggarwal A, Vaidya S, Shah S, Singh J, Desai S, Bhatt M. Reversible Parkinsonism and T1W pallidal hyperintensities in acute liver failure. *Mov Disord.* 2006;21(11):1986-1990.
12. Klos KJ, Ahlskog JE, Kumar N, et al. Brain metal concentrations in chronic liver failure patients with pallidal T1 MRI hyperintensity. *Neurology*. 2006;67(11):1984-1989.
13. Shulman LM, Minagar A, Weiner WJ. Reversal of parkinsonism following liver transplantation. *Neurology.* 2003;60(3):519.
14. Yoshikawa K, Matsumoto M, Hamanaka M, Nakagawa M. A case of manganese induced parkinsonism in hereditary haemorrhagic telangiectasia. *J Neurol Neurosurg Psychiatry*. 2003;74(9):1312-1314.
15. Powell EE, Pender MP, Chalk JB, et al. Improvement in chronic hepatocerebral degeneration following liver transplantation. *Gastroenterology.* 1990;98(4):1079-1082.
16. Pujol A, Pujol J, Graus F, et al. Hyperintense globus pallidus on T1-weighted MRI in cirrhotic patients is associated with severity of liver failure. *Neurology.* 1993;43(1):65-69.
17. Counsell C, Warlow C. Failure of presumed hepatic myelopathy to improve after liver transplantation. *J Neurol Neurosurg Psychiatry.* 1996;60(5):590.
18. Troisi R, Debruyne J, de Hemptinne B. Improvement of hepatic myelopathy after liver transplantation. *N Engl J Med.* 1999;340(2):151.
19. Spahr L, Vingerhoets F, Lazeyras F, et al. Magnetic resonance imaging and proton spectroscopic alterations correlate with parkinsonian signs in patients with cirrhosis. *Gastroenterology*. 2000;119(3):774-781.
20. Stracciari A, Guarino M, Pazzaglia P, Marchesini G, Pisi P. Acquired hepatocerebral degeneration: full recovery after liver transplantation. *J Neurol Neurosurg Psychiatry*. 2001;70(1):136-137.
21. Lazeyras F, Spahr L, DuPasquier R, et al. Persistence of mild parkinsonism 4 months after liver transplantation in patients with preoperative minimal hepatic encephalopathy: a study on neuroradiological and blood manganese changes. *Transpl Int.* 2002;15(4):188-195.
22. Weissenborn K, Tietge UJ, Bokemeyer M, et al. Liver transplantation improves hepatic myelopathy: evidence by three cases. *Gastroenterology.* 2003;124(2):346-351.
23. Mattarozzi K, Stracciari A, Vignatelli L, D'Alessandro R, Morelli MC, Guarino M. Minimal hepatic encephalopathy: longitudinal effects of liver transplantation. *Arch Neurol.* 2004;61(2):242-247.
24. Papapetropoulos S, Singer C. Management of the extrapyramidal syndrome in chronic acquired hepatocerebral degeneration (CAHD). *Mov Disord.* 2005;20(8):1088-1089.
25. Servin-Abad L, Tzakis A, Schiff ER, Regev A. Acquired hepatocerebral degeneration in a patient with HCV cirrhosis: complete resolution with subsequent recurrence after liver transplantation. *Liver Transpl.* 2006;12(7):1161-1165.
26. Nardone R, Buratti T, Oliviero A, Lochmann A, Tezzon F. Corticospinal involvement in patients with a portosystemic shunt due to liver cirrhosis: a MEP study. *J Neurol.* 2006;253(1):81-85.
27. Pinarbasi B, Kaymakoglu S, Matur Z, et al. Are acquired hepatocerebral degeneration and hepatic myelopathy reversible? *J Clin Gastroenterol*. 2009;43(2):176-181.
28. Fernández-Rodriguez R, Contreras A, de Villoria JG, Grandas F. Acquired hepatocerebral degeneration: clinical characteristics and MRI findings. *Eur J Neurol*. 2010;17(12):1463-1470.
29. Web site of MoCA. Accessed September 20, 2011. Available at: www.mocatest.org.
30. VanWoerkem W. La cirrhose hepatique avec alterations dans les centres nerveux evoluant chez des sujets d'age moyen. Nouvelle Iconographie de la Salpetriere. *Clinique des Maladies du Systeme Nerveux.* 1914;7:41-51.
31. Lewis MB, MacQuillan G, Bamford JM, Howdle PD. Delayed myelopathic presentation of the acquired hepatocerebral degeneration syndrome. *Neurology.* 2000;54(4):1011.
32. Stracciari A, Mattarozzi K, D'Alessandro R, Baldin E, Guarino M. Cognitive functioning in chronic acquired hepatocerebral degeneration. *Metab Brain Dis.* 2008;23(2):155-160.
33. Papapetropoulos S, Tzakis A, Sengun C, et al. Case of pediatric acquired chronic hepatocerebral degeneration. *Pediatr Neurol.* 2008;38(1):67-70.
34. Taylor-Robinson SD, Oatridge A, Hajnal JV, Burroughs AK, McIntyre N, deSouza NM. MR imaging of the basal ganglia in chronic liver disease: correlation of T1-weighted and magnetisation transfer contrast measurements with liver dysfunction and neuropsychiatric status. *Metab Brain Dis.* 1995;10(2):175-188.
35. Park NH, Park JK, Choi Y, et al. Whole blood manganese correlates with high signal intensities on T1-weighted MRI in patients with liver cirrhosis. *Neurotoxicology.* 2003;24(6):909-915.
36. Pal PK, Samii A, Calne DB. Manganese neurotoxicity: a review of clinical features, imaging and pathology. *Neurotoxicology.* 1999;20(2-3):227-238.
37. Basile AS, Jones EA. Ammonia and GABA-ergic neurotransmission: interrelated factors in the pathogenesis of hepatic encephalopathy. *Hepatology.* 1997;25(6):1303-1305.

38. Rose C, Butterworth RF, Zayed J, et al. Manganese deposition in basal ganglia structures results from both portal-systemic shunting and liver dysfunction. *Gastroenterology*.1999;117(3):640-644.
39. Huang CC, Lu CS, Chu NS, et al. Progression after chronic manganese exposure. *Neurology.* 1993;43(8):1479-1483.
40. Huang CC, Chu NS, Lu CS, Chen RS, Schulzer M, Calne DB. The natural history of neurological manganism over 18 years. *Parkinsonism Relat Disord.* 2007;13(3):143-145.
41. Stepens A, Logina I, Liguts V, et al. A Parkinsonian syndrome in methcathinone users and the role of manganese. N Engl J Med. 2008 6;358(10):1009-1017.
42. Scheuhammer AM, Cherian MG. The influence of manganese on the distribution of essential trace elements. II. The tissue distribution of manganese, magnesium, zinc, iron, and copper in rats after chronic manganese exposure. *J Toxicol Environ Health*. 1983;12(2-3):361-370.
43. Butterworth RF. Complications of cirrhosis III. Hepatic encephalopathy. *J Hepatol.* 2000;32(1 Suppl):171-180.