Journal of Clinical and Translational Hepatology **2024** vol. 12(4) | 436–442
DOI: 10.14218/JCTH.2023.00487

Illuminating and Instructive Clinical Case

Liver Transplantation Reverses Hepatic Myelopathy in the Decompensated Phase of Cirrhosis: Case Report and Literature Review

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Received: 27 October 2023 | **Revised:** 14 January 2024 | **Accepted:** 5 February 2024 | **Published online:** 13 March 2024

Abstract

Hepatic myelopathy (HM) is a rare neurological complication in the end stage of many liver diseases and is characterized by bilateral spastic paraparesis without sensory and sphincter dysfunction. It occurs owing to metabolic disorders and central nervous system dysfunction associated with cirrhosis. Without timely and effective clinical intervention, the prognosis of these patients is devastating. Although liver transplantation (LT) is an effective treatment for HM, the prognosis of these patients remains unsatisfactory. Early recognition and diagnosis of this disease are essential for improving patient prognosis. Here, we report a case of hepatitis B virus-associated decompensated cirrhosis with HM. The patient recovered well after LT. We also summarize the clinical characteristics and post-transplant outcomes of 25 patients with HM treated by LT through 2023, including this case.

Citation of this article: Li J, Wan S, Wen F, Li Q, Cui Y, Lu Z, *et al*. Liver Transplantation Reverses Hepatic Myelopathy in the Decompensated Phase of Cirrhosis: Case Report and Literature Review. J Clin Transl Hepatol 2024;12(4):436–442. doi: 10.14218/JCTH.2023.00487.

Introduction

Hepatic myelopathy (HM) is a rare complication of chronic liver disease combined with cirrhosis. It is usually thought to be related to the spontaneous formation of portal shunt channels or secondary to surgery in patients with liver disease.[1] It is characterized by bilateral chronic, progressive, symmetric spastic paraparesis with rare sphincter and sensory involvement and myasthenia gravis with extensive portal collateral circulation.[2,3] Early spinal cord injury in HM is characterized by bilateral symmetric demyelinating lesions of the lateral cord of the spinal cord, mostly accumulating below the cervical cord, with a minority of cases involving the entire length of the spinal cord. Injury to the segments may be one of the reasons why the lower limbs of patients with HM are more susceptible than the upper limbs.[4] Demyelination is reversible if the underlying liver disease or portal system shunt is managed promptly. Progression to the stage of axonal loss will result in irreversible damage as the disease progresses.[5]

The diagnosis of HM requires excluding other causes of spastic paraplegia, such as amyotrophic lateral sclerosis, hereditary and toxic spondylotic myelopathies, multiple sclerosis, and paraneoplastic syndromes.[6] Laboratory tests are primarily associated with varying degrees of hepatic insufficiency or manifestations of cirrhosis. Regarding imaging, it has been reported that in patients with HM, the characteristic change of cranial magnetic resonance imaging (MRI) is a high signal at T1WI.[7,8] However, most imaging does not show a neurological abnormality.

By examining the motor-evoked potentials (MEPs) of 13 patients with cirrhosis, portal system shunts, and 20 healthy individuals, Nardone *et al*.[9] found significant differences in motor-evoked potential (MEP) values between cirrhotic and healthy individuals. Six patients with clinical signs of spinal cord involvement demonstrated a significant prolongation of the central motor conduction time (CMCT). In contrast, mild MEP was detected in four out of seven patients with normal clinical examination abnormalities. The patients were included in three groups depending on the degree of central motor involvement indicated by the MEP. Group A included patients with normal motor evoked potentials (MEPs), group B included patients with a slight prolongation of CMCT (between 18 ms and 22 ms), and group C included patients with a significant increase in CMCT (more than 24 ms). The clinical and neurophysiological characteristics of patients with mild MEP abnormalities improved after LT but no changes were found in patients with advanced disease (and more severe MEP abnormalities). Therefore, central motor studies are a sensitive method for detecting, localizing, and monitoring spinal cord injury in HM, revealing damage to corticospinal pathways at the preclinical stage and providing evidence for early diagnosis and subsequent immediate LT.

When CMCT is significantly increased, post-transplant neurologic recovery may be significantly diminished from earlier stages, and MEP/CTMT testing has a reference value

Keywords: Hepatic myelopathy; Hepatic encephalopathy; Spastic paraparesis; Portosystemic shunt; Liver transplantation.

Abbreviations: CMCT, central motor conduction time; HAV, hepatitis A virus; HBV, hepatitis B virus; HCV, hepatitis C virus; HM, Hepatic myelopathy; LT, liver transplantation; MEP, motor-evoked potential; MRI, magnetic resonance imaging; PBC, primary biliary cirrhosis; TIPS, transjugular intrahepatic portosystemic shunt.

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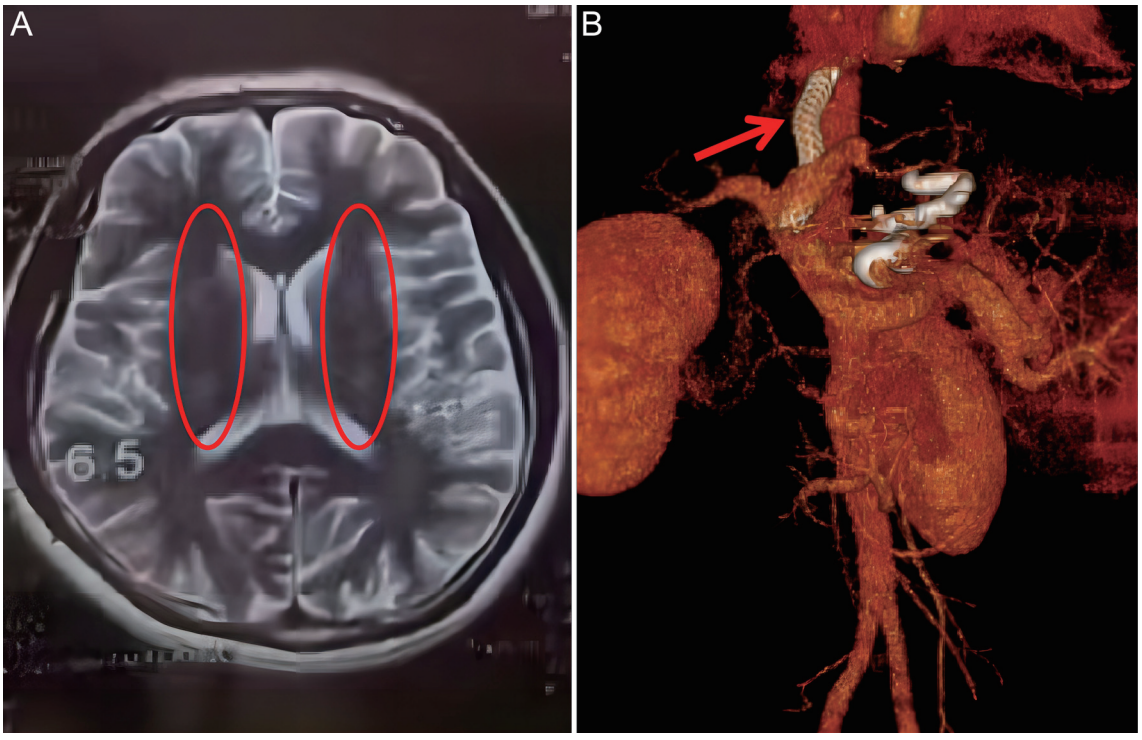

Fig. 1. Patient imaging data. (A) Red circle shows lesions in the patient's bilateral basal ganglia region; (B) Red arrows show the patient's post-TIPS stents.

superior to that of imaging. However, the sensitivity, specificity, and predictive value of specific MEP/CMCT and grading criteria need validation by larger studies.

Currently there is no proven effective treatment for HM, but a summary of the available literature indicates that LT can significantly alleviate clinical symptoms in patients with HM and may be effective. In 2017, diBiase *et al*.[10] reported that HM in patients with hepatitis C virus infection can be treated with sofosbuvir and ribavirin. Reports also exist of severe spasmodic truncation of HM by embolization of part of the splenic artery to substantially reverse severe spastic paraplegia owing to HM,[11] and Sun *et al*.[12] pioneered the application of fecal colony transplantation to treat HM.

Here, we report a case in a male adult who developed spasticity and paralysis of the extremities 6 months after transjugular intrahepatic portosystemic shunt (TIPS) placement and recovered well after LT. We searched Pubmed, China Knowledge Network Infrastructure, Wanfang Data Knowledge Platform, and Wipu Chinese Journal Service Platform for Chinese and English literature published between 1988 and 2023 using the keywords "hepatic spondylosis" and "liver transplantation." We collected reports of cases diagnosed with HM reviewed through radiologic or neurophysiologic tests and receiving liver transplantation. A total of 62 cases were retrieved, and upon excluding duplicates and severe cases with missing information 25 valid cases were included in our review.

Case report

A 42-year-old man presented in November 2021 with unexplained hematemesis and a ruptured variceal hemorrhage of the esophagogastric fundus vein. Cirrhosis, viral hepatitis B, and diabetes mellitus were concurrently detected. Sclerotherapy was administered at that time. Hematemesis recurred after 4 months, leading to TIPS treatment in July 2022 (Fig. 1). The patient experienced hepatic encephalopathy for the first time 3 months after the TIPS procedure, with a recurrence 7 months later, accompanied by lower-limb stiffness, weakness, and unsteady walking. After symptom onset, the patient's blood ammonia was 38.4 mmol/L (normal range: 10–47 mmol/L).

Cranial MRI revealed lesions in the bilateral basal ganglia region, indicating degeneration (Fig. 1). A spinal MRI of the entire spine was normal except for mild dilatation of the central spinal canal at the level of the C6–C7 interspinal disk. Electromyographic evaluation revealed peripheral neurogenic damage in both lower extremities with no other abnormalities. After consultation with a neurologist to rule out other causes, the patient was diagnosed with HM and placed on the waiting list for LT.

The patient was admitted to the Department of Liver Surgery of the First Affiliated Hospital of Harbin Medical University for LT in May 2023, with a diagnosis of hepatitis B-associated decompensated cirrhosis (model for end-stage liver disease score of 13), upper gastrointestinal bleeding, ascites, hypersplenism, and HM. Neurologic examination on admission revealed spastic paraplegia of both lower extremities with grade 2 muscle strength, increased muscle tension in the lower extremities, inability to stand on his own, normal function of the upper extremities, and no sensory bladder or bowel disturbances. A cranial brain CT performed after admission revealed no obvious abnormality. After completing relevant examinations, the patient underwent brain-dead donor LT.

Post surgery, the patient was transferred to the transplantation intensive care unit. Six hours later, the ventilator was removed, and the patient resumed spontaneous breathing. On the third postoperative day, the patient developed a fever of 39.2°C. After excluding other conditions, a novel coronavirus nucleic acid test confirmed that the patient was infected

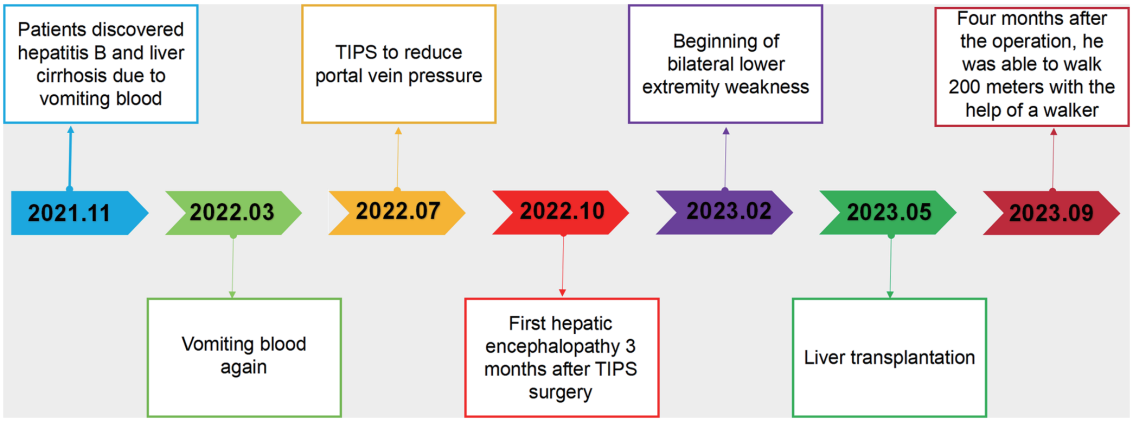

Fig. 2. Flow chart of the patient's treatment. TIPS, transjugular intrahepatic portosystemic shunt.

with the novel coronavirus. Given the absence of abnormalities other than fever, no special treatment was administered except for symptomatic antipyretic treatment.

The patient was transferred to the general ward on the sixth postoperative day. At that time, the patient still could not lift his legs off the bed, but stiffness reduction was reported. The patient was discharged on the fifteenth postoperative day. The treatment history after the discovery of cirrhosis is shown in Figure 2.

The patient underwent regular follow-up with weekly checkups in the first month after discharge and biweekly outpatient visits starting in the second month. One month post-hospital discharge, continuous exercise training, and rehabilitation commenced. Four months post-transplantation, the patient exhibits normal liver function and total bilirubin level, grade 4 muscle strength, and can walk approximately 200 meters with the assistance of a walker. He has had no other neurological symptoms during consultation.

Literature review

We conducted a retrospective study of patients diagnosed with HM between 1988 and 2023, treated with LT and reported in the Chinese and English literature. The literature screening process is shown in Figure 3. Excluding duplicates and severe cases with missing information, 25 valid cases, including the patients reported herein, were included in our study. The patients' clinical characteristics and post-transplantation outcomes are shown in Table 1.[2,7–9,13–23] The lack of standardized reporting parameters limited the summary analysis of the literature. However, our analysis led to the following conclusions (Table 2).

Analysis of the published data showed that over 70% of the patients had a portal shunt before disease onset, and over 60% had a medical origin. Brain MRI or CT findings were reported in 14 cases. Of those cases, five patients exhibited results, and of the remaining nine, four had abnormal pallid globe high signal and three had basal ganglia area lesions. Only one case had abnormal, high corticospinal fluid attenuated inversion recovery signals on MRI. In an autopsy study, Maeda *et al*.[24] found that manganese deposition may be involved in the pathogenesis of acquired hepatic encephalopathy, often affecting the basal ganglia region, especially the pallid bulb and the cerebellum. They also noted that the toxic effect of portal blood is most obvious in the basal ganglia, possibly owing to its high metabolic activity.[25] Therefore, verifying whether the lesions in the basal ganglia region are characteristic of HM requires confirmation in more cases.

The duration of HM symptoms before LT ranged from 2 to 25 months. While it is unclear whether the thicker shunt was ligated during transplantation in this patient group, it is certain that, except for four patients whose neurological symptoms did not improve after transplantation, the remaining patients with decompensated cirrhosis experienced significant improvement in cirrhosis symptoms. None suffered complications such as portal vein thrombosis, hepatic encephalopathy, or graft dysfunction after the operation. This indicates that all patients in this group had improved perfusion after surgery, and the lack of relief of neurologic symptoms in some patients after transplantation was likely owing to inappropriate timing of the procedure.

Ligation of hemodynamically significant shunts is recommended to prevent decreased portal venous flow, secondary portal vein atrophy, and thrombosis.[26,27] Preoperative detection of large shunts by Doppler ultrasound and abdominal CT requires preemptive development and optimization of surgical and interventional treatment plans, essential for improving postoperative recovery and survival of HM patients with transplanted livers. Over 80% of the reported patients diagnosed with HM experienced neurologic improvement after *in situ* transplantation, but reports of the duration and degree of improvement after LT varied widely.

Analysis of the aforementioned cases indicates that portal shunts cause HM and that LT significantly improved the symptoms of HM. Significant and timely recovery is likely when LT is performed early during HM.

Discussion

HM is a rare disease often neglected or misdiagnosed in clinical practice owing to its low incidence. The pathogenesis of HM is still unclear and it is considered to include a combination of factors. Currently, there is evidence of the following. (1) The liver's ability to inactivate toxic substances decreases in cirrhosis. Simultaneously, after the portal and autogenic shunts, many toxic substances bypass the liver, causing direct damage to the spinal cord.[28,29] (2) Owing to decreased substance absorption and synthesis caused by liver insufficiency and portal shunts, substances with protective and nutritive effects on the spinal cord and nerves, especially vitamin B12, are lacking. (3) Some scholars speculate that the immune response caused by viral infection directly leads to spinal cord injury, to immune complexes that are widely deposited in the nervous system, and activation of complement

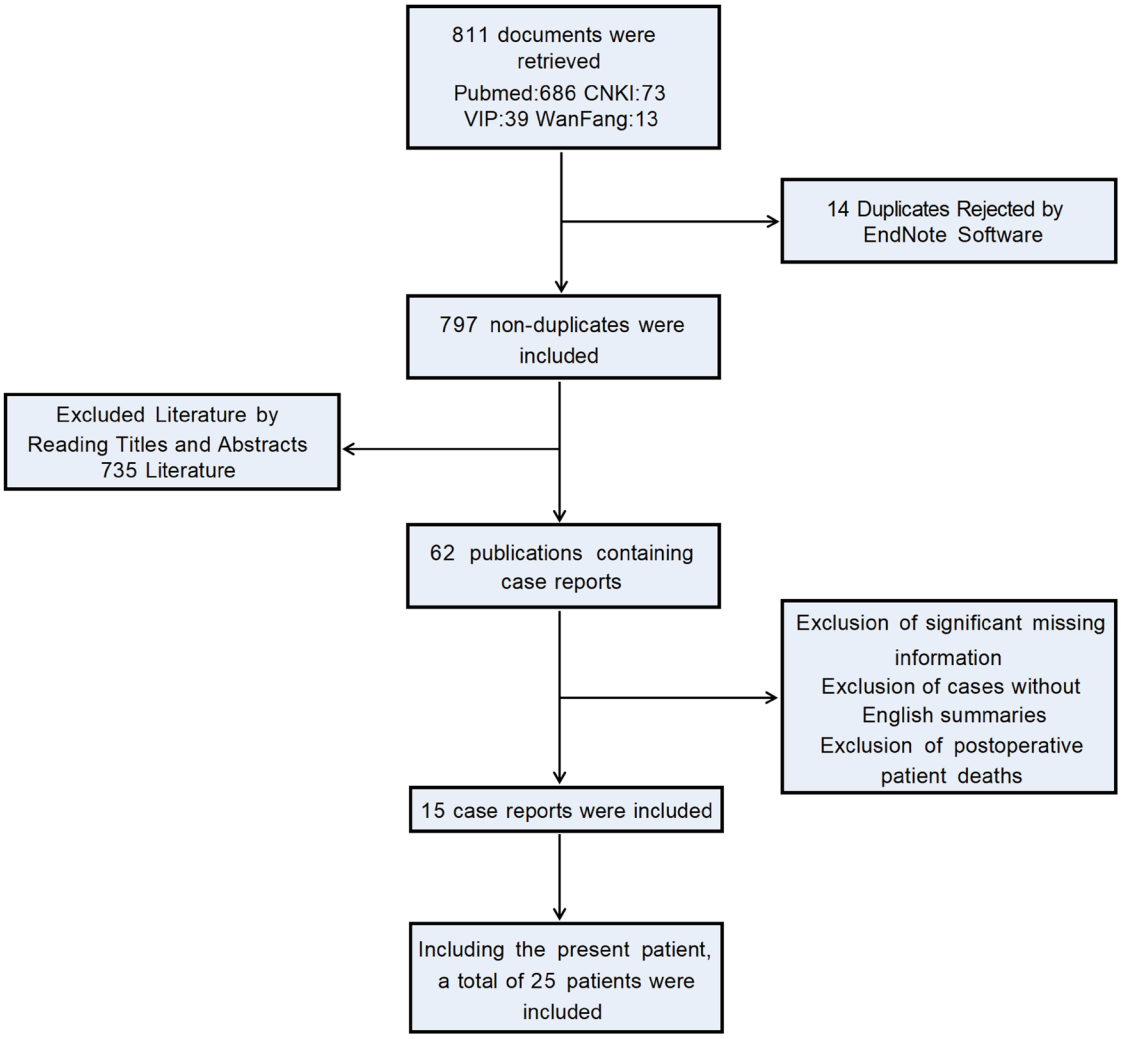

Fig. 3. Literature search strategy and selection flowchart.

to cause nodular polyarteritis and subsequent spinal cord damage.[30] (4) Prolonged portal hypertension can lead to the stagnation of the vertebral venous plexus in the thoracic and lumbar segments, causing chronic ischemia, hypoxia, and nutrient metabolism disorders of the thoracolumbar spinal cord after the portal venous shunt, ultimately resulting in degeneration and necrosis.[31] Portal shunts are considered essential for the development of HM. However, it has been previously reported that even in the absence of a portal venous system shunt, a large amount of blood may enter the somatic circulation from the portal venous system via a small lateral branch, leading to symptoms in some patients with HM. This may explain why patients without portosystemic shunts still develop HM.[17] Therefore, the purpose and effect of multiple treatment modalities are to improve liver function and reduce shunting, not to eradicate the cause of advanced liver disease. Some patients have experienced relief or even cure of neurological symptoms after treatment with TIPS blockade, splenic artery embolization, and LT, but the cause of liver disease persisted.

Summarizing previous reports, it is evident that HM should be diagnosed and treated early to increase the chances of complete spinal cord recovery. Although HM after chronic liver disease is rarely life-threatening in the short term, it often seriously affects quality of life. Therefore, timely and effective management of HM is clinically significant, and patients need to improve their ability for early diagnosis and strive for early treatment. Notably, HM can occur in patients with congenital hepatic fibrosis and focal nodular hyperplasia,[32] emphasizing that the severity of HM does not necessarily parallel the degree of hepatic dysfunction. Therefore, reconsideration is needed regarding whether patients with HM should be evaluated for transplant eligibility by the conventional criteria. Early transplantation therapy may improve the chances of complete spinal cord recovery. Simultaneous recovery from spinal cord disease after LT for HM owing to chronic liver disease is slow and may be incomplete. However, recovery is rapid and complete in spinal cord disease associated with acute liver failure because these patients have only demyelinating changes without axonal loss.[22] It cannot be ignored that while immunosuppressive regimens after LT have improved the survival of liver transplant recipients, the side effects of immunosuppressive agents pose a significant threat to postoperative quality of life and long-term prognosis. Calcineurin inhibitor-induced neurotoxicity is a common neurologic complication after LT, occurring in approximately

Table 1. Clinical data of 25 patients diagnosed with HM and treated by and underwent liver transplantation

Country	Age	Sex	Etiology	Shunt	Brain CT/ MRI	Symptom duration, months	Post-transplantation situation
1 (UK)[13]	52	Male	Alcohol	/	Normal	16	No improvement after 18 months
2 (Belgium)[14]	60	Female	HCV	Portocaval	/	9	Walked independently after 18 months
3 (Germany)[7]	35	Male	HBV+HCV	/	Normal	25	Walked 1–2 km with a cane after 13 years
4 (Germany)[7]	40	Male	HCV	TIPS	T1 pallidal hyperintensity	8	Walked several kilometers with a cane after 2.5 years
5 (Germany)[7]	42	Male	HBV	TIPS	T1 pallidal hyperintensity	10	Walked a few meters with a cane after 9 months
6 (China)[15]	38	Male	HBV	Portocaval	/	2	Walked with support after 12 month
7 (China)[15]	53	Male	HBV	Portocaval	/	10	Walked with support after 18 months
8 (Italy)[9]	42	Male	PBC	TIPS	/	/	Normal strength after 6 months
9 (Italy)[9]	39	Female	PBC	TIPS	/	/	Normal strength after 6 months
10 (Italy)[9]	54	Male	HBV	TIPS	/	/	No improvement after 6 months
11 (Italy)[9]	64	Female	Alcohol	TIPS	/	/	No improvement after 6 months
12 (Italy)[9]	58	Male	HBV	Spontaneous	/	/	No improvement after 6 months
13 (Korea)[2]	39	Male	HBV	Spontaneous	Normal	6	Walked 100 meters after 3 years
14 (China)[16]	35	Male	HBV	Splenorenal	/	3	Assisted walking after 6 years
15 (China)[8]	32	Male	HBV	/	T1 pallidal hyperintensity	2	Walked with a cane after five months
16 (China)[8]	29	Male	HBV	TIPS	T1 pallidal hyperintensity	3	Walked 2–3 km with a cane after 18 months
17 (Turkey)[17]	48	Male	HBV	Splenorenal	Basal ganglia abnormalities	/	Walking independently after 8 months
18 (USA)[18]	50	Male	HCV	/	FLAIR corticospinal tract hyperintensity	14	Walked independently
19 (Italy)[19]	47	Male	HCV	TIPS	Mild cerebral atrophy	6	Walked independently after 3 months
20 (Turkey)[20]	39	Female	Cryptogenic cirrhosis	TIPS	/	36	Walked independently after 3 months
21 (China)[21]	61	Female	HBV	TIPS	/	12	Assisted walking 100 meters after 3 months
22 (India)[22]	5	Male	HAV	/	Normal	/	Walked independently after 2 months
23 (India)[22]	5	Female	HAV	/	Normal	/	Walked after 2 months
24 (China)[23]	48	Male	HBV	/	Basal ganglia abnormalities	/	Walked independently after 15 months
25 (China)	42	Male	HBV	TIPS	Basal ganglia abnormalities	3	Assisted walking 200 meters after 4 months

CT, computed tomography; MRI, magnetic resonance imaging; HAV, hepatitis A virus; HBV, hepatitis B virus; HCV, hepatitis C virus; PBC, primary biliary cirrhosis; TIPS, transjugular intrahepatic portosystemic shunt; FLAIR, fluid attenuated inversion recovery; UK, United Kingdom; USA, United States of America.

40% of liver transplant recipients, usually in the first month post-transplantation.[33,34] However, HM patients often have a preoperative history of hepatic encephalopathy, making them more sensitive to neurotoxic drugs after transplantation. In this context, calmodulin phosphatase inhibitors, such as tacrolimus and cyclosporine, can exacerbate underlying neurologic damage and induce neurologic disease. With the advent of mammalian targets of rapamycin inhibitors, the range of

Table 2. Analysis of clinical data and prognosis of enrolled patients

Feature	Values*	Feature	Cases, *n* (%)
Sex		Shunt	
Male	19 (76)	Iatrogenic	18 (72)
Female	6 (24)	Spontaneous	2 (8)
Age in years	42 (5–64)	Brain CT/MRI	
		Normal	5 (20)
Cause of cirrhosis		Pallidal hyperintensity	4 (16)
HBV	13 (52)	Basal ganglia abnormalities	3 (12)
HCV	4 (16)	FLAIR corticospinal tract hyperintensity	1 (4)
HAV	2 (8)		
Alcohol	2 (8)	Cerebral atrophy	1 (4)
PBC	2 (8)	Prognostic results	
Cryptogenic cirrhosis	1 (4)	Enhancement	21 (84)
HBV+HCV	1 (4)	Null	4 (16)

*Data are *n* (%) or median (range). CT, computed tomography; FLAIR, fluid attenuated inversion recovery; HAV, hepatitis A virus; HBV, hepatitis B virus; HCV, hepatitis C virus; PBC, primary biliary cirrhosis; MRI, magnetic resonance imaging.

viable alternatives for these patients has increased.[35] Therefore, HM patients should be promptly tapered or replaced with immunosuppressive medications upon developing peripheral manifestations, such as neuropathy and tremor, or central nervous system symptoms, such as headache, mood changes, numbness, and seizures, after transplantation.

In summary, evaluation of the overall results of the available case confirmed that LT is an effective treatment for HM, and early diagnosis and transplantation therapy play a critical role in improving patient prognosis. However, the number of reports on the efficacy of LT in treating HM is still relatively small, and there is no systematic study on its long-term efficacy. Confirmation by prospective studies is still needed.

Acknowledgments

We express our gratitude to the patients who generously provided the experimental samples and to our teachers for providing funding.

Funding

This work was supported by The National Natural Scientific Foundation of China (Grant No. 81972230).

Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Concept and design (JL, SW), drafting of the manuscript (JL, FW), statistical analysis (JL, QL), data collection (JL, SW, FW, QL YC), and revision of the manuscript for important intellectual content (ZL, HL).

Ethical statement

The study was conducted following the ethical standards of the involved institution and the Declaration of Helsinki, as revised in 2013. Written informed consent was obtained from the patient for the publication of this anonymized case report.

Data sharing statement

All data generated or analyzed during this study are included in this published article.

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