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Case Report

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# Hepatic Myelopathy: Case Report and Review of the Literature

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## ABSTRACT

**Background:** Hepatic Myelopathy (HM) is a rare complication of chronic liver disease usually associated with extensive portosystemic shunt of blood, which has been created surgically or has occurred spontaneously, causing progressive spastic paraparesis. Some single cases or short clinical reports describing patients suffering from HM have been published worldwide, but are often scattered.
**Material and method:** One additional case of HM with typical symptoms was presented, and a retrospective survey of the literature in a manner of comprehensive review was undertaken.
**Results:** 46 case reports with 98 patients of HM including ours have been eligibly selected. General information on all cases was summarized. Detailed analysis of the clinical characteristics of HM patients was undertaken.
**Conclusion:** Liver cirrhosis caused by hepatitis B infection and alcoholism is the most frequent causes of HM. Portosystemic shunt which resulted in chronic exposure to toxic substances bypassing the liver play an important role in the pathogenesis. The pathology study consistently disclosed a selective and symmetrical severe loss of myelin in both lateral pyramidal tracts. The predominant neurologic abnormality of HM is the progressive spasticity and weakness in the lower extremities. A typical manifestations, such as triparesis or quadriparesis, sensory deficit, urinary or bladder incontinence and non-pyramidal manifestations such as dysarthria, tremor and ataxia can also occur, which render the disorder more complicated to be diagnosed. Plasma ammonia concentrations were frequently found to be elevated. MEP provides evidence of the early diagnosis of HM and assesses different degrees of neurological involvement. The spinal cord MRI imaging shows no abnormality. Abnormalities of brain magnetic resonance combined with syndrome of brain dysfunction, hepatocerebral degeneration should be taken into consideration. Appending case studies suggest that liver transplantation is a promising therapeutic strategy.

**KEYWORDS:** Hepatic myelopathy; Spastic paraparesis.

**ABBREVIATIONS:** HM: Hepatic Myelopathy; CLD: Chronic Liver Disease; HE: Hepatic Encephalopathy; AHCD: Acquired hepatocerebral degeneration; HTLV-1: Human T-cell Lymphotrophic Virus; MRI: Magnetic Resonance Imaging; TIPS: Transjugular Intrahepatic Portosystemic Shunt; HIV: Human Immunodeficiency Virus; OLT: Orthotopic Liver Transplantation.

## INTRODUCTION

Patients with Chronic Liver Disease (CLD) frequently experience neurologic sequel, usually associated with extensive portosystemic shunt of blood, a liver bypass either by portosystemic anastomosis or as a result of the development of an extensive portosystemic collateral

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circulation. The most common and widely recognized is the reversible syndrome of Hepatic Encephalopathy (HE). There are also comparatively rare and largely irreversible conditions such as Acquired hepatocerebral degeneration (AHCD)[1] and hepatic myelopathy (HM),[2] especially the knowledge on HM is sparse. The predominant neurologic abnormality of HM is the progressive spasticity and weakness in the lower extremities which often render the patient to become wheelchair bound. Since Leigh and Card, firstly described the occurrence of HM in 1949, some single cases or short clinical reports describing patients suffering from HM have been published worldwide,[3] but are often scattered. Herein the author presented one additional case of HM with typical symptoms and undertook a retrospective survey in a manner of comprehensive review in order to determine the clinical and pathophysiological features and treatment of HM.

## CASE REPORT

A 29-year-old man was admitted on November 25, 2009, because of a progressive spastic paraparesis which had proceeded over the previous 2 months. The patient complained for the first time of symptoms of stiffness and weakness of legs. Gradually his walking became unsteady, tripping over objects. On admission, he could stand without support but was not able to walk without help. He walked leaning forward with his feet close together, with 'step page' or puppet-like gait. He was suffering from posthepatitic cirrhosis caused by hepatitis B with a history of 6 years, having ascites as the initial presentation in 2003, but constantly without prior recurrent episodes of hepatic encephalopathy. Four years back, he had recurrent jaundice and pedal edema but no hematemesis. In 2008, he received blood transfusion because of thrombocytopenia. He had neither history of alcohol consumption nor family history of liver or neurological illness. On examination, the patient was alert, cooperative and orientated. He had no speech disturbance. He had palmar erythema, spider-angioma, and peripheral edema. The abdomen showed small venous collaterals and marked generalized distension with fluid wave due to ascites. The enlarge spleen was palpable three finger-breadths below the costal margin, firm and nontender. Liver and kidney was not palpable. There were no Kayser-Fleischer corneal rings. On neurological examination, cranial nerve examinations were normal. Spastic paraparesis was observed. Muscle tone was markedly increased, particularly in the lower limbs, with pathologically brisk deep tendon reflexes and bilateral extensor plantar responses, and there was clonus at the ankles, but no sensory loss. Muscle strength in the lower limbs was decreased (MRC grade 4). There was neither atrophy nor fasciculation. Bowel and bladder function were normal. There was no evidence of cerebellar or extrapyramidal dysfunction. Laboratory findings revealed increased plasma bilirubin and ammonia levels. Prothrombin time was prolonged. Hemogram disclosed thrombocytopenia, leucocytopenia and normocytic hypochromic anemia. Liver function tests revealed normal serum bilirubin, minimally raised alanine aminotransferase and aspartate aminotransferase, reduced albumin, and reversed albumin/globulin ratio. Serum Vitamin B12 and foliate values were within normal ranges. Serum antibodies to Human T cell lymphotrophic virus (HTLV-1) and Hepatitis C virus were absent. Anti-HBs was negative, and HBsAg, anti-HBc, anti-HBe positive. Copper values of serum and urine were normal. Small esophageal and gastric varices were demonstrated during the upper gastrointestinal endoscopy. Lumbar puncture could not be performed because of his severely impaired coagulation status. Ultrasound (abdomen) exhibited features of cirrhosis of liver: irregular liver surface and different echogenicity in the underlying liver. Doppler study showed functioning lienorenal shunt, recanalized umbilical venous and extensive collateralization. EEG was normal. Cranial Magnetic Resonance Imaging (MRI) showed no abnormalities. MRI of the whole spinal cord was normal except degenerative bone changes in the area of L4-5, L5-S1 without evidence of spinal cord compression. The electromyographic evaluation for second motor neuron involvement was also normal. It was suggested that the features in our patient were typical of HM: spastic paraplegia occurred during the course of liver cirrhosis, which is progressive and permanent. After several weeks of lactulose administered by rectum, neomycin, protein restriction, combined with oral lioresal, he had improved mobility, with decreased spasticity but no significant changes in the remainder of his neurological examination and was discharged one month later.

## REVIEW OF LITERATURE

A computerized search of the US National Library of Medicine database of literature (Pubmed), ISI Web of Knowledge databases and cross-referencing was conducted. Broad key word phrases, including "hepatic", "liver", "cirrhosis", "postshunt", "portacaval", "portosystemic", "portal-systemic" were used in conjunction with the terms, including "myelopathy", "spinal", "paraplegia". English language articles published are included. To identify further published and unpublished, reference lists of relevant articles were searched. Abstracts were reviewed and articles unrelated to the specific topic were excluded. Duplicate references and redundant publications were discarded by the first author.

The patients were classified into 4 classes with the Expanded Disability Status Scale (EDSS) disability scale[4] according to the severity of the motor dysfunction. Patients who did not complain of neurological symptoms nor did objective examination reveal any were grade 0; Patients who had mild neurological abnormalities (hyperreflexia, extensor plantar responses) without disability were grade 1; Patients who experienced minimal disability (stiffness, nocturnal spasms and leg cramps) were grade 2; Patients who had neurological abnormalities (mild or moderate paraparesis) were grade 3.

## RESULTS

46 case reports with 98 patients of HM including ours

have been eligibly selected. General information on all cases was recorded (see supplement Materials Table 1, Table 2). Detailed analysis of the clinical characteristics of HM patients was undertaken.

89 cases had detailed information in the Etiology. The underlying Etiology of HM was as follows (summarized Table 1): 74(83.1%) liver cirrhosis including 34(38.2%) posthepatitic cirrhosis, 21(23.6%) alcoholic cirrhosis, 3(3.4%) biliary cirrhosis, 16(18.0%) cryptogenic cirrhosis, and 15(17%) cryptogenic cirrhosis, the remaining 15(16.9%) non-Liver cirrhosis diseases including 8(9.0%) longstanding alcoholism without cirrhosis, 3(3.4%) idiopathic portal hypertension,[5] 1(1.1%) chronic active hepatitis, 2(2.2%) congenital hepatic fibrosis,[6,7] and 1(1.1%) adult-onset type II citrullinemia.[8]

Among the 93 patients who had detailed information about the history of portosystemic shunting, 57(61.3%) had taken different types of shunting surgery, including portocaval shunt (25/57, 43.9%), splenorenal shunt (11/57, 19.3%) and transjugular intrahepatic portosystemic shunt (8/57, 14.0%). Besides this, 16(18.3%) cases were demonstrated to have spontaneously occurred portosystemic collateral circulation with no history of surgical shunting. However, there were still 20 cases (21.5%) with either surgical or idiopathic shunting.

| Characteristic | |
|---|---|
| Etiology (n=89) | |
| Liver cirrhosis | 74(83.1%) |
| Posthepatitic cirrhosis | 34(38.2%) |
| Alcoholic cirrhosis | 21(23.6%) |
| Biliary cirrhosis | 3(3.4%) |
| Cryptogenic cirrhosis | 16(18.0%) |
| non- Liver cirrhosis | 15(16.9%) |
| Alcoholism without cirrhosis | 8(9.0%) |
| Idiopathic portal hypertension | 3(3.4%) |
| Chronic active hepatitis | 1(1.1%) |
| Congenital hepatic fibrosis | 2(2.2%) |
| Adult-onset type II citrullinemia | 1(1.1%) |
| Portosystemic shunt | |
| Created surgically | 57(58.2%) |
| Portacaval shunt | 25/57(43.9%) |
| Splenorenal shunt | 11/57(19.3%) |
| TIPS | 8/57(14.0%) |
| Unknown | 13/57(22.8%) |
| Occurred spontaneously | 16(18.3%) |
| No | 20 (21.5%) |
| Unknown | 5 |

**Table1:** Etiology of HM.

We are able to retrieve 8 articles with 9 cases of postmortem pathological studies which described the histological changes of HM in detail (summarized in Table 2). In the spinal cord, a selective and symmetrical severe loss of myelin was noted in both lateral pyramidal tracts in all cases, sometimes (4/9) associated with various degree of axonal loss.[9,10] Such finding first becomes noticeably evident in the low cervical cord and becomes more intense at lower levels.[11,12] The degeneration of lateral columns does not extend beyond the upper cervical cord.[8] In a majority of the cases (7/9) secondary reactive changes due to demyelination with significant numbers of macrophages with an abundance of intracytoplasmic sudanophilic materials (so-called lipid-laden macrophages)[12] were found,[13] but only in 2 cases (2/9) rare perivascular lymphocytic infiltration was present.[10,13] Occasionally, Minor demyelination had also been found in the ventral pyramidal tracts (2/9), the posterior columns (5/9),[9,10] the spinothalamic tracts or spinocerebellar tracts (2/9).[12] There was no loss of myelin within the dorsal roots at any level of the spinal cord, and the gray matter was relatively intact.[10] Histological examination of the arterial and venous spinal vessels revealed normal findings.[12]

| Characteristic | |
|---|---|
| Cerebral changes | 8/9 |
| Betz cell count decreased | 2/9 |
| Cerebrum | 8/9 |
| Globus pallidus | 5/9 |
| Putamen | 5/9 |
| Spinal cord changes | 9/9 |
| Demyelination | 9/9 |
| the lateral pyramidal tracts | 9/9 |
| the ventral pyramidal tracts | 2/9 |
| the posterior columns | 5/9 |
| the spinocerebellar tracts | 2/9 |
| Axonal loss | 4/9 |
| Secondary reactive changes | 7/9 |
| Perivascular round cell infiltration | 2/9 |

**Table 2:** Pathological features of HM (n=9).

In the brain, cortical structures were normal. In the motor cortex the number of Betz cells was decreased in only 2 cases.[10,12,14] The pyramidal tracts were noted to be normal as they pass through the internal capsules and brainstem.[8,15] Significant numbers of protoplasmic astrocytes, the so-called Alzheimer type II astrocytes and spongy degeneration[3] were found in the cerebrum (8/9), globus pallidus (5/9) and putamen (5/9), which was a histologic feature of HE. When combined with AHCD, the neuropathologic findings included diffuse but patchy cortical necrosis, and uneven neuronal loss in the cerebral cortex, basal ganglia, and cerebellum.[10,14,16,17]

Clinical features were summarized in Table 3. The patients ranged in age from 14-76 years with the mean age of 45. The sex ratio (male/female) was 6.3/1(82/13), male was strikingly predominant in HM. The interval between shunt surgery and onset of neurological illness varied from 1 month to 33 years, with a median of 24 months (n=49). According to the de-

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tailed history in 71 patients, a majority of 50 cases (70.4%) had a history of relapsing HE. Among them, 41(82.0%) cases suffered from paraparesis with HE or after several episodes of HE, but in 6(12.0%) patients, HM was precede HE. 21(21.4%) developed HM onset without any episodes of encephalopathy.

| Characteristic | |
|---|---|
| Demography | |
| Mean age (years±SD) (n=98) | 45±13 |
| Sex (n=95) | |
| Male | 82(86.3%) |
| Female | 13(13.7%) |
| Hepatic encephalopathy | |
| Yes | 50(51.0%) |
| Before HM | 41/50(82.0%) |
| After HM | 6/50 (12.0%) |
| UK | 3/50 (6.0%) |
| No | 21(21.4%) |
| UK | 27(27.6%) |
| Shunt history (median, n=49) | 24 months |
| Progression Time (median, n=46) | 6 months |
| Clinical manifestation | 21(23.6%) |
| Involvement of the upper limbs (n=84) | 11/84(13.1%) |
| Superficial sensation deficit (n=73) | 6/73(8.2%) |
| Deep sensation deficit (n=75) | 14/75(18.7%) |
| Sphincter incontinence (n=74) | 8/74(10.9%) |
| non-pyramidal manifestation (n=81) | 21/81(25.9%) |
| EDSS disability scale ( n=46) | |
| grade 1 | 9/46(19.6%) |
| grade 2 | 20/46(43.5%) |
| grade 3 | 17/46(37.0%) |
| Blood ammonia elevated (n=67) | 54/67(80.6%) |
| Brain MRI abnormality (n=45) | 21/45(46.7%) |

**Table 3:** Clinical features (n=98).

The clinical manifestations of hepatic myelopathy are gait difficulty with insidious onset and progressive course varying from 1 months to 7 years (median 6 months, n=46) finally reaching a relatively stable condition. After months, the process plateaus, leaving most patients relatively stable with different conditions of patterns, either mild neurological abnormalities (hyperreflexia, extensor plantar responses) without disability (9/46, 9.6%) or minimal disability (stiffness, nocturnal spasms and leg cramps, dependent upon an assistive device) (20/46, 43.5%) or neurological abnormalities (mild or moderate paraparesis, confined to a wheelchair) (17/46, 37.0%).

The upper extremities affection is affected minimally and not common but there are still 11 cases (13.1%) well documented.[15,18] In addition to spastic paraparesis or quadriparesis, 6 cases (8.2%) manifested superficial sensation deficit,[2,3,18-22] 14 cases (18.7%) had deep sensation deficit and 8 cases (10.9%) had sphincter incontinence.[3,16,18,23] Non-pyramidal manifestation such as dysarthria, tremor and ataxia was observed in 21 cases (25.9%).

In a majority of the cases (54/67, 80.6%), plasma ammonia concentrations were found to be elevated. The spinal cord MRI imaging shows no abnormality. MRI of the brain showed high signal intensity on T1-weighted sequences within the basal ganglia including pallidum, lentiform nucleus, putamen, internal capsule and extensive white matter disease on T2-weighted sequences[7,18] in 21 cases (46.7%).

To date, there were only 15 cases undergone OLT in the English literature, altogether 11 cases showed quite impressive improvement,[18,21,24-26] mostly recovered to be ambulatory.

## DISCUSSION

### Etiology

HM has been associated with a broad range of liver diseases, especially those involving portosystemic shunt. Since patients with HM now have prolonged survival due to technological advances including liver transplantation, greater understanding and recognition of this rare cause of morbidity will become even more important.

Liver cirrhosis due to hepatitis B and alcoholism are the most frequent causes of HM. The majority of the patients manifested typical symptoms in the end stage of liver disease with prior evidence of liver dysfunction such as hepatic encephalopathy, upper gastrointestinal tract hemorrhage, ascites or otherwise a history of portosystemic shunt. However, 15 cases without cirrhosis have been reported including longstanding alcoholism and chronic active hepatitis. It seems that cirrhosis is not the only form of liver dysfunction which results in the chronic toxic substances bypassing the liver that causes both HM.

### Pathophysiology

At present, the pathophysiology of HM remains poorly understood. In 1960, Zieve[16] pathologically described HM as a symmetric loss of myelin in the lateral corticospinal tracts; this may have led to the finding that HM is characterized by motor involvement of the lower limbs without clinical sensory abnormalities.

The fact that HM occurred most often in cirrhosis patients accompanied by HE onset suggested that HM might involve mechanisms similar to HE. Portocaval shunts, or less commonly splenorenal shunts appear to have a substantive role in the neurologic deterioration.[20] The common belief is that the nitrogenous breakdown products or a neurotoxin by-passing the liver through the portocaval shunts even in the absence of liver dysfunction.[6,8] Demirci, et al.[6] reported a case with total

portosystemic shunt, which developed spontaneously due to congenital hepatic fibrosis. Cellular functions of the liver, except for an elevated blood ammonia level, were within normal limits, as is usual in congenital hepatic fibrosis. This case showed that spastic paraparesis following portosystemic shunt may occur without liver failure. The structure alteration occurs only after a fairly long-term exposure to ammonia and other putative neurotoxins shunt around the liver. Shunt is the key event for the long-term process in the pathogenesis of this disorder. The portocaval shunts can occur either spontaneously, after surgery, or due to 'functional shunting' – filtration of portal blood through a non-functioning liver. However, there were still 20 cases (21.5%) without either surgical or idiopathic shunting. This may be due to the difficulty in finding some hiding collateral circulation such as the retroperitoneal varices.[18] Patients with AHD or HM should initially be evaluated for the presence of portosystemic shunts.

Given the apparent relationship to shunt, it would seem most likely that it is chronic exposure to toxic substances bypassing the liver that causes both AHCD and HM, with different pathologic response in the brain or spinal cord.[7] Ammonia is the most frequently implicated agent. In Tazawa's case,[8] the patient diagnosed as adult-onset type II citrullinemia (CTLN2) which is characterized by highly elevated levels of citrulline and ammonia in the plasma, is unique in developing hepatic myelopathy without portocaval shunt. Delivery of nitrogen containing substances into the systemic circulation results in nervous system intoxication. Otherwise, Sage, et al.[27] and Imai, et al.[28] respectively reported 5 and 1 alcoholic cases without substantial liver disease. The absence of portacaval shunt or notable liver dysfunction in these patients suggests that a direct toxic effect of alcohol must be considered a possible mechanism of spinal cord damage. Other candidate substances such as high manganese or mercaptan levels may play a role in etiopathogenesis of HM. Although the cerebral deposition of manganese may have a role in the etiopathogenesis of AHD, there was no report in HM.[18] Though various hypotheses were suggested, the above seems to gain agreement consistently. However, the possibility of a deficiency of a needed liver-synthesized material cannot be excluded.

Regarding the topography of the spinal cord lesions in HM, it has been suggested that HM might be related to hemodynamic factors because the lesions observed are located just within those spinal segments that miss an extensive collateral circulation,[13,29] this was once assisted by Giangaspero's case that degeneration of the lateral corticospinal tracts was associated with diffuse bilateral ischemic changes of the spinal gray matter in absence of any anatomical cause of spinal cord infarction, although to date no other support this contention. HM might also be caused by nutritional factors because similar pathologic changes have been described in the spinal cord of prisoners of war and patients suffering from malnutrition.[3,29,30]

Some investigators have raised the question of whether spinal cord damage is direct or only a secondary effect of damage to cerebral cortical Betz cells. Pant, et al.[9] noted a decrease in the number of Betz cells in the cerebral cortex in their two cases, and discussed the more distal demyelination at the lateral column as a "dying back" phenomenon from the peripheral to the neuron. In the vast majority of reported cases, episodes of overt hepatic encephalopathy preceded the appearance of myelopathy, and thus it is likely that this corticospinal tract lesion simply represents the damage accumulated from multiple episodes of hepatic encephalopathy.[31]

The author also noted the selectivity of the disease to the corticospinal tracts, sparing other system in the cord, and suggested damage to the cerebral cells of origin; it is more likely a restricted encephalopathy rather than a myelopathy. However, more cases with a normal number of Betz cells and spinal cord demyelination and gliosis involving, but not limited to, the corticospinal tracts, have been reported subsequent to the report of Pant, et al.[9] In addition, as pointed out by Lefer, et al.[10] the rather abrupt cessation of demyelination at the cervical segment in almost all cases despite greatly varying durations of the disease is not the case expected for a progressive dying back process. It seems that either the pathogenic mechanism affects the corticospinal tracts directly at the spinal cord, or less likely, some other factors limit the dying back below the cervical level.[6]

Thus, while portosystemic shunting may precipitate both HM and AHCD, it probably does so by diverse mechanism. The fact that HM and AHCD differ pathologically is consistent with this supposition.[32] A discrepancy exists between the tissue reaction in the corticospinal tract and sparing of other systems in the spinal cord, where axonal degeneration and demyelination, cytoplasmic astrocytosis and round cell infiltration occur, and the reaction in the brain and brain stem, where there is proliferation of Alzheimer type II glial cells. This discrepancy of the sensitivities indicates that there are two pathogenic mechanisms, one responsible for the lesions in the brain and brain stem and the other for those in the spinal cord. Alternatively, a single factor may be responsible for the development of both lesions, and morphologic discrepancy reflects differences in the sensitivity of the tissues in these two general areas.[10]

### Clinical Features

The intervals between the construction of a shunt and the diagnosis of portosystemic myelopathy were shorter in Transjugular Intrahepatic Portosystemic Shunt (TIPS) than in portacaval shunts or splenorenal shunt respectively (see Table 4). This suggests that not only the shunt itself but also the shunted volume contributes to the development of the syndrome, which was approved by Conn, et al.[2] However, it was not agreeable that the difference was not significant between the portacaval shunts and the splenorenal shunt.

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| | Portacaval shunt | Splenorenal shunt | TIPS |
|---|---|---|---|
| n | 23 | 9 | 8 |
| Median interval (months) | 24.0 | 34.0▲ | 6.5*,** |

p<0.05, comparison of portacaval shunt, splenorenal shunt and TIPS using K independent nonparametric Kruskal-Wallis Test.
*p<0.01, comparison of portacaval shunt and TIPS using 2 independent nonparametric Mann-Whitney Test.
*p<0.01,comparison of splenorenal shunt and TIPS using 2 independent nonparametric Mann-Whitney Test.
▲No significance, comparison of portacaval shunt and splenorenal shunt using 2 independent nonparametric Mann-Whitney Test.

**Table 4:** Intervals between the time of shunt construction and onset of portosystemic myelopathy.

No relation between episodes of HE and presentation or exacerbation of HM was evident. Patients can develop HM at a time when their HE was well controlled.[32]

It can be ignored because walking difficulty can be all too easy to attribute this to a multitude of other problems commonly seen in this group of patients, including peripheral edema, malnutrition, and electrolyte disturbances.[24] Most commonly, symptoms will develop after several bouts of HE, although rarely myelopathy may be the presenting manifestation of liver failure. The signs of corticospinal tract damage appear to accumulate with each episode, although other neurologic signs resolve completely. Initially, the symptoms may be slightly asymmetric, but will invariably affect both legs and steadily worsen. Increased muscle tone and hyperreflexia are the most prominent findings only except one case which might be explained peripheral neuropathy due to HCV infection.[33,34] Almost in all cases, the tendon reflexes were exaggerated in the legs. Various plantar responses including Flexor responses have been described,[19,23,30,35] even in patients with ankle and knee clonus.

In most cases, lower extremities weakness is permanent, but Campellone, et al.[20] reported one case with full recovery over the following 6 months and was fully independent and ambulatory before the onset of his once more neurologic complaints. Reason for this may be explained by the description reported by Conn that his patient's improvement was attributed to decreased portosystemic shunt through the liver, resulting from the occlusion of the TIPS shunt.

Decreased appreciation of pin-prick and vibratory stimulation may be the result of mild peripheral neuropathy and affection of the posterior column degeneration[27,28] mostly in the alcoholic patients. Imai, et al.[28] describe a patient with alcoholic myelopathy presenting sudden electric-like sensations on flexion of the neck, which spread down the body, to the back, or to the extremities, so-called "Lhermitte's sign" as an initial symptom consistent with the MRI finding of posterior column degeneration.

Since HM may be accompanied by the AHCD, if the patient manifests neuropsychiatric (apathy, lethargy, excessive somnolence, secondary dementia, etc) and/or extra pyramidal (focal dystonia, postural tremor, myoclonus, rigidity, dysarthria, choreoathetosis, etc) symptoms, AHCD should be taken into consideration.[7]

### Laboratory Findings

There were no significant findings with EEG except a basic rhythm in the theta and occasionally in the delta range, without epileptiform discharge, no phase reversal and no voltage suppression. Lumbar puncture usually reveals no abnormalities other than an elevated glutamine level,[14,35] although increased protein content is rarely noted.[12] Thyroid functions, serum Vitamin B12 and folate values were in normal ranges. Serum antibodies to human T cell lymphotrophic virus (HTLV-1), Human Immunodeficiency Virus (HIV), antinuclear antibodies, syphilis serology were absent. Copper values of serum and urine were normal. Small esophageal and gastric varices might be demonstrated during the upper gastrointestinal endoscopy.

### Radiographic Characteristics

Negative spinal cord MRI results supported HM in the differential diagnosis, because MRI was essential to rule out such etiologies involving infarction, myelitis or compression of the spinal cord (epidural cord compression or intrinsic cord tumor). MRI of the brain showed high signal intensity on T1-weighted sequences within the basal ganglia including pallidum, lentiform nucleus, putamen, internal capsule and extensive white matter disease on T2-weighted sequences.[7,18] The toxic effect of the portal blood is greatest in the basal ganglia, probably because of high metabolic activity in this area. The distribution of lesions of this area with greater vulnerability seems to be influenced by blood-derived substances. Such abnormalities were consistent with the non-pyramidal manifestation (see Table 5). The common neuropathological finding in hepatic encephalopathy is the presence of Alzheimer type II glia diffusely with spongy degeneration scattered throughout the cerebral hemispheres including the cerebral cortex, basal ganglia and cerebellum[10] while the spinal cord is intact. In contrast, the reported features of hepatic myelopathy were pyramidal tract lesions located predominantly in the spinal cord, especially in the thoracic cord, with no involvement of the brain stem.[12] We suggest that abnormalities of brain magnetic resonance combined with syndrome of brain dysfunction, AHCD should be taken into consideration.[7] When the posterior column of the cord if affected, MR imaging may reveal abnormal signal intensity in the posterior column spanning the whole length of the upper cervical cord, which is consistent with Lhermitte's sign.[28]

| | | Brain MRI finding | | Total |
|---|---|---|---|---|
| | | + | - | |
| non-Pyramidal Manifestation | + | 10 | 1 | 11 |
| | - | 11 | 23 | 34 |
| Total | | 21 | 24 | 45 |

p=0.001<0.01, using Pearson Chi-Square.

**Table 5:** The consistence between Brain MRI finding and non-pyramidal manifestation.

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### Motor Evoked Potentials (MEPs)

Clinical detection of spinal cord dysfunction is difficult in the early stage of the disease. Spinal cord involvement was evident even at the preclinical stage and became more overt as the disease progressed. Transcranial Magnetic Stimulation (TMS) is a reliable method for testing the integrity of the motor pathways and of locating the sites of disruption. MEP studies elicited by TMS which is non invasive may disclose an impairment of the corticospinal pathways even before HM is clinically manifest and provide evidence that early diagnosis of HM. Abnormality of Central Motor Conduction Time (CMCT) for lower limb muscles associated with a normal CMCT for muscles supplied by upper cervical segments suggesting a lesion below the cervical outflow in the spinal cord causing the motor conduction delay.

Otherwise, Clinical conditions and MEP patterns of abnormality were significantly correlated.[36] MEP in assessing different degrees of neurological involvement could be relevant for therapeutic purposes, and in monitoring the progression of the disease. The clinical and neurophysiological features of patients with slight MEP abnormalities improved after OLT, whereas the patients with a more advanced stage of disease (severe MEPs abnormalities) did not, indicating that subsequent immediate liver transplantation have to be recommended.[37]

### Differential diagnose

There is no special diagnostic tool for HM. The diagnosis of HM has to be established presumptively on clinical grounds after exclusion of other possible causes of spastic paraparesis, such as demyelination myelopathy, amyotrophic lateral sclerosis, hereditary spastic paraplegia, subacute combined degeneration, Wilson syndrome, cerebral vascular disease, and HIV/human T cell lymphoma virus 1 (HTLV-1) infection.

HM must also be differentiated from other neurological complications of liver disease. AHCD is a permanent, progressive degeneration of the nervous system, causing cognitive, cerebellar, pyramidal, and extrapyramidal dysfunction in various combinations. The typical clinical features are dementia, dysarthria, ataxia, intention tremor, and choreoathetosis. Patients may also exhibit transient upper motor neuron signs.[38] One must be noted that the imaging abnormalities of brain and evidence of spinal cord involvement from cortical magnetic stimulation, in the setting of the clinical findings of significant non-pyramidal neurological signs such as dysarthria, tremor, ataxia, and paraparesis without sensory involvement, suggest that the patient may have both AHCD and HM.

Some degree of pyramidal symptoms is typically seen in the even uncomplicated cases of HE with mild hepatic failure, probably associated with ammonia levels, making it difficult to distinguish early or mild cases of HM, which usually start following an attack of encephalopathy. Usually, non-pyramidal neurologic abnormalities in HE – dysarthria, ataxia, tremor, rigidity, and disturbances of consciousness – are reversible with established treatment for HE. In contrast, spastic paraparesis caused by HM has been shown to be refractory with HE treatment, which aims at lowering plasma ammonia concentrations. This may be explained best as reversible, short-term toxic effects of ammonia on the neuron function, not on neuron structure. Such case would be more appropriate to be considered as a form of hepatic encephalopathy complicated by some symptoms of myelopathy.[39] In contrast, spastic paraparesis caused by HM has been shown to be refractory with HE treatment, which aims at lowering plasma ammonia concentrations.

### Treatment

Treatment strategies for HM include liver protection, neurotrophic drugs, measures to control blood ammonia concentration, and liver transplantation. Unlike HE, the conservative treatment of HM is usually considered inefficient. In most patients, therapy directed at reducing nitrogen absorption such as protein restriction,[10,35] oral neomycin,[6,10,16,35] lactulose,[6] and colonic exclusion or lowering plasma ammonia levels has been generally unrewarding.[20,25,30,32] At best, these measures prevented or decreased the numbers of encephalopathic episodes.[19,23] Even so, progressive paraparesis was observed even when encephalopathy was effectively averted. Oral lioresal may be tried to improve mobility with decreased spasticity, although the effectiveness is not confirmed.[20,30] The effectiveness of Orthotopic Liver Transplantation (OLT) has not yet been determined. To date, there were only 15 cases undergone OLT in the English literature. Although the first HM receiving an OLT was reported to have no appreciable improvement in his neurological symptoms or signs despite normalization of his liver function,[11] some appending case studies have reported altogether 11 cases showing quite impressive improvement,[18,21,24-26] mostly recovered to be ambulatory. The duration of clinical manifestations of HM before OLT may be the main factor affecting the therapeutic outcome. Liver transplantation should be considered as the first therapeutic option and should be performed before spinal cord damage becomes irreversible. This also implies that the spinal cord damage is irreversible at the end stage, which is compatible with the axonal loss seen at necropsy in some cases.[30]

## CONFLICTS OF INTEREST

The authors have no potential conflicts of interest to be disclosed.

## CONSENT

The patient has provided written permission for publication of the case details.

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## SUPPLEMENTMATERIALS

| Time | Author | Age | Sex | Etiology | Surgical Shunt | Type | Sponta-neously Shunt | Type | Shunt History(mo) | HE/Before Or After | Progres-sion Time(mo) | EDSS disability scale* | Involvement of the Upper Limbs | Superficial Sensation Deficit | Deep Sensation Deficit | Sphincter Incontinence | non-Pyramidal Manifes-tation | Blood Ammonia Elevated | Brain MRI Abnormal-ity |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1949 | Leigh AD et al | 50 | M | CC | UK | UK | UK | - | UK | Yes/After | UK | UK | UK | UK | Yes | Yes | UK | UK | UK |
| 1960 | Zieve L et al | 53 | M | AC | Yes | PCS | UK | - | 36 | Yes/Before | UK | 3 | No | No | No | Yes | No | Yes | UK |
| | | 38 | M | CC | Yes | PCS | UK | - | 54 | Yes/Before | 3 | 3 | No | No | No | Yes | No | UK | UK |
| 1964 | Scobie BA et al | 63 | M | AC | Yes | PCS | Yes | Other | UK | UK/- | UK | 1 | No | No | No | Yes | dysarthria | Yes | UK |
| 1964 | Drake A et al | 54 | M | AC | Yes | PCS | UK | - | 72 | Yes/Before | UK | UK | UK | UK | UK | UK | UK | UK | UK |
| 1966 | Liversedge LA et al | 42 | M | UK | Yes | PCS | UK | - | 12 | No/- | UK | 2 | No | UK | UK | UK | No | UK | UK |
| | | 45 | M | CC | No | - | Yes | UK | UK | Yes/After | UK | 3 | No | UK | UK | UK | dysarthria, tremor | Yes | UK |
| | | 33 | M | UK | Yes | PCS | UK | - | 4 | No/- | 6 | 3 | Yes | UK | UK | UK | No | UK | UK |
| | | 37 | M | CC | Yes | PCS | UK | - | 12 | Yes/Before | UK | UK | No | UK | UK | UK | No | UK | UK |
| | | 41 | M | UK | Yes | SRS | UK | - | 72 | Yes/UK | UK | 3 | Yes | UK | Yes | UK | dysarthria, ataxia | UK | UK |
| | | 41 | M | UK | No | - | UK | - | - | No/- | UK | 1 | No | UK | UK | UK | dysarthria, ataxia | Yes | UK |
| 1968 | Pant SS et al | 48 | M | AC | No | - | UK | - | - | Yes/UK | 24 | 1 | No | No | No | No | No | Yes | UK |
| | | 53 | M | AC | Yes | PCS | UK | - | 6 | Yes/Before | UK | 3 | No | No | No | No | No | Yes | UK |
| 1969 | Krishnaswami V et al | 33 | M | UK | Yes | PCS | UK | - | 10 | Yes/Before | UK | UK | UK | UK | UK | UK | UK | UK | UK |
| 1970 | Bechar M et al | 31 | M | CC | Yes | SRS | UK | - | 20 | Yes/Before | UK | UK | UK | UK | UK | UK | UK | UK | UK |
| | | 31 | M | CC | Yes | PCS | UK | - | 6 | Yes/Before | UK | UK | UK | UK | UK | UK | UK | UK | UK |
| | | 29 | M | CC | Yes | SRS | UK | - | 72 | Yes/Before | UK | UK | UK | UK | UK | UK | UK | UK | UK |
| 1972 | Lefer LG et al | 40 | M | BC | Yes | SRS | UK | - | 5 | Yes/After | UK | 3 | No | No | No | No | No | Yes | UK |
| 1975 | Gauthier G et al | 62 | M | CAH | Yes | PCS | UK | - | 18 | UK/- | UK | UK | UK | UK | UK | UK | UK | UK | UK |
| 1976 | Mousseau R et al | 53 | F | AC | No | - | Yes | Other | UK | Yes/Before | UK | 2 | No | No | No | No | No | No | UK |
| 1978 | Robinson CE et al | 37 | M | AC | Yes | PCS | UK | - | 20 | Yes/Before | UK | UK | UK | UK | UK | UK | UK | UK | UK |
| 1979 | Budillon G et al | 19 | M | AC | Yes | PCS | UK | - | 36 | Yes/Before | UK | UK | UK | UK | UK | UK | UK | UK | UK |
| 1982 | Cosnett JE et al | 18 | UK | AC | Yes | SRS | UK | - | 24 | No/- | UK | UK | No | UK | UK | UK | UK | UK | UK |
| | | 17 | UK | AC | Yes | SRS | UK | - | 96 | Yes/Before | UK | UK | No | UK | UK | UK | UK | UK | UK |
| 1983 | Sarin SK et al | 42 | F | IPH | Yes | SRS | UK | - | 34 | Yes/Before | UK | UK | UK | UK | UK | UK | UK | UK | UK |
| 1984 | Sage JI et al | 61 | M | AWC | No | - | No | - | - | No/- | 24 | UK | No | No | Yes | No | No | No | UK |
| | | 63 | M | AWC | No | - | No | - | - | No/- | 48 | UK | No | No | Yes | No | No | No | UK |
| | | 56 | F | AWC | No | - | No | - | - | No/- | 2 | UK | No | No | Yes | No | No | No | UK |
| | | 53 | M | AWC | No | - | No | - | - | No/- | 24 | UK | No | No | Yes | No | No | No | UK |
| | | 63 | M | AWC | No | - | No | - | - | No/- | 12 | UK | No | No | Yes | No | No | No | UK |
| 1985 | Lebovics E et al | 52 | M | AC | Yes | PCS | UK | - | 60 | Yes/Before | UK | 2 | No | No | Yes | No | No | No | No |
| | | 67 | M | BC | Yes | PCS | UK | - | 14 | Yes/Before | UK | 2 | No | No | No | No | No | No | UK |
| 1985 | Giangaspero F et al | 60 | M | AC | Yes | PCS | UK | - | 13 | Yes/Before | UK | 3 | No | No | No | No | dysarthria | Yes | UK |
| 1985 | Rab SM et al | 40 | M | CC | Yes | PCS | UK | - | 25 | Yes/Before | UK | UK | UK | UK | UK | UK | UK | UK | UK |
| | | 60 | F | UK | No | - | No | - | - | Yes/Before | UK | UK | UK | UK | UK | UK | UK | UK | UK |
| 1991 | Bain VG et al | 39 | F | AC | Yes | PCS | UK | - | 96 | Yes/Before | UK | 3 | No | UK | UK | UK | UK | UK | UK |
| 1992 | Demirci M et al | 45 | M | CHF | No | - | Yes | Other | UK | Yes/Before | 6 | 2 | No | No | No | No | dysarthria , ataxia | Yes | UK |
| 1992 | Anand BA et al | 30 | M | IPH | Yes | PCS | UK | - | 121 | Yes/Before | UK | UK | No | UK | UK | UK | ataxia | UK | UK |
| 1993 | Bourgeois S et al | 24 | M | AC | No | - | No | - | - | Yes/After | 1 | UK | Yes | No | No | No | No | Yes | Yes |
| 1993 | Tsuchiya K et al | 46 | F | AWC | UK | - | UK | - | - | No/- | 2 | UK | No | No | No | No | ataxia | UK | Yes |
| | | 58 | M | AWC | UK | - | UK | - | - | No/- | 4 | UK | No | No | No | No | No | UK | Yes |
| 1994 | Sobukawa E et al | 76 | M | PHC | No | - | UK | - | - | Yes/After | 1 | 3 | No | No | No | No | No | Yes | No |
| 1994 | Mendoza G et al | 44 | M | AC | Yes | PCS | UK | - | 24 | Yes/Before | 2 | 2 | No | No | No | No | No | UK | UK |
| | | 66 | M | AC | Yes | PCS | UK | - | 36 | Yes/Before | 2 | 3 | No | No | No | No | No | UK | Yes |
| | | 61 | M | PHC | Yes | PCS | UK | - | 12 | Yes/Before | 18 | 3 | No | No | No | No | No | UK | No |
| 1996 | Counsell C et al | 52 | M | AC | No | - | Yes | Other | UK | Yes/Before | 1 | 2 | No | No | Yes | No | No | No | No |
| 1996 | Campellone JV et al | 35 | M | IPH | Yes | SRS | Yes | Other | 396 | Yes/After | 84 | 2 | Yes | Yes | Yes | No | tremor | Yes | Yes |
| 1999 | Troisi R et al | 60 | M | PHC | Yes | PCS | UK | - | 132 | Yes/Before | 2 | 3 | No | Yes | Yes | No | tremor | UK | UK |
| 2000 | Lewis MB et al | 45 | M | CHF | Yes | PCS | UK | - | 324 | No/- | 12 | 1 | No | No | No | No | dysarthria, tremor | Yes | Yes |
| 2000 | Spencer DC et al | UK | UK | AC | UK | - | UK | - | - | UK/- | UK | UK | UK | UK | UK | UK | UK | UK | UK |
| 2000 | Gospe SJ et al | 14 | M | CC | No | - | No | - | - | No/- | 2 | UK | No | Yes | No | No | No | No | Yes |
| 2001 | Yengue P et al | 29 | M | UK | Yes | SRS | UK | - | UK | UK/- | UK | UK | UK | UK | UK | UK | UK | UK | UK |
| 2001 | Wang MQ et al | 41~56 | 3M 1F | PHC | Yes | TIPS | UK | - | 2 | No/- | UK | 1 | No | No | No | No | No | Yes | UK |
| | | | | CC | Yes | TIPS | UK | - | 1 | UK/- | UK | UK | No | No | No | No | No | Yes | UK |
| | | | | CC | Yes | TIPS | UK | - | 3 | UK/- | UK | UK | No | No | No | No | No | Yes | UK |
| | | | | CC | Yes | TIPS | UK | - | 5 | UK/- | UK | UK | No | No | No | No | No | Yes | UK |
| 2002 | Obama R et al | 48 | F | UK | UK | UK | UK | - | UK | UK/- | UK | 2 | No | UK | UK | UK | No | UK | Yes |
| 2003 | Weissenborn K et al | 35 | M | PHC | No | - | UK | - | UK | Yes/UK | UK | 2 | No | No | No | No | dysarthria,ataxia,tremor | Yes | No |
| | | 40 | M | PHC | Yes | TIPS | UK | - | 19 | Yes/Before | 6 | 2 | No | No | No | Yes | No | Yes | Yes |
| | | 42 | M | PHC | Yes | TIPS | UK | - | 9 | Yes/Before | 2 | 3 | No | Yes | Yes | Yes | dysarthria,ataxia,tremor | UK | Yes |
| 2005 | Utku U et al | 45 | M | PHC | No | - | Yes | SRS | UK | No/- | 6 | 2 | No | No | No | No | No | Yes | No |
| | | 41 | M | CC | No | - | Yes | SRS | UK | No/- | 12 | 2 | No | No | No | No | No | Yes | No |
| 2005 | Imai T et | 35 | M | AWC | No | - | No | - | - | No/- | 48 | UK | No | No | Yes | No | No | No | No |
| 2006 | Nardone R et al | 39 | F | BC | Yes | UK | No | - | UK | UK/- | UK | 1 | No | No | No | No | dysarthria | Yes | UK |
| | | 49 | M | AC | No | - | Yes | UK | UK | UK/- | UK | 1 | No | No | No | No | No | Yes | UK |
| | | 54 | M | PHC | Yes | UK | No | - | UK | UK/- | UK | 1 | No | No | No | No | No | Yes | UK |
| | | 60 | M | PHC | Yes | UK | No | - | UK | UK/- | UK | 1 | No | No | No | No | No | Yes | UK |
| | | 64 | F | AC | Yes | UK | No | - | UK | UK/- | UK | 2 | No | No | No | No | No | Yes | UK |
| | | 58 | M | PHC | No | - | Yes | UK | UK | UK/- | UK | 2 | No | No | No | No | No | Yes | UK |
| 2006 | Panicker J et al | 19 | M | CC | Yes | SRS | Yes | SRS | 24 | No/- | 24 | 2 | No | No | No | No | No | Yes | No |
| 2006 | Conn HO et al | 31 | M | PHC | Yes | TIPS | UK | - | 60 | Yes/Before | UK | 3 | Yes | Yes | Yes | No | No | Yes | Yes |
| 2007 | Tazawa K et al | 31 | M | CTLN2 | No | - | No | - | - | Yes/Before | 12 | 2 | No | No | No | No | No | Yes | No |
| 2008 | Koo JE et al | 39 | M | PHC | No | - | Yes | SRS | UK | No/- | 3 | 2 | No | No | No | No | ataxia | Yes | UK |
| | | 64 | M | PHC | No | - | Yes | SRS | UK | No/- | 6 | 2 | No | No | No | No | No | Yes | UK |
| 2009 | Qu B et al | 32 | M | PHC | No | - | UK | - | - | Yes/Before | 2 | 3 | No | No | No | No | No | Yes | Yes |
| | | 29 | M | PHC | Yes | TIPS | UK | - | 8 | Yes/Before | 3 | 3 | No | No | No | No | ataxia | Yes | Yes |
| 2009 | Yin YH et al | 46 | M | 12/13 PHC | Yes | UK | UK | - | 12 | UK/- | 3 | UK | No | No | No | No | No | 11/13 Yes 2/13 No | No |
| | | 60 | M | | Yes | UK | UK | - | 144 | UK/- | 66 | UK | No | No | No | No | No | | No |
| | | 44 | M | | Yes | UK | UK | - | 66 | UK/- | 48 | UK | No | No | No | No | No | | No |
| | | 18 | M | | Yes | UK | UK | - | 18 | UK/- | 6 | UK | No | No | No | No | No | | No |
| | | 55 | M | | Yes | UK | UK | - | 36 | UK/- | 24 | UK | No | No | No | No | No | | No |
| | | 41 | M | | Yes | UK | UK | - | 36 | UK/- | 11 | UK | No | No | No | No | No | | No |
| | | 35 | M | | Yes | UK | UK | - | 6 | UK/- | 3 | UK | No | No | No | No | No | | No |
| | | 67 | F | | Yes | UK | UK | - | 108 | UK/- | 18 | UK | No | No | No | No | No | | No |
| | | 58 | M | | Yes | UK | UK | - | 18 | UK/- | 9 | UK | No | No | No | No | No | | No |
| | | 48 | M | | No | - | UK | - | - | UK/- | 36 | UK | No | No | No | No | No | | No |
| | | 51 | M | | No | - | UK | - | - | UK/- | 18 | UK | No | No | No | No | No | | No |
| | | 45 | M | | No | - | UK | - | - | UK/- | 7 | UK | No | No | No | No | No | | No |
| | | 50 | M | | No | - | UK | - | - | UK/- | 8 | UK | No | No | No | No | No | | No |
| 2009 | Pinarbasi B et al | 41 | M | PHC | Yes | SRS | No | - | UK | Yes/Before | UK | UK | Yes | No | No | No | ataxia | Yes | Yes |
| | | 50 | M | AC | No | - | Yes | SRS | UK | Yes/Before | UK | UK | No | No | No | No | No | Yes | Yes |
| | | 37 | M | PHC | Yes | PCS | No | - | UK | Yes/Before | UK | UK | Yes | No | No | No | dysarthria, tremor | Yes | Yes |
| | | 48 | M | PHC | No | - | Yes | SRS, RUV | UK | Yes/Before | UK | UK | No | No | No | Yes | No | Yes | Yes |
| | | 49 | M | PHC | No | - | Yes | RUV | UK | Yes/Before | UK | UK | Yes | No | No | No | dysarthria | Yes | Yes |
| | | 56 | M | CC | No | - | No | - | - | Yes/Before | UK | UK | Yes | No | No | No | No | Yes | Yes |
| | | 28 | F | CC | No | - | Yes | ECV | UK | Yes/Before | UK | UK | Yes | No | No | No | dysarthria, ataxia | Yes | Yes |
| | | 31 | F | PHC | No | - | Yes | ECV | UK | Yes/Before | UK | UK | Yes | Yes | No | Yes | ataxia | Yes | Yes |
| 2010 | Present Case | 35 | M | PHC | No | - | Yes | RUV | UK | No/- | 2 | 2 | No | No | No | No | No | Yes | No |

*The detailed described patients were classified according to the EDSS disability scale. Patients who did not complain of neurological symptoms nor did objective examination reveal any were grade 0; Patients who have mild neurological abnormalities (hyperreflexia, extensor plantar responses) without disability were grade 1;Patients who experienced minimal disability (stiffness, nocturnal spasms and leg cramps)were grade 2; Patients who had neurological abnormalities (mild or moderate paraparesis) were grade 3.

**Abbreviations:** AC=alcoholic cirrhosis; AWC=alcoholism without cirrhosis; BC=biliary cirrhosis; CAH= chronic active hepatitis; CC=cryptogenic cirrhosis; CHF=congenital hepatic fibrosis; CTLN2=adult-onset type ii citrullinemia; ECV=enlarged coroner venous; F=female; HE=hepatic encephalopathy; HM=hepatic myelopathy; IPH=idiopathic portal hypertension; M=male; PCS=portocaval shunt; PHC= posthepatitic cirrhosis; RUV=recanalized umbilical venous; SRS=splenorenal shunt; TIPS=transjugular intrahepatic portosystemic shunt; UK=unknown

**Supplement Table 1:** Review on the clinical features of HM.

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| time | author | Cerebral changes | | | | | Spinal cord | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | betz cell count decreased | cerebrum | globus pallidus | putamen | | demyelination | the lateral pyramidal tracts | the ventral pyramidal tracts | the posterior columns (fasciculus gracilis) | spino-cerebellar tracts | axonal loss | secondary reactive changes | perivascular round cell infiltration |
| 1949 | Leigh AD et al | - | + | + | + | | + | + | - | + | - | - | - | - |
| 1960 | Zieve L et al | - | + | + | + | | + | + | + | + | - | - | - | + |
| 1966 | Liversedge LA et al | - | + | - | - | | + | + | + | + | + | + | + | |
| 1968 | Pant SS et al | + | + | - | - | | + | + | - | - | - | + | + | - |
| 1968 | Pant SS et al | + | + | - | - | | + | + | - | + | - | - | + | - |
| 1972 | Lefer LG et al | - | + | + | + | | + | + | - | + | - | + | + | + |
| 1985 | Giangaspero F et al | - | + | + | + | | + | + | - | - | - | + | + | - |
| 1994 | Sobukawa E et al | - | - | - | - | | + | + | - | - | + | - | + | - |
| 2007 | Tazawa K et al | - | + | + | + | | + | + | - | - | - | - | + | |

**Supplement Table 2:** Review on the pathological features of HM.