Spinal cord involvement in patients with cirrhosis

Raffaele Nardone, Yvonne Höller, Monica Storti, Piergiorgio Lochner, Frediano Tezzon, Stefan Golaszewski, Francesco Brigo, Eugen Trinka

INTRODUCTION

Patients with chronic liver disease frequently experience neurological problems, with hepatic encephalopathy (HE) being the most common. Comparatively rare is the involvement of the spinal cord; the so-called hepatic myelopathy (HM) is usually associated with an extensive portosystemic shunt of blood, either surgically created or occurring spontaneously.

Abstract

A severe spinal cord involvement may rarely occur in patients with cirrhosis and other chronic liver diseases; this complication is usually associated with overt liver failure and surgical or spontaneous porto-systemic shunt. Hepatic myelopathy (HM) is characterized by progressive weakness and spasticity of the lower extremities, while sensory and sphincter disturbances have rarely been described and are usually less important. The diagnosis is assigned in the appropriate clinical setting on clinical grounds after the exclusion of other clinical entities leading to spastic paraparesis. Magnetic resonance imaging is often unremarkable; however, also intracerebral corticospinal tract abnormalities have been reported recently. The study of motor evoked potentials may disclose central conduction abnormalities even before HM is clinically manifest. HM responds poorly to blood ammonia-lowering and other conservative medical therapy. Liver transplantation represents a potentially definitive treatment for HM in patients with decompensated cirrhosis of Child-Pugh B and C grades. Other surgical treatment options in HM include surgical ligation, shunt reduction, or occlusion by interventional procedures.

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Key words: Hepatic myelopathy; Spastic paraparesis; Cirrhosis; Chronic liver disease; Porto-systemic shunt; Liver transplantation; Endovascular procedures

Core tip: This review article is worth reporting, because it provides a comprehensive and updated review of the most pathophysiological, clinical and therapeutical aspects of the hepatic myelopathy.
In this review we will focus on the studies that have investigated the pathophysiology and the therapeutic strategies of this important, but likely often overlooked, neurological complication of chronic liver diseases. The MEDLINE, accessed by Pubmed (1966-August 2013) and EMBASE (1980-August 2013) electronic databases were searched using the medical subject headings (MeSH) “hepatic myelopathy”, “liver cirrhosis”, “spastic paraparesis”, “chronic liver disease”, “therapy”, “liver transplantation”.

Two review authors (YH and SL) screened the titles and abstracts of the initially identified studies to determine if they satisfied the selection criteria. Any disagreement was resolved through consensus. Full-text articles were retrieved for the selected titles, and reference lists of the retrieved articles were searched for additional publications.

The two reviewers independently assessed the methodological quality of each study and risk of bias, focusing on blinding and other potential sources of bias. The search strategy described above yielded 44 results. We excluded 2 studies after reading the full published papers; thus, 42 studies contributed to this review: the earliest was published in 1949 and the most recent in 2013.

CLINICAL FINDINGS AND EPIDEMIOLOGY

Clinically, HM presents with an insidious onset of spasticity and weakness in the lower extremities, which slowly progresses over several years (decades) and causes the patients to become wheelchair-bound. Clinical findings of spastic paraparesis, usually without any motor deficits rostral to the cerebral spinal cord segments, with hyperreflexia, extensor plantar responses and a puppet-like gait are characteristic of HM.

The most characteristic and distinctive feature in HM is a progressive lower extremity corticospinal tract deficit. Involvement of the upper extremities has rarely been described.

There are only a few reports of sensory or sphincter impairment. Moreover, a delayed onset posterior column dysfunction (proprioception and vibratory sensory loss) and a small fiber length-dependent axonal sensorimotor neuropathy has been recently documented, both progressing concomitantly with the motor deficits. Most HM patients display normal or minimal sensory findings, but some patients exhibit more significant sensory deficits.

Since the first description of HM in 1949, there have been approximately 90 cases reported in the literature. In rare instances, HM may be a presenting sign of liver disease. Ben Amor et al. recently reported two patients who had no history of previous liver cirrhosis. In most of the reported cases, episodes of overt HE have preceded the development of the myelopathy. HM can occur before or after HE, but also patients without any episodes of HE have been reported. In the vast majority of the reported cases, the patients were males in the 5th decade of life at the time of their presentation with HM. The middle age of onset is reported as 47 years.

The first reports of HM patients occurred when surgical shunting was more commonly performed. Some authors have hypothesized that the incidence would eventually decrease as shunting became replaced by other less invasive treatments. However, with the transjugular intrahepatic portosystemic shunt (TIPS) becoming the standard procedure for refractory variceal bleeding, increasing reports of HM have emerged. To date, there has been one case report describing reversal of HM by occlusion of TIPS.

HISTOLOGY

The histology of HM consists of symmetrical loss of myelin in the lateral pyramidal tracts, with demyelination beginning in the cervical spine, becoming more intense at lower levels, and occasionally being associated with axonal loss. In the early stages, demyelination seems to predominate, but as the disease progresses, axonal loss occurs, and this is likely to be irreversible. Occasionally, demyelination has also been found in the ventral pyramidal tracts, in the posterior columns and spinocerebellar tracts. These pathological findings in the posterior columns of patients with HM were first described by Leigh et al. in 1949 and by Mendoza et al. in 1994. These findings raise the possibility that posterior column spinal cord pathology may be more common in HM than previously realized. Even if the lesions have shown up typically within the spinal cord, there are occasional reports of lesions within the brainstem without involvement of other tracts. Additionally, Alzheimer type-II cells and spongiform degeneration in the cerebral cortex have been described in HM.

PATHOPHYSIOLOGY

The pathophysiology of HM is not yet completely understood. There is a close relationship between an extensive PSS and the occurrence of HM, even in the absence of liver dysfunction. This observation supports the hypothesis that the shunting of blood may allow nitrogenous breakdown products or a neurotoxin to bypass the liver and damage the spinal cord. In particular, nitrogenous products such as ammonia have been identified as a major contributor to the development of HM. Portocaval shunts or less commonly spleno-renal shunts seem to play a substantial role in the occurrence of HM-associated neurologic disturbances. Shunts can occur spontaneously, after surgery, or due to “functional shunting” filtration of portal blood through a dysfunctional liver.

Impairment of neurological function in the form of encephalopathy was recognized in the early 20th century in patients undergoing surgical shunting or portocaval anastomosis (PCA) and was later described as “portal-systemic encephalopathy” by Sherlock et al. Because some of the earliest reported patients with HM had undergone PCA, shunting was considered a possible
explaination for the development of myelopathy, and a similar mechanism causing both HE and HM has been postulated. However, in most of the reported cases, episodes of overt HE have preceded the development of the myelopathy. It has been suggested that a nutritional deficiency may underlie HM as a result of dietary restriction in patients with precedent episodes of HM. However, this hypothesis is unlikely, because there are also reports of patients in whom HE never occurred and who had been following a normal diet. Moreover, in contrast to HE, HM usually do not respond to blood ammonia-lowering therapies. Therefore, the pathophysiology is most likely different in HM and HE. Protein restriction, as well as the use of lactulose and neomycin treatments, were not found to be beneficial for HM. Moreover, surgical colonic diversion is helpful for HE, but does not reverse HM. Treatments with lactulose, rifaximin, gabapentin, and pentoxyfylline were also attempted in the interesting case reported by Caldwell et al, and none of the treatments was successful. Moreover, none of the HM patients who had eventually undergone LT had any reported neurological improvement in response to standard medical therapies for PSE.

Reversal of HM by occlusion of TIPS, as reported by Conn et al, lends support to some mechanism inherent to the presence of PSS. Approximately 20% of the patients (3/15) in the recent review by Caldwell et al had no demonstrable evidence of PSS in 10% of HM patients previously reported in the literature. In addition to the possibility of a putative neurotoxin causing HM in patients with PSS, other etiological factors should be considered, including nutritional deficiencies and metabolic abnormalities. Nutritional deficiency was first considered by Leigh et al as a possible cause of the permanent spinal cord abnormalities observed in their patients. Vitamin B12 deficiency was taken into consideration in the two gastrectomy patients who later developed HM. However, the hematological profiles and vitamin B12 levels in these individuals were normal. Serum vitamin B12 levels were normal in previously published HM patients, as well as in the patient reported by Caldwell et al, in whom serum vitamin B12, folate, and methylmalonic acid levels were within normal limits.

It has been suggested that altered circulation could increase spinal cord susceptibility to injury in HM. This was discussed in the context of portal hypertension, perhaps occurring in individuals with anatomic variants. The topography of the spinal cord lesions in HM suggests that HM may be related to hemodynamic factors, as the observed lesions are located just within those spinal segments that miss an extensive collateral circulation. HM can occur in patients with congenital hepatic fibrosis and with focal nodular hyperplasia, and this observation underscores the point that the severity of HM does not necessarily parallel the degree of hepatic dysfunction.

**DIAGNOSIS**

Diagnosing HM is often difficult, but it can be achieved after the exclusion of other causes of spastic paraparesis in the appropriate clinical setting. A detailed history, along with an accurate neurological examination including appropriate neurophysiological tests and neuroimaging procedures, are of crucial importance for the early detection of the disease. Other myelopathies with normal spine imaging should be included in the neurological differential diagnosis. These are listed in the algorithm proposed by Caldwell et al: metabolic/nutritional diseases (renal disease, vitamin B/E or copper deficiency, lathyris); vascular events (arteriovenous malformation, infarct, vasculitis), spirochetes (Lyme, syphilis) or fungal (Cryptococcus, Aspergillus) infections, postinfection (transverse myelitis), autoimmune (systemic lupus erythematosus, sarcoidosis, Sjogren’s), neoplasm (lymphoma, paraneoplastic syndrome), toxicity (chemotherapy, radiation), genetic factors (leukodystrophy, Friedrich’s ataxia), and motor neuron disease (amyotrophic lateral sclerosis). Magnetic resonance imaging (MRI) of the entire spinal cord and, when indicated, the brain is essential in the evaluation of HM. Infectious myelopathies can be assessed by patient history, spinal fluid analysis, imaging procedures, and serologies/cultures. Infectious etiologies to consider include human immunodeficiency virus, human T-lymphotropic virus type-1, syphilis, and Lyme disease. A demyelinating syndrome that was recently reported in a patient with hepatitis B virus (HBV) manifested as a recurrent transverse myelitis with paraparesis and urinary retention. Similarly, hepatitis A has also been implicated as a possible etiology for transverse myelitis with paraparesis and urinary retention. However, none of the hepatotropic viruses (hepatitis A virus, HBV) has been implicated in HM. In the review by Caldwell et al regarding HM patients after liver transplantation (LT), all 3 HCV patients exhibited reversal of the myelopathy, despite persistent viremia.

A paraneoplastic syndrome is another possible differential diagnostic consideration in the workup of HM, even if it has not been reported in the literature. The liver explanted by the Caldwell et al contained a 1-cm hepatocellular carcinoma (HCC). One of the 2 patients with HM from the group of Koo and colleagues also had HCC, but they had not undergone LT. That patient was a 64-year-old man with a 2.5-cm HCC who had undergone successful radiofrequency ablation of the lesion but exhibited no clinical or electrophysiological improvement up to 16 mo after treatment. HCC has been associated with necrotizing myelopathy in one case report, but in the most recent comprehensive review of HM, none of the 61 patients had an underlying diagnosis of HCC.

Table 1 shows the differential diagnosis and Table 2 the recommended diagnostic evaluation of patients with HM.

**NEUROPHYSIOLOGICAL FINDINGS**

To determine the frequency and gravity of HM, Nardone
et al[27] performed a study examining motor evoked potentials (MEP) elicited by transcranial magnetic stimulation in thirteen patients with liver cirrhosis associated with PSS.

The six patients with clinical signs of spinal cord involvement exhibited severe neurophysiological abnormalities, more precisely, a prolonged central motor conduction time (CMCT), whereas interestingly milder but unequivocal MEP abnormalities were found in four of the seven patients with normal clinical examination. These findings indicate that the electrophysiological evaluation of central motor conduction may disclose an impairment of the corticospinal pathways even before HM is clinically manifest. The clinical and neurophysiological features of patients with slight MEP abnormalities improved after LT, whereas the patients with a more advanced stage of disease (severe MEPs abnormalities) did not.

The findings of Nardone et al[27] and Utku et al[23] support the potential value of evaluating CMCT in the preclinical and early stages of HM. Patients who undergo transplantation with preclinical or early HM by MEP/CMCT appear to have a greater likelihood of recovery both clinically and electrophysiologically[23]. It is thus possible that MEP/CMCT have greater sensitivity in detecting preclinical or early HM and in assigning a prognosis for recovery after LT. Although a larger study comparing the sensitivity, specificity, and predictive value of MEP/CMCT has yet to be conducted, central motor system neurophysiological studies are an important consideration in the workup of patients with HM.

Utku et al[23] performed a MEP study in two patients and found an absence of cortical MEPs in both the low-er and upper extremities, and normal MEP values with radicular magnetic stimulation, suggesting that the lesion was localized within the cervical levels of spinal cord.

However, they could not perform any neuropathological investigations to corroborate this diagnosis. Nardone et al[27] found an abnormal CMCT to the lower lumbar spinal segments and a normal CMCT to the upper cervical spinal segments, thus supporting localization to the thoracic spinal cord. Additionally, a MEP study of HM patients from Seoul[23] indicated that the sites of higher vulnerability are located between the upper thoracic and lumbar spinal cord.

Further MEP studies may not only provide a means for an early diagnosis, but also shed light on the spinal topography of HM.

### NEUROIMAGING FINDINGS

Most case reports have not documented MRI abnormalities in the spinal cord. This suggests that MRI may be less sensitive than MEP/CMCT in the early detection of HM or that, to date, abnormal corticospinal tract signals on MRI may have been underappreciated.

Negative spinal cord MRI findings support HM in the differential diagnosis, because MRI is essential to rule out compression of the spinal cord or myelitis[23].

However, abnormal spinal cord MRI imaging has been reported in HM patients[29,30]. In particular, the MRI finding of intracerebral corticospinal tract abnormalities in a recently reported patient[30] suggests the occurrence of HM-related pathology above the level of the foramen magnum. In fact, an increased FLAIR signal in the subcortical white matter and subcortical spi-
nal tracts was reported. This is the first report of an abnormal MRI intracerebral corticospinal tract FLAIR signal in HM, and indicates that the pathology of HM may not be confined to the spinal cord or that it may be tied to preclinical PSE. A similar abnormal FLAIR signal has also been described in PSE and cirrhosis. Hyperintensity of the putamen and globus pallidus on T1-weighted MRI, attributed to manganese deposition in these nuclei, is not unique to HM and has been noted in other patients with chronic liver failure. Although not specific to HM, these radiological findings correlated with the clinical findings in that patient. Interestingly, the improvement in abnormal brain imaging findings parallels the clinical improvement in spastic paraparesis after LT.

**THERAPY**

HM has a poor prognosis because of its progressive and irreversible nature. Today, no therapy for this disorder has been established. Conservative treatment strategies for HM include liver protection, neurotropic drugs, and measures to control blood ammonia concentration. However, as previously mentioned, HM responds poorly to conservative medical therapy. In particular, in contrast to HE, HM usually does not respond to blood ammonia-lowering therapies.

Surgical treatment options in HM currently include LT, surgical ligation, shunt reduction, or occlusion by interventional procedures. Surgical ligation has been reported to be effective, but is only used occasionally.

**Endovascular interventional procedures**

Interventional endovascular shunt occlusion has been commonly used to treat encephalopathy due to postsurgical shunt and post-TIPS. By contrast, the usefulness of this technique for post-surgical shunt HM has not yet been determined.

Recently, Wang et al. first reported reversal of HM by occlusion of a surgical splenorenal shunt using an AVP. In this interesting case, an impaired gait and a progressive decline in mobility were observed 14 mo after surgical splenorenal shunt. The patient had no history of HE, and his laboratory findings showed no liver dysfunction (with the exception of an increase in his serum ammonia level). Therefore, occlusion of the splenorenal shunt represented an alternative therapeutic option, and the large splenorenal shunt was successively occluded using an AVP. Other possible embolizing materials for the embolization of the PSS are coils, and a detachable balloon. AVP implantation for this patient was chosen due to the relatively large size of the surgical splenorenal shunt. Moreover, coil migration can occur when used in short shunt tracts. AVPs were recently found to be effective for the occlusion of internal iliac arteries, the treatment of pulmonary arteriovenous malformations and the occlusion of a splenorenal shunt arising after TIPS. AVPs have an advantage over coils in that they can be repositioned or removed, if necessary.

Following AVP embolization, a gradual improvement in leg strength and balance was observed; seven months after AVP embolization, the patient was able to walk 1 to 2 km aided by crutches, with only mild residual spasticity of the lower extremities.

After PSS embolization a sudden increase in portal pressure may constitute a severe complication, resulting in aggravation of esophageal varices or even development of new varices. Therefore, embolization should be performed only in patients with absent or mild esophageal varices and without signs of hepatic failure (i.e., ascites or jaundice). Moreover, routine periprocedural endoscopy is recommended to minimize the incidence of embolization-related complications. Wang et al. used an occlusion balloon catheter initially to occlude the surgical shunt. Because further monitoring of the patient over a few days revealed no evidence of induced varices or ascites, an AVP was used to enable closure of the shunt.

Thus, Wang et al. are the first to report a surgical shunt related-HM successfully embolized with an AVP, which resulted in an immediate improvement in intrahepatic portal perfusion, a normalization of blood ammonia, and a gradual improvement of HM-related symptoms. The authors were also able to document a temporary balloon occlusion of the surgical shunt prior to permanent embolization, which also may be used to predict clinical and laboratory improvement.

**Liver transplantation**

Campellone et al. were the first to suggest the use of urgent LT for HM because of the progressive and irreversible nature of the disease.

Until the advent of LT, slow progression of spastic paraparesis over several years inevitably caused HM patients to become wheelchair bound. In the reviewed literature, nearly all patients with symptomatic HM who eventually underwent LT had severe paraparesis before the operation and required either a cane or a wheelchair. LT appears to be the only promising effective treatment modality for HM, as supported by several previously published reports. In particular, outcomes for those patients who had undergone LT sooner after being diagnosed with HM suggest a potential neurological benefit. In the case reported by Counsell and Warlow, LT was performed at least 18 mo after the onset of the myelopathy, and there was no improvement. In fact, LT earlier during the clinical course of HM and/or in the absence of marked abnormalities in MEP/CMT is important in achieving satisfactory reversal of the neurological motor deficit.

It should be considered that, in HM patients with established cirrhosis, the degree of spastic paraparesis and the risk of permanency are discordant with the Child-Pugh score. Interestingly, Caldwell et al. introduced the first use of a Model for End-Stage Liver Disease (MELD) points for the condition of HM to enable early LT resulting in
the reversal of marked spastic paraparesis. The patient underwent LT approximately 1.5 years after being diagnosed with HM. In this case there was no overt HE. Both the spastic paraparesis and posterior column deficits rapidly and markedly improved within 3 mo after successful orthotopic LT. Expedited orthotopic LT may lead to a favorable neurological outcome after the granting of MELD exception points for HM as the primary indication for LT. Thus, the MELD system does not automatically prioritize these patients for LT, and submission of an appeal is necessary. Increased awareness will aid earlier diagnosis of HM, and because good neurological outcomes can be achieved by prompt LT, the transplant community should consider early and rapid transplant evaluation for those patients with HM. On the basis of their review, Caldwell et al concluded that patients with HM should be prioritized for LT with the consideration of MELD exception points.

CONCLUSION

HM should be always considered in the differential diagnosis in patients with spastic paraparesis in the setting of chronic liver disease and/or portosystemic shunt. The diagnosis of HM should be established as early as possible to enhance the chance of a complete recovery of the spinal cord. Importantly, MEP studies may be suitable for the early diagnosis of HM, even in patients with preclinical stages of the disease. Even if HM is thought to be related to the increased shunting of portal venous toxins to the systemic circulation, conservative therapies are, unlike for HE, usually inefficient.

An early diagnosis of HM should prompt recognition of predisposing factors such as PSS or TIPS, which can be considered for shunt occlusion by interventional procedures. However, in most cases, LT represents the only option for patients with HM. In particular, LT remains a potentially definitive treatment for HM in patients with decompensated cirrhosis of Child-Pugh B and C grades, while for patients with normal liver function Child-Pugh A grade cirrhosis the choice of LT vs other treatments remains debatable. In these patients, shunt occlusion may represent a suitable alternative therapy to LT, and occlusion can help to relieve shunt-induced HM symptoms. In fact, in the case described by Wang et al, a large surgical splenorenal shunt was successfully occluded using an AVP, which resulted in significant clinical improvement of the shunt-induced HM symptoms. This technique represents a viable alternative to surgery or coil embolization, although further research is necessary. In addition, trial balloon occlusion of the shunt prior to performing permanent embolization can be used to predict clinical and laboratory improvement.

In conclusion, HM is a rare cause of spastic paraparesis, but clinical history, along with appropriate laboratory, neurophysiological and neuroimaging findings, may allow an early diagnosis in patients with chronic liver diseases.

We provide a comprehensive and updated review of the most pathophysiological and clinical aspects of HM. Moreover, we also discussed the appropriate and effective treatments for this possibly underrecognized neurological complication of liver cirrhosis.

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