Clinical Reasoning: A Middle-aged Man With Progressive Gait Abnormalities

Junyu Lin, MD,* Yanbing Hou, MD,* and Huifang Shang, MD

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Correspondence

Dr. Shang
hfshang2002@126.com

Abstract

Progressive spastic paraplegia is the core symptom of hereditary spastic paraplegias (HSPs), a group of monogenic disorders characterized pathologically by degeneration of the corticospinal tract and dorsal column and leading to irreversible neurologic deficits. However, acquired causes, such as structural, vascular, inflammatory, infectious, metabolic, toxic, neurodegenerative, and iatrogenic causes, can also cause acquired spastic paraplegia. We describe the case of a middle-aged man presenting with progressive spastic paraplegia combined with ataxia and parkinsonism. No mutation of HSP genes was detected. After a comprehensive diagnostic workup, hyperintensities in the bilateral basal ganglia, mesencephalon, pons, and cerebellum on T1-weighted images were found, which demonstrated hypointensity on susceptibility-weighted imaging. Furthermore, an increased blood ammonia level and diffuse slow-wave activity in EEG were detected. The patient had a 7-year history of hypertension, alcoholic liver cirrhosis, and transjugular intrahepatic portosystemic shunt operation 2 years before the onset of spastic paraplegia symptoms. Current workup combined with patient history resulted in a diagnosis of acquired hepatocerebral degeneration and hepatic myelopathy. This case provided a detailed diagnostic approach for progressive spastic paraplegias and exhaustive differential diagnoses of basal ganglia deposits. The take-home message from this case was that acquired causes, especially curable causes, should always be excluded first when dealing with patients with progressive spastic paraplegia.

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*These authors contributed equally to this work.

From the Department of Neurology, West China Hospital, Sichuan University, Chengdu, China.

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Figure 1 MRI Images of the Patient

(A) Sagittal T2-weighted MRI findings show thin corpus callosum; (B–C) T1-weighted images show hyperintense signals in the mesencephalon, pons, and cerebellum (red arrows); (D) T1-weighted image shows the bilateral symmetrical hyperintense signal in the basal ganglia (red arrows); (E) T2-weighted image shows no abnormal signal in the basal ganglia; and (F) SWI shows the bilateral symmetrical hypointense signal in the globus pallidus (red arrows).

Section 1

A 51-year-old Chinese man presented with progressive gait disturbance for 18 months. Eighteen months earlier, he developed mild spasticity and weakness of the lower limbs when walking. His symptoms exacerbated gradually, and he developed unsteady and shuffling gait 1 year ago, accompanied by bradykinesia of the limbs. He occasionally experienced urinary incontinence without bowel symptoms in the past 6 months. He had a 7-year history of hypertension and alcoholic liver cirrhosis and underwent transjugular intrahepatic portosystemic shunt (TIPS) 2 years earlier due to bleeding esophageal varices. He had a 20-year history of alcohol use and no history of smoking and toxins exposure. He came from a non-consanguineous family with no remarkable family history. A local hospital initially diagnosed hereditary spastic paraplegia (HSP). Subsequently, he was referred to our department. Brain

magnetic resonance imaging (MRI) in the local hospital demonstrated thin corpus callosum (TCC) (Figure 1A). Neurologic examination revealed mild dysarthria, horizontal gaze-evoked nystagmus, normal muscle bulk and strength, bradykinesia and lead-pipe rigidity of the left upper limb, spasticity of the lower limbs, diffuse hyperreflexia, ankle clonus, extensor plantar responses, impaired vibration sensation in the left lower limb, limb ataxia during finger-to-nose and heel-to-shin tests, difficulty in tandem walking, and a spastic, wide-based, and shuffling gait, but no tremor or postural instability (Video 1, <http://links.lww.com/WNL/B519>). The Montreal Cognitive Assessment (MoCA) score was 21/30 (naming, 1; attention, 2; abstraction, 1; language, 1; and delay recall, 4).

Questions for Consideration:

1. Can a HSP diagnosis explain all symptoms of the patient?
2. Which subtype of HSP was most likely?

GO TO SECTION 2

Section 2

The patient presented with middle-age onset of spasticity-ataxia-parkinsonism syndrome with predominantly progressive spastic paraplegia. HSPs are a group of monogenic disorders characterized pathologically by degeneration of the corticospinal tract and dorsal column and clinically by progressive spastic paraplegia accompanied occasionally by impaired vibration sensation and urinary incontinence. In addition, complicated HSP may have other neurologic

features such as ataxia, dysarthria, neuropathy, and parkinsonism syndrome.¹ HSP-TCC, a subtype of complicated HSP, exhibits progressive spastic paraparesis with extrapyramidal symptoms, cognitive impairment, and TCC, similar to our patient. *SPG11* and *SPG15* are the most common causative genes for HSP-TCC.¹

Questions for Consideration:

1. What examinations are required?
2. What other causes should be considered?

GO TO SECTION 3

Section 3

Up to 79 HSP genes have been identified, including autosomal dominant, autosomal recessive, and X-linked. Therefore, a gene panel for HSP was chosen. However, no pathogenic mutations were revealed. Although additional genes associated with HSP still need to be identified, the negative family history, nonconsanguineous parents, and a relatively late age at onset suggest acquired causes rather than genetic HSP.¹ Structural, vascular, inflammatory, infectious, metabolic, toxic, neurodegenerative, and iatrogenic causes can all result in acquired spastic paraplegia. Therefore, additional examinations were conducted. Besides decreased albumin (31 g/L, normal: 40–55 g/L) and increased direct bilirubin (10.2 $\mu\text{mol/L}$, normal: 0–8.0 $\mu\text{mol/L}$), other parameters, including serum

electrolytes, ferritin, folate, homocysteine, vitamin B12, vitamin E, copper, ceruloplasmin, liver enzymes, kidney functions, and CSF, were normal. HIV and syphilis test results were negative. Kayser-Fleischer (K-F) ring and retinal degeneration were absent. Electromyogram finding was normal. Brain MRI was reexamined. Besides TCC, hyperintensities in the bilateral basal ganglia, mesencephalon, pons, and cerebellum on T1-weighted images and hypointensity in the bilateral globus pallidus on susceptibility-weighted imaging (SWI) with normal T2 images were found (Figure 1B–F). Spinal cord MRI and brain CT findings were normal.

Questions for Consideration:

1. What do the brain abnormal signals signify?
2. What disease should be considered?

GO TO SECTION 4

Section 4

SWI hypointensity indicates paramagnetic brain deposits such as copper, iron, calcium, and manganese. As a reversible disease, Wilson disease (WD) caused by *ATP7B* mutations was first considered. Extrapyraridal, pyramidal, psychiatric symptoms, and abnormal liver function may occur in WD along with T1 hyperintensity and SWI hypointensity in the lenticular nucleus, which was consistent with our patient. However, the most characteristic imaging feature of WD is the concurrence of hyperintense and hypointense signals on T2-weighted images,² which was absent in our patient. Normal serum ceruloplasmin and absence of K-F ring also excluded WD.

Iron is another paramagnetic substance easily deposited in the brain. Neurodegeneration with brain iron accumulation (NBIA) is a group of genetically heterogeneous disorders.³ *FA2H* can cause diverse phenotypes, including HSP type 35, leukodystrophy, and NBIA, leading to complex neuropsychiatric symptoms. *FA2H*-associated neurodegeneration (FAHN) fits best with our patient's phenotype. The characteristic MRI findings of FAHN can be summarized by the acronym "WHAT": white matter changes, T2 hypointensity in the basal ganglia, pontocerebellar atrophy, and TCC.⁴ Despite the overlapping clinical symptoms, TCC, and SWI characteristics, the distinctive T2 hypointensity of iron accumulation was absent in our patient. Moreover, the age at onset of FAHN is much younger.

Basal ganglia calcification can cause neuropsychological, cognitive, and movement disorders. It can be primary when caused by heterozygous mutations of *SLC20A2*, *PDGFRB*, *PDGFB*, and *XPR1* and homozygotic or compound heterozygous mutations of *MYORG* and *JAM2*.⁵ Various conditions can cause secondary basal ganglia calcification, most

commonly parathyroid disturbances related to metabolic dysfunctions of calcium/phosphorus.⁶ Hyperintensities on T1-weighted and T2-weighted images and hypointensities on SWI were observed in brain calcification. However, the absence of hyperdensity on the CT scan excluded calcification in our patient.

Manganese deposition in the brain shows T1 hyperintensity and SWI hypointensity mainly in the globus pallidus with normal T2 images, concordant with our patient. Manganese deposition can be inherited, through mutations of the manganese transporter genes including *SLC30A10* and *SLC39A14*,⁷ or acquired from environmental overexposure to manganese and impairment of manganese excretion in chronic liver disease. Patients with chronic liver disease or portosystemic shunts may develop neurologic syndromes, such as acquired hepatocerebral degeneration (AHD) and hepatic myelopathy (HM), characterized by extrapyramidal symptoms and spastic paraplegia, respectively.⁸ Impaired vibration sensation and urinary incontinence can also occur in some patients with HM. Although spinal cord demyelination has been detected in autopsy, spinal cord MRI is usually normal in those with HM. The neuroimaging findings, clinical symptoms, and medical history of alcoholic liver cirrhosis and TIPS raised a strong suspicion of AHD and HM in our patient. Furthermore, we found an increased blood ammonia level (210.8 $\mu\text{mol/L}$, normal: 9.0–30.0 $\mu\text{mol/L}$) and diffuse slow-wave activity in EEG, consistent with the characteristics of AHD and HM.^{9,10} To exclude potential genetic causes, we performed whole-exome sequencing, and no mutation was found. The patient reported experiencing episodes of hepatic encephalopathy twice after TIPS. Therefore, concurrent AHD and HM were diagnosed.

Questions for Consideration:

1. What treatments are indicated?
2. How to explain the TCC?

GO TO SECTION 5

Section 5

Although the pathogeneses of AHD and HM remain unclear, portacaval shunts or less commonly splenorenal shunts may play important roles even in the absence of liver dysfunction. After portosystemic shunting, toxic metabolites, particularly manganese and ammonia, cannot be removed by the hepatobiliary system, causing deposition in the brain and spinal cord, with subsequent neurodegeneration. Ammonia-reducing treatment may be beneficial in treating AHD and HM. The condition of our patient improved slightly with ammonia-reducing treatment by L-ornithine-L-aspartate. Limb rigidity and spasticity showed mild response to pramipexole and baclofen. Although efficacy of liver transplantation has been shown in some cases,¹⁰ our patient declined it. At the 1-year follow-up, despite slightly decreased muscle strength of the right lower limb, he still walked unaided (Video 1).

Considering alcoholism history and TCC, concomitant Marchiafava-Bignami disease (MBD) was considered for the patient. MBD is a complication of alcohol abuse characterized pathologically by demyelination and atrophy of corpus callosum and clinically by epilepsy, cognitive decline, impaired walking, dysarthria, and pyramidal signs.¹¹ A previous research found lesions in corpus callosum of 27.9% patients with MBD, disappeared during the follow-up, and only 20.9% patients with MBD experienced seizures.¹¹ Therefore, TCC in our patient might also ascribe to a possible concomitant MBD, irrespective of the absence of abnormal signals in the MRI and EEG.

Discussion

Both AHD and HM are rare complications of cirrhotic liver disease,^{9,10} and their combination has been previously reported.¹² Both have poor prognosis with mostly irreversible neurologic deficits. A previous study on 16 patients with AHD or HM found 12 patients who had died while awaiting for liver transplantation during a median follow-up of 29 months.¹⁰ Liver transplantation in the early stage is the only effective treatment to reverse neurologic impairments and improve survival. Therefore, early recognition of AHD or HM is critical. As shown in the case, the presence of extrapyramidal symptoms or progressive spastic paraplegia, a precondition of portosystemic shunts in combination with a characteristic neuroimaging picture of abnormal signal mainly in the globus pallidus, namely, T1 hyperintensity and SWI hypointensity, is a strong indicator of AHD or HM.

Another important takehome lesson is that cognitive bias can influence clinicians' judgment on differential diagnosis. In this patient, the initial suspicion of complex HSP was guided by the complex symptoms and TCC; consequently, we focused on this rather than the less "exciting" explanation of cirrhosis. Therefore, being rational and logical is important in clinical

practice. For instance, in patients with progressive spastic paraplegia, acquired causes, especially curable causes, should always be excluded first. In the absence of a pathogenic HSP mutation in a patient with spastic paraplegia, a new genetic mutation should only be assumed after a comprehensive examination ruling out acquired causes.

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Disclosure

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Appendix Authors

Name	Location	Contribution
Junyu Lin, MD	West China Hospital, Sichuan University, Chengdu, China	Study design and conceptualization, drafted and revised the article, and analyzed and interpreted data
Yanbing Hou, MD	West China Hospital, Sichuan University, Chengdu, China	Revised the article and interpreted the data
Huifang Shang, MD	West China Hospital, Sichuan University, Chengdu, China	Revised the article and approved all final changes

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