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Tremor and Other Hyperkinetic Movements

Case Reports

Uncommon Movement Disorders in Chronic Hepatic Disease with Response to Rifaximin

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Abstract

Background: Chronic hepatic disease can present with extrapyramidal symptoms. We describe two cases that presented with highly unusual movement disorders: ballism and gait freezing.

Case report: Patient 1 is a 42-year-old man with previous episodes of hepatic encephalopathy (HE) who presented with upper limb dystonia and generalized chorea that progressed to ballism. Patient 2 is a 55-year-old woman who presented with pronounced gait freezing. In both patients, features of HE and acquired hepatocerebral degeneration coexisted. They improved markedly, though transiently, with rifaximin.

Discussion: Ammonia-reducing treatments should be considered in patients presenting with movement disorders due to chronic liver disease.

Keywords: Hepatic disease, ballism, freezing, rifaximin

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Introduction

Compromised liver function as a consequence of either acute hepatic failure or advanced chronic liver disease leads to insufficient detoxification of neurotoxic substances, which accumulate in the blood and are responsible for a broad range of neurological manifestations. These include hepatic encephalopathy (HE) and acquired hepatocerebral degeneration (AHD).[1] Clinical manifestations usually involve movement disorders and cognitive features. In HE, improvement may be seen with purgative ammonia-lowering therapies such as lactulose. However, in AHD liver transplant is considered the only effective treatment. We present two cases of advanced liver disease with uncommon movement disorders (freezing of gait and ballismus) that reversed with rifaximin.

Case reports

Case 1

A 42-year-old male was first seen in the Neurology clinic due to involuntary movements. His medical history included past alcohol and drug abuse, hepatitis C virus (HCV) infection, and hepatic cirrhosis Child-Pugh C with portal hypertension and hepatopulmonary syndrome. He had been on methadone and olanzapine 2.5 mg id for the last 18 months. There were reports of HE episodes in the previous 8 months with consciousness and attention fluctuation, dysarthria, and motor incoordination that subsided with lactulose treatment. On neurological examination, he presented generalized chorea with orolingual, cervical, and asymmetric limb involvement (worse on the left), exacerbated by movements. There was also a symmetric dystonia of both hands. The gait was slightly ataxic (Video 1, segment 1). Additional neurological examination showed moderate dysarthria and dysphagia. Brain MRI revealed T1-weighted hyperintensities in the globus pallidus (GP), subthalamic nuclei, and midbrain (Figure 1). T2-weighted sequences showed mild bilateral putaminal hyperintensities, particularly on the right side. Ammonia levels were elevated (126 μmol/L, normal range 26–47 μmol/L) and manganese levels were normal (16.5 ng/mL, normal range 4.7–18.3 ng/mL). A basic metabolic screen revealed hypoalbuminemia, thrombocytopenia, and an INR of 1.89 and excluded other metabolic alterations. One month later he was seen at the

Video 1 **(case 1). Neurological examination of patient 1. Segment 1**: Patient at age 42 showing slight dysarthria, generalized chorea (worse on the left) with oromandibular involvement, bilateral hand dystonia and ataxic gait. **Segment 2**: worsening of involuntary movements, with bilateral ballistic movements of limbs. **Segment 3**: after rifaximin treatment, chorea and ballism disappeared. A mild hand dystonia and a slightly ataxic gait is evident. **Segment 4**: clinical worsening with mental slowness, hypomimia, positive upper limb myoclonus with axial and appendicular hypotonia, without chorea. This segment is part of a fluctuating disease course, despite treatment.

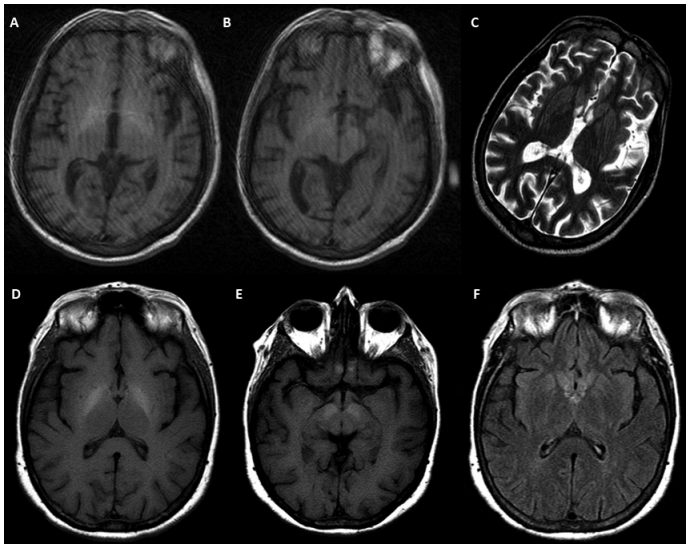

Figure 1. **Brain MRI.** Case 1: Axial T1-weighted images showing hyperintensities in GP(A) and mesencephalon(B); Axial T2-weighted image showing mild bilateral hyperintensities in striatum and global CSF space enlargement(C). Case 2: Axial T1-weighted images revealing symmetric hyperintensities in the GP(D) and substantia nigra(E); Axial T2-FLAIR image showing slight increase in the striatum signal(E).

emergency department, awake and fully oriented, with rapid, involuntary, nonstereotypical, violent ballistic limb movements and choreic movements of the tongue and perioral area (Video 1, segment 2). Ammonia levels were 150 μmol/L. He was treated with haloperidol 5 mg IM with no response and later with lactulose and rifaximin 800 mg id with marked improvement of the ballistic and choreic movements (Video 1, segment 3). Ammonia values 3 days after treatment were 61 μmol/L.

Video 2 **(case 2). Neurological examination of patient 2. Segment 1**: Patient at age 53 presenting abnormal gait with start and turn hesitation. **Segment 2**: gait improvement after rifaximin treatment, with remaining mild hesitation when turning. **Segment 3**: Severe gait disorder with marked freezing and magnetism in forward gait, which improves when walking backwards or side to side.

Since then, maintaining treatment with rifaximin, he oscillated between a fully conscious and oriented state with marked hypotonia and dysarthria and episodes of confusion with severe generalized chorea (Video 1, segment 4). Ammonia levels also showed significant variation (between 78 and 327 μmol/L), with higher values usually in the context of a concurrent infection or constipation. There were, however, some doubts on medication adherence.

Case 2

A 55-year-old woman was referred to our movement disorder clinic due to gait imbalance and falls with a fluctuating pattern. She had had a liver transplant due to alcoholic cirrhosis and developed graft dysfunction in the first year after transplant, coinciding with imbalance onset. Six years later, she had a self-limited period of confusion associated with hyperammonemia. During the following year, she maintained episodic confusion and developed difficulty initiating gait, turning, and walking through narrow spaces. In her first neurological observation, she presented slight mental slowness, hypomimia, a wide-based gait with small shuffling steps with evident start and turn hesitation, freezing, and impaired postural reflexes (Video 2, segment 1). The remaining neurological evaluation was normal. Brain MRI revealed bilateral and symmetric T1-weighted hyperintensities involving the GP and *substantia nigra* (SN) (Figure 1). T2-FLAIR sequences showed small subcortical and deep white matter hyperintensities in both hemispheres alongside slight increase in the striatum signal. Ammonia levels were elevated, fluctuating between 100 and 200 μmol/L. Metabolic screen showed mild stable hyperbilirrubinemia without coagulopathy. At last, she was admitted to the emergency unit confused and unable to walk. Hepatic ultrasound and liver biopsy showed regenerative nodular hyperplasia causing portal hypertension, without cirrhosis or rejection. She was initiated on rifaximin with impressive improvement in cognition and gait, which became practically normal in 1 month (Video 2, segment 2). Manganese levels at this point were within the normal range (10.2 ng/mL). Ammonia levels also showed significant reduction from

Table 1. **Clinical and Imaging Findings Suggestive of HE or AHD in Each Patient**

		Patient 1	Patient 2
Suggest hepatic encephalopathy	Fluctuating course	+	+
	Transient consciousness and attention impairment	+	+
	Hyperammonemia	+	+
	T2 hyperintensities of basal ganglia	+	+
	Improvement with rifaximin	+	+
Suggest AHD	Persistent gait alteration	+ (ataxia)	+
	Dystonia	+	−
	Orobucolingual dyskinesia	+	−
	Chorea	+	−
	Cerebellar dysarthria and ataxia	+	−
	Hypermanganesemia	−	NA
	T1 hyperintensity of globus pallidus	+	+

HE: hepatic encephalopathy; AHD: acquired hepatocerebraldegeneration; NA: non applicable; "+": present; "−": absent.

pretreatment (249 μmol/L) to posttreatment levels (55 μmol/L, 1 month later). Neuropsychological evaluation at this point revealed a mild multidomain cognitive impairment; brain MRI showed reduction of the SN T1-weighted hyperintensity.

Despite initial clinical improvement under rifaximin, during the following months she oscillated between days with a normal gait and others in which forward gait was impossible due to freezing. Freezing partially improved with backward and side-to-side gait, but was not affected by visual or auditory cues (Video 2, segment 3). The patient was proposed for liver retransplant.

Discussion

Herein, we report two patients with chronic hepatic disease presenting with unusual movement disorders, in which features of both HE and AHD are present (Table 1).

The presence of portosystemic shunt in cirrhotic or noncirrhotic portal hypertension allows neurotoxic substances such as ammonia, glutamine, and manganese to bypass the liver and gain access to the cerebral circulation. A proinflammatory state leads to brain blood barrier disruption and accumulation of these substances intraparenchymally.[1] Intracellularly, ammonia is converted into glutamine that produces oxidative stress, metabolic disruption, and astrocyte structural changes. Ammonia also interferes in the communication between astrocytes and neurons, leading to widespread neurological manifestations.[1]

Hepatic encephalopathy presents with consciousness fluctuation ranging from somnolence to coma, neuropsychiatric symptoms including attention deficit, psychomotor slowing, and sleep disturbances. Movement disorders associated with HE are less prominent than mental status features and include asterixis, tremor, hypokinesia, and rigidity.[2] HE usually has a fluctuating course and can be episodic, recurrent, or persistent.[1] It is generally considered to be caused by hyperammonemia and, hence, potentially reversible. Treatment involves reduction of ammonia production through laxatives and nonabsorbable antibiotics such as rifaximin.[2] On the contrary, AHD is a chronic disorder thought to be related primarily to manganese deposition in basal ganglia, where it causes presynaptic dopaminergic dysfunction and loss of postsynaptic dopaminergic receptors.[3] The manganese theory is supported by MRI findings, including T1-high signal intensities in GP and adjacent areas. This preferential deposition is linked to a different clinical phenotype, mainly with cognitive deterioration and movement disorders, including tremor, parkinsonism, dystonia, chorea, and ataxia.[2] These symptoms are usually irreversible, progressive, and resistant to pharmacological treatment.[1] The main therapeutic option is hepatic transplantation.[1]

In our cases, the fluctuating course with attention and consciousness impairment, hyperammonemia, and the impressive improvement with rifaximin are suggestive of HE. On the contrary, the combination of dystonia, oromandibular dyskinesias, and ballistic movements (case 1) and a persistent gait disorder (case 2) with typical T1 hyperintensities in both patients support an AHD diagnosis. Patient 1 had previously been on olanzapine, which could contribute to the oromandibular dyskinesias; it cannot, however, justify the whole clinical presentation, giving its fluctuating pattern. This patient also presented a HCV infection, which has also been associated with movement disorders.[4] Hyperkinetic disorders have been described in patients with HCV while under inferferon-alpha treatment, but these have disappeared with treatment interruption.[5] Case 1 was not under any HCV treatment and therefore we believe the virus had no role in the clinical presentation.

Ballismus and isolated gait abnormalities constitute exceptional manifestations of chronic hepatic disease. Choreic and ballistic movements are usually attributed to decreased output from basal ganglia, caused by lesion or dysregulation of subthalamic afferents.[6] The T1-hyperintense lesions involving the subthalamic nuclei in the brain MRI of case 1

seem to be the cause of his movement disorder. We found only two previous reports of two patients with bilateral ballism associated with hepatic disease, preceded by episodes of HE. They responded to treatment with haloperidol and lactulose.[7,8] A previous paper reported on three patients with hepatic cirrhosis and akinetic-rigid parkinsonian syndromes that also improved after rifaximin. This was accompanied by a T1 signal reduction in GP.[9]

Regarding the phenotype of the second patient, there are several reports of gait abnormalities and postural instability in patients with hepatic disease.[1,2] Usually, they are noticed as part of a parkinsonian syndrome and are more often related to AHD than HE. We have not found cases reporting freezing in the setting of hepatic disease.[10] Our patient presented with freezing of gait without other parkinsonian signs apart from hypomimia, evoking a frontal gait. The frontal lobe has a crucial role in gait initiation, resulting in freezing and magnetism when damaged. Furthermore, disruptions in the networks connecting the cortical areas (frontal and parietal), basal ganglia, and the mesencephalic locomotor region involved in gait control are considered the main pathogenic mechanisms of freezing and parkinsonian motor features.[1,11] This patient presented GP damage/T1 hyperintensities and although these are usually associated with AHD, the improvement with rifaximin suggests that ammonia (and, hence, HE) has an essential role. In fact, HE can also display GP T1 hyperintensities as well as white matter/periventricular T2 hyperintensities, as our patient did.[1,2] The presence of abnormalities in both T1W1 and T2-FLAIR sequences also argues in favor of the coexistence of ammonia and manganese as pathogenic elements (HE and ADH) in the same patient. The link between freezing and hyperammonemia has also been described in epileptic patients under valproate treatment.[12] It is conceivable that ammonia is toxic to basal ganglia and its gait networks, particularly in susceptible individuals as ours.

Lastly, it is interesting to notice that our patient's freezing improved with backward or side-to-side gait. Freezing associated with parkinsonism is usually exacerbated in nonforward gait. Isolated backward freezing has even been described in patients with neurodegeneration with iron brain accumulation.[13] A mechanism of external cueing (such as touching the wall) in a parkinsonian gait may be responsible for this phenomenon. Alternatively, we hypothesize that backward or side-to-side gait improvement could be a form of geste antagoniste in a dystonic gait, despite the fact that no leg dystonia is evident. A "crab-like" gait that improves in side-to-side walking has been described in dystonia.[14]

A clear distinction between HE and AHD is probably artificial, as both processes may happen simultaneously and share pathogenic pathways. Other cases with overlapping features between HE and AHD have been reported.[8] In a small case series of AHD, previous episodes of HE could be identified in up to 60% of patients.[10] Whether HE constitutes a risk factor for AHD remains to be clarified.

In conclusion, ballism and freezing of gait should be included in the neurological manifestations of portal hypertension, with or without cirrhosis. Treatments that reduce ammonia production, such as rifaximin, must be considered even in patients with atypical manifestations. However, these cases illustrate that improvement may be transient and that the disease will still progress, favoring the use of rifaximin as a bridge to hepatic transplantation in patients with persistent movement disorders.

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