Late-onset neurodegenerative manifestations in patients with cirrhosis: acquired hepatocerebral degeneration – a neglected diagnosis

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Abstract

Acquired hepatocerebral degeneration (AHCD) is an acquired, extrapyramidal, neurodegenerative condition, encountered in patients with cirrhosis. It is an uncommon and usually irreversible condition, resulting in widespread cerebral, basal ganglia and cerebellar damage. We describe here four cases of AHCD, with varying presentations, highlighting the need for increased awareness of this condition, to avoid diagnostics delays and unnecessary management.

Introduction

Acquired hepatocerebral degeneration (AHCD) is an acquired, extrapyramidal, neurodegenerative condition, encountered in patients with cirrhosis [1]. It is an uncommon and usually irreversible condition, resulting in widespread cerebral, basal ganglia and cerebellar damage.

The term AHCD is restricted to patients with cirrhosis resulting from a variety of causes but specifically excludes Wilson disease [1, 2]. It is often termed acquired, non-Wilsonian, hepatocerebral degeneration to ensure this distinction. Due to lack of awareness, patients with AHCD are often mistakenly labelled as having "chronic hepatic encephalopathy". This is best avoided, as AHCD is clinically distinct from hepatic encephalopathy. Patients with AHCD do usually, but not always, have multiple prior episodes of hepatic encephalopathy [3]. They present with gradual onset neurological dysfunction including cognitive dysfunction (dementia), extrapyramidal signs (rigidity, dysarthria, tremor and choreoathetosis) and gait abnormalities (gait ataxia) [1].

Although the pathophysiology of AHCD is uncertain, portosystemic shunting is likely to play a central role [1, 2]. Manganese overload is also believed to be important in the pathogenesis [1, 2]. On MRI imaging with T1 weighted images, there is intrinsic high signal intensity in the globus pallidus and/or subthalamic region, and midbrain (substantia nigra). This is thought to be due to increased tissue concentrations of manganese which may reverse following liver transplantation. On T2 weighted images, there is increased signal in the middle cerebellar peduncles (MCP sign) [1, 4-8].

AHCD is generally thought to be irreversible, but is not a contraindication for liver transplantation. In fact, recovery of AHCD following liver transplantation has been reported [9].

We describe here four cases of AHCD with varying presentations highlighting the need for increased awareness of this condition.

Case series

Case 1

A 60-year-old woman was admitted to hospital with drowsiness and abnormal limb-movements of 3 days duration. She had a history of cryptogenic cirrhosis with portal hypertension and oesophageal varices, diagnosed 4 years previously. She was also being treated for type 2 diabetes, hypertension and dyslipidemia. Since the diagnosis of cirrhosis, she had a history of recurrent episodes of drowsiness and confusion with high blood ammonia levels which had been treated as hepatic encephalopathy, but with only partial response; resulting in a diagnosis of "persistent hepatic encephalopathy". She had also been having episodes of behavioral and personality changes, difficulty in speech, swallowing and walking, and these had increased in frequency and severity over the past month; she was currently unable to walk without assistance. Her father had cirrhosis and

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hepatocellular carcinoma, but there was no family history of neurological diseases. She had been extensively investigated over this time, and although there was evidence of hepatic decompensation and portal hypertension, she had no Keyser-Fleischer (K-F) rings in her eyes and the serum caeruloplasmin and 24-hour urinary copper levels were normal on at least three separate occasions. CT brain was also normal. At the present admission, the patient was afebrile, not pale, mildly icteric, but had no abdominal distension. She was drowsy, confused, agitated and had severe choreiform movements of her limbs and mouth (pouting), with slurred and incoherent speech. She could not swallow. Her serum bilirubin was 3.0 mg/dl, serum albumin 2.6 g/dl), INR 1.2, serum creatinine 1.2mg/dl (within normal range), serum sodium 121mmol/l and serum potassium 3.7mmol/l. Ultrasound abdomen showed cirrhosis with evidence of portal hypertension, but no hepatic masses, portal vein thrombosis or ascites. Her blood ammonia levels were elevated, but the EEG was unremarkable and a repeat CT brain was normal. Her abnormal movements responded partially to oral haloperidol. Her drowsiness improved with correction of hyponatremia with fluid restriction and treatmentfor hepatic encephalopathy with bowel enemas, lactulose, metronidazole and L-ornithine, L-aspartate infusions. However, her other symptoms, especially the dysarthria and dysphagia persisted. MRI brain showed abnormal increased signal on T1-weighted images in the globus pallidus and substantia nigra while the caudate, putamen, thalamus, and cerebellum were spared. Her neurological condition continues to deteriorate, and because of increasing dysphagia, insertion of a gastric feeding tube is being planned. A liver transplant is not being considered.

Case 2

A 68-year-old man with cryptogenic cirrhosis diagnosed 1 year ago, presented following an acute esophageal variceal bleed which has occurred 3 months previously and from which he had recovered with medical treatment. Endoscopic banding ligation was performed for large esophageal varices with red signs. At follow-up 4 weeks later, the varices were controlled and his cirrhosis was compensated (Child-Pugh Score 6, MELD 14). However, he complained of "slowness", with difficulty in walking and speech. His family complained that he appeared withdrawn and far less active than usual. There was no family history of hepatic or neurological diseases. On examination he was alert, rational and oriented, and had no flapping tremor. However, he had slowness of psychomotor activity, and a shuffling gait with bilaterally decrease arm swing. CT brain, blood ammonia and copper studies were normal, and he had no K-F rings in his eyes. MRI brain showed abnormal increased signal on T1-weighted images in the globus pallidus and substantia nigra. He has shown only partial improvement of his Parkinsonism like features on treatment with carbidopa-levodopa. A liver transplant is not being considered.

Case 3

A 57-year-old man with 4-year history cryptogenic cirrhosis with portal hypertension and Type 2 diabetes presented with feeling unwell and unsteadiness on walking. His family reported recent behavioral changes (psycho-motor slowness) and episodes of slurred speech. There was no family history of hepatic or neurological diseases. He had two past episodes of cellulitis and recurrent episodes of melena due to gastric antral and small bowel vascular ectasia (diagnosed at upper gastro-intestinal endoscopy and capsule endoscopy) related to portal hypertension. On examination had an unsteady gait and slight dysarthria. His cirrhosis was decompensated (Child-Pugh score 8, MELD 16). CT brain was normal. Serum electrolytes, blood ammonia, copper studies and EEG were normal and he had no K-F rings in his eyes. MRI brain showed abnormal increased signal on T1-weighted images in the globus pallidus and substantia nigra. The patient has been listed for a liver transplant.

Case 4

A 70-year-old woman with 6-year history cryptogenic cirrhosis with portal hypertension presented with poor mobility, difficulty in walking and slurred speech for the past 18 months. Her family reported that she had appeared withdrawn. Apart three episodes of melaena due to severe gastric antral vascular ectasia related to portal hypertension, she had no other complications related to cirrhosis, and there was no family history of hepatic or neurological diseases. Her neurological symptoms had been investigated, and a CT brain, serum electrolytes, blood ammonia, copper studies and EEG had been normal, and there were no K-F rings in her eyes. A diagnosis of parkinsonism had been made at that time and she had been started on carbidopa-levodopa. On examination during the current presentation, she was rational and oriented, but could not walk without assistance, had non-expressive facies, limb rigidityand slight dysarthria. Her cirrhosis was fairly well compensated (Child-Pugh score 6, MELD 9). MRI brain showed abnormal increased signal on T1-weighted images in the globus pallidus and substantia nigra (Figure 1 and 2). A liver transplant is not being considered.

Discussion

Hepatic encephalopathy is the commonest neuro-psychiatric manifestation of decompensated cirrhosis [10]. Transient and potentially reversible cognitive dysfunction is the hallmark of hepatic encephalopathy, but prominent extra-pyramidal and gait abnormalities are not typical features [10].

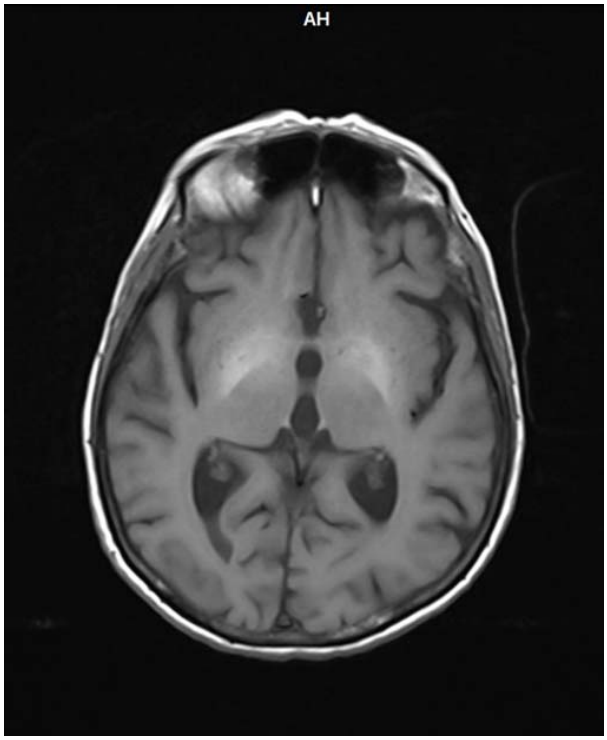

Figure 1. **Axial MRI T1-weighted image shows typical symmetrical hyperintense signal changes in bilateral globus pallidi.**

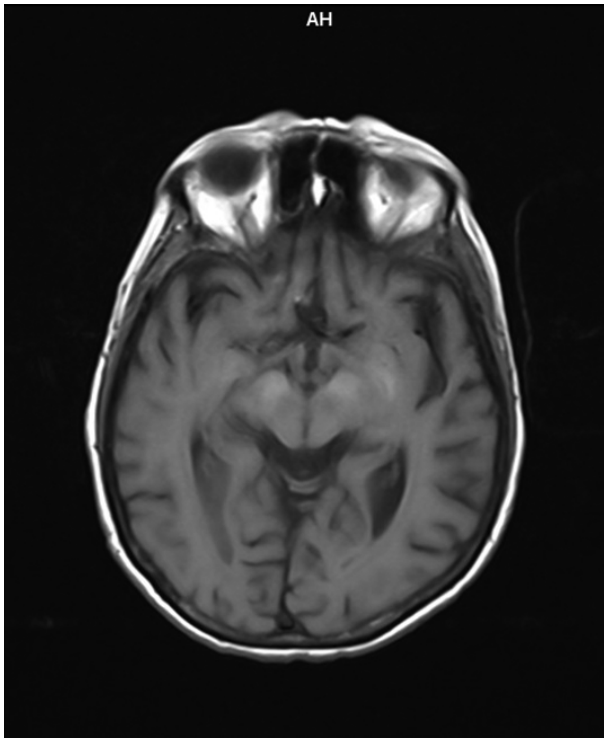

Figure 2. **Axial MRI T1-weighted image shows symmetrical hyperintense signal changes in bilateral midbrain in the region of the substantia nigra.**

The four cases we describe are middle-aged patients with decompensated cirrhosis and portal hypertension, presenting with recent onset or worsening neuro-psychiatric symptoms, which included extrapyramidal and gait abnormalities. These were not typical features of hepatic encephalopathy, although they were described as having recurrent, "refractory" or "persistent" hepatic encephalopathy. Furthermore, although the combination of chronic liver disease and neuro-psychiatric symptoms usually alerts the attending physician, as was the case in all our cases, to consider and exclude a diagnosis of Wilson disease (an inherited hepato-cerebral degeneration), the age of presentation of both the liver disease and neurological symptoms were late onset, and not typical for Wilson disease [11]. The absence of clinical (K-F rings) and biochemical (copper studies including low ceruloplasmin and elevated 24-hour copper excretion) features clearly excluded Wilson disease in the patients we describe [11].

Apart from Wilson disease, Parkinson plus syndromes, which may be unrelated to the underlying cirrhosis, has to be included in the differential diagnosis. This may be relevant in elderly patients with cirrhosis presenting with gait abnormalities, slowness, rigidity, dysarthria and choreoathetosis, similar to some patients described in present case series. However, we suspected the diagnosis of AHCD due to the late age of onset of neuro-psychiatric symptoms in the presence of combination of cirrhosis and portal hypertension, the prominent extrapyramidal and gait abnormalities and the poor response to treatment of hepatic encephalopathy. The diagnosis was confirmed in the absence of other features of Wilson disease and the typical features on MRI neuroimaging.

The typical imaging features of intrinsic high signal intensity in the globus pallidus and/or subthalamic region, and midbrain (substantia nigra) on T1 weighted images on MRI scanning were seen in all our patients (Figures 1-2) [6]. No corresponding signal changes are evident in the globus pallidi in the T2-weighted image (Figure 3). Increased signal in the middle cerebellar peduncles (MCP sign) on T2 weighted images was not observed. It is important to note that CT scans, which were normal in our patients, fail to detect AHCD.

A high degree of clinical suspicion is needed to detect AHCD among older cirrhotic patients with new onset neuro-psychiatric symptoms, with prominent extra-pyramidal and gait abnormalities. Importantly, cranial MRI and not CT, should be part of the evaluation of such patients. The cases described here highlight the need for increased awareness of this condition, to avoid diagnostics delays and unnecessary management.

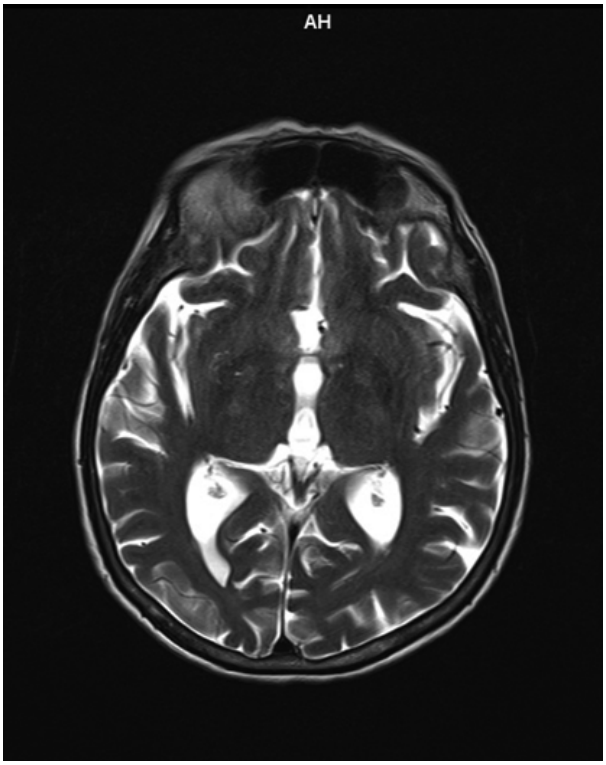

Figure 3. **No corresponding signal changes are evident in the globus pallidi in the MRI T2-weighted image.**

Declarations

Consent statement

Written informed consent was obtained from the patients for publication of this case series.

Ethic Approval

Not applicable

Competing interests

The authors declare that they have no competing interests.

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None.

Availability of data and materials

Data supporting this case series can be only obtained through corresponding author on special request

Authors' contributions

HJdeS and ATA were involved in the clinical management of the patient. MAN drafted the initial manuscript. MAN, ATA and HJdeS completed a review of the literature and revised it critically for important intellectual content. We will be accountable for all aspects of the work. All authors read and approved the final manuscript.

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