Acquired Hepatocerebral Degeneration: A Case Series of a Rare Condition

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ABSTRACT **Background:** Acquired hepatocerebral degeneration (AHD) is a neurologic complication of severe chronic liver disease (CLD) with portosystemic shunts. The proposed etiology is manganese accumulation in the brain tissue, especially in the basal ganglia. Combination of clinical manifestation, mostly extrapyramidal movement disorders, and hyperintensities on T1-weighted brain magnetic resonance imaging (MRI) is diagnostic. Although liver transplantation controversial, it is suggested for AHD.

Objectives: To depict clinical and neuroimaging characteristics and response to treatments in patients diagnosed with AHD at Sheba Medical Center.

Methods: Review of patients with AHD diagnosis at the Liver Diseases Center at Sheba Medical Center between 2012 and 2017, data of clinical and neuroimaging, follow-up, and response to treatments, including liver transplantation were recorded.

Results: Five patients with diagnosis of AHD were identified, median age at diagnosis 55 years (range 45–64 years). Four patients had cirrhosis at the time of AHD diagnosis. The main risk factor for AHD was the presence of portosystemic shunts. The most prevalent clinical manifestations were movement disorders, specifically a combination of extrapyramidal and cerebellar signs including instability, rigidity, tremor, bradykinesia, and cognitive impairment. Brain MRI revealed hyperintensities on T1-weighted images in the basal ganglia in all patients. Administration of antiparkinsonian drugs showed clinical improvement, whereas liver transplantation performed in two patients was not associated to neurological improvement.

Conclusions: AHD is related to portosystemic shunts. The combination of Parkinsonism and cerebellar signs and MRI pallidal lesions should alert physicians to the diagnosis. The role of liver transplantation in AHD is still controversial.

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KEY WORDS: acquired hepatocerebral degeneration, cirrhosis, orthotopic liver transplantation, portal hypertension, Parkinsonism

Chronic advanced liver diseases give rise to variable degrees of neurological impairments, ranging from hepatic encephalopathy caused by the toxic effects of ammonia on the brain to acquired hepatocerebral degeneration (AHD) [1]. This entity was first described by Victor et al. in 1965 [2] and since then, several case reports and case series have described this disorder. The clinical manifestations of AHD are heterogeneous and include neuropsychiatric changes, such as delirium, apathy, lethargy, somnolence, and emotional instability [3]; movement disorders such as tremor, Parkinsonism, akinesia, choreoathetosis, myoclonus, ataxia, asterixis, dystonia, and pyramidal signs [4]; and myelopathy [5].

The prevalence of AHD is estimated to be 1–2%, and although not very rare, the condition remains underdiagnosed [6]. The pathogenesis of the disease is not known but appears to be associated with diversion of portal blood into the systemic circulation allowing a neurotoxic substance to bypass hepatic metabolism. Manganese (Mg) is one such potential neurotoxin that could accumulate in the mitochondria of the globus pallidum, leading to glial cell damage and disruption of their energy metabolism [7]. The manganese hypothesis is supported by classical basal ganglia. Hyperintensities observed on T1-weighted sequences of brain magnetic resonance imaging (MRI) in patients with AHD, which are suggestive of paramagnetic substance deposition within the brain tissue [8]. Currently, no proven treatment for AHD exists, although some case reports have emphasized the usefulness of several medical approaches as will be discussed in this paper.

We report the prevalence, clinical spectrum, neuroimaging features, treatment, and outcome of a case series of patients with AHD who were followed at our center.

PATIENTS AND METHODS

Charts of patients diagnosed with AHD were reviewed from a database of 819 patient charts with chronic liver diseases (CLD)

at the Sheba Medical Center between January 2012 and December 2017. AHD was diagnosed based on one or more of the following signs: tremor, dysarthria, gait disorders, rigidity, bradykinesia, myoclonus, chorea, dyskinesia, or other motor disorders and combined with classical neuroimaging findings of basal ganglia hyperintensities on T1-weighted sequences of brain MRI. Patients with prior neurological impairment (stroke, Parkinson's disease, infection, epilepsy) were excluded from this study.

Wilson's disease was ruled out by copper metabolism tests (plasma copper and ceruloplasmin concentrations and 24-hour urinary copper excretion) or a liver biopsy.

Liver disease was confirmed by liver imaging (abdominal computed tomography [CT], abdominal MRI, and/or liver biopsy. Severity was classified using the Child-Pugh score and the MELD-Na score. The existence of portosystemic shunts was confirmed using liver imaging studies mentioned above.

Data collected from the electronic medical records included patient baseline characteristics (age, sex, medical history) etiology of liver disease, neurological manifestations, and brain MRI findings, as well as type of therapy administered for AHD and clinical outcome.

RESULTS

Between 2012 and 2017, five patients with AHD at Sheba Medical Center were identified, four had established cirrhosis. Prevalence was 0.6%. Patient baseline and clinical characteristics, MRI findings, neurological manifestations, and clinical outcome are summarized in Tables 1, 2, and 3. Three patients were male. Median age at AHD diagnosis was 55 years (range 4–64). Mean follow-up period was 16.2 months. Etiology of CLD was NASH cirrhosis in two patients and idiopathic in another two patients. One patient (Patient 5) had non-cirrhotic portal hypertension at the time of AHD diagnosis. All patients had evidence of portosystemic shunts on imaging studies.

PATIENT 1

Patient 1 had cirrhosis of unknown etiology. Five years after diagnosis the patient presented with rigidity, instability, and cognitive impairment. Ophthalmologic examination was negative for Kayser Fleischer rings. Brain MRI revealed globus pallidus hyperintensity on T1 and signs of accentuated brain volume in the caudate nucleus and cerebellum. Therapeutic trial for 8 months with zinc and penicillamine did not improve his neurological

Table 1. Clinical manifestations of patients with AHD

Patient number	1	2	3	4	5
Sex	Male	Male	Male	Female	Female
Etiology of chronic liver diseases	Idiopathic cirrhosis	NASH cirrhosis	NASH Cirrhosis	Idiopathic cirrhosis	HCV
Child-Pugh score at diagnosis	9	6	11	9	N/A
MELD-Na score at diagnosis	9	7	17	16	N/A
Age at diagnosis	55	50	64	58	45
Duration of cirrhosis until onset of neurological symptoms, years	5	0	5	3	N/A
Porto-systemic shunts (yes/no)	Yes	Yes	Yes	Yes	Yes
Medical treatment for AHD	Penicillamine zinc	Rifaximin, ferrous levodopa+carbidopa, EDTA	Rifaximin, lactulose		
EDTA	Levodopa+ carbidopa	Clonazepam, amantadine			
Treatment outcome	Improvement	Unchanged	Unchanged	Improvement	Improvement
Liver transplantation (yes/no)	Candidate	Yes	No	Yes	No
Clinical outcome	Deceased	Alive	Deceased	Alive	Alive
Follow-up period since diagnosis (months)	18	27	2	7	27
Episodes of hepatic encephalopathy, number	0	0	1	3	0

AHD = acquired hepatocerebral degeneration, DM2 = diabetes mellitus type 2, EDTA = ethylenediaminetetraacetic acid, HCV = hepatitis C virus, IHD = ischemic heart disease, NASH = nonalcoholic steatohepatitis, OSA = obstructive sleep apnea

Table 2. Neurological manifestations of patients with acquired hepatocerebral degeneration

Patient number	1	2	3	4	5
Tremor	–	+	+	+	–
Rigidity	+	–	+	+	+
Akinesia/ bradykinesia	–	–	+	+	+
Dysarthria	–	–	–	–	–
Gait impairment	+	+	+	+	+
Myoclonus/ asterixis	–	+	+	–	+
Hypophonia	–	+	–	+	+
Dystonia	–	–	–	–	+
Cognitive impairment	+	–	+	+	–

Table 3. Magnetic resonance imaging findings of patients with acquired hepatocerebral degeneration

Patient number	1	2	3	4	5
Globus pallidus	+	+	+	+	+
Putamen	N/A	+	+	+	+
Caudate nucleus	Loss of brain tissue	+	No information	+	No information
Cerebellum	Loss of brain tissue	–	–	+	–
White matter	+	–	+	+	–

+ or – refers to hyperintensities observed on T1-weighted sequences

status. The patient was on the national waiting list for liver transplantation until he was hospitalized in the intensive care unit for recurrent pleural effusions, which were later complicated by severe sepsis and fungemia. Shortly after his admission he died.

PATIENT 2

Patient 2 first presented with weight loss and sudden neurological symptoms including tremor, instability, myoclonus, and gait instability. During a medical work-up non-alcoholic steatohepatitis (NASH) cirrhosis was diagnosed. A brain MRI showed broad involvement of the basal ganglia. Medical treatment with rifaximin, ferrous, dopicar, and Ethylene-diamine-tetra-acetic acid (EDTA) failed. The patient underwent a successful liver transplantation, but no improvement in his neurological symptoms was achieved.

PATIENT 3

Patient 3 was diagnosed with a NASH cirrhosis at the age of 59 years. During his follow-up, several episodes of hepatic encephalopathy were noted. Five years after his liver disease diagnosis, he presented with extra-pyramidal symptoms and cognitive impairment. He was hospitalized for investigation. Rifaximin and lactulose were initially administered for a suspected recurrent episode of hepatic encephalopathy and were later substituted with a trial of intravenous EDTA courses following ADH diagnosis based on neurological complaints and MRI findings. The patient endured several episodes of sepsis during his hospitalization and eventually died.

PATIENT 4

Patient 4 had cryptogenic cirrhosis and at least three episodes of hepatic encephalopathy and two episodes of severe anemia combined with pre-renal azotemia without evidence of bleeding esophageal varices. Three years after diagnosis of liver disease, symptoms of tremor, recurrent falls, and changes in her voice appeared. Physical examination revealed hypophonia, essential tremor, bradykinesia, and gait instability. Brain MRI showed remarkable involvement of the globus pallidus, subthalamic region, and midbrain. She was under evaluation at the neurological unit of our institution and treatment with levodopa had been initiated. After treatment initiation, a marked relief of neurological symptoms was achieved. She underwent a successful liver transplantation.

PATIENT 5

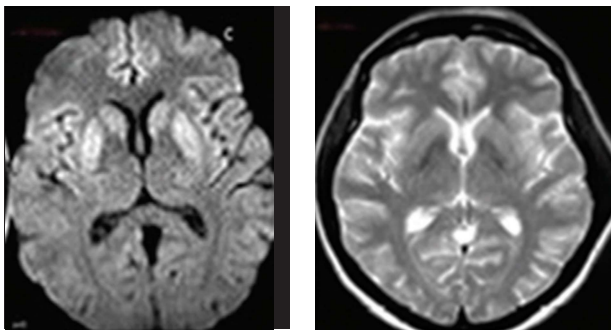
Patient 5 was the only patient without any evidence of cirrhosis. She presented with evaluation of massive hematemesis and syncope. On admission, emergency gastroscopy showed bleeding varices in the gastric fundus, which were ligated. Following an early re-bleeding episode, a CT angiography demonstrated thrombosis of splenic vein, multiple venous collaterals at the splenic hilum, and gastric fundus varices. Splenic artery embolization was performed. Concomitantly, the patient reported slowness, rigidity, gait difficulties, changes in speech, and involuntary spasms of both hands. Neurologic examination revealed hypomimia, hypophonia, bradykinesia, marked symmetric rigidity, and dystonic posture of both hands distally and the right foot. Ophthalmologic examination was negative for Kayser-Fleischer rings. Brain MRI images showed high intensities in the basal ganglia [Figure 1A] on T2-weighted images and low intensities [Figure 1B] on T1-weighted images.

Treatment with amantadine and clonazepam was initiated, resulting in gradual improvement of her extrapyramidal signs and symptoms. Medical treatment was discontinued 6 months after first clinical presentation. A repeated brain MRI evaluation 9 months after the first MRI demonstrated hypointensities on T2-weighted images and hyperintensities on T1-weighted images.

DISCUSSION

In this case series, we described five patients with chronic liver disease diagnosed with acquired hepatocerebral degeneration.

Figure 1. Hyperintensity in the basal ganglia



[A] Observed on T2-weighted brain magnetic resonance imaging

[B] Hypointensity on T1-weighted sequences

All the patients were in their sixth decade of their life and had confirmed portosystemic shunts. AHD prevalence was found to be 0.6% with a male:female ratio of 3:2. Of the four patients with cirrhosis, time from diagnosis of cirrhosis to ADH development ranged 0–5 years. The most prevalent symptom was gait impairment (5/5) followed by rigidity (4/5), hypophonia, tremor, and akinesia/bradykinesia (3/5). None of the patients had dysarthria. Three patients showed neurological improvement after therapeutic trial of anti-Parkinsonian drugs. Two patients eventually underwent orthotopic liver transplantation (OLT).

AHD is a neurologic complication of cirrhosis, regardless of the underlying etiology [9]. In addition to neuropsychiatric and extra-pyramidal manifestations, it can cause cognitive impairment, especially in visuospatial attention [3], which can lead to misdiagnosis of hepatic encephalopathy. AHD pathophysiology is thought to involve manganese deposition in the basal ganglia resulting from loss of its natural hepatobilliary clearance following portosystemic shunt development. Manganese is thought to have neurotoxic effects leading to selective neuronal loss in basal ganglia structures and reactive gliosis [10]. The proposed central role of basal ganglia manganese accumulation in AHD etiology is supported by the identically clinical and neuroimaging reported in manganese-intoxicated individuals [11]. Manganese levels in the serum are not routinely measured in suspected AHD patients, since manganese tends to accumulate in cirrhotic patients as a rule, and its levels do not correlate with the neurological sequelae of AHD [12].

Prevalence of AHD in our CLD population was 0.6%. Previous reports estimated a prevalence of 1–2% among cirrhotic patients [6], whereas a recent cohort found a prevalence of 0.8% among patients with liver cirrhosis [13]. The age of onset has been reported to usually during fifth and sixth decades of life [6], which is consistent with the ages of onset in our case series. Most reported AHD patients have been male [14].

Although Most patients reported to have AHD were cirrhotic, the presence of portal hypertension of any etiology is considered to be the main risk factor. Our case series included one AHD patient with non-cirrhosis portal hypertension and portosystemic shunts. Several case reports have suggested that AHD can develop in patients without underlying liver disease [15-17].

Due to lack of conventional diagnostic criteria, the diagnosis of AHD is primarily based on clinical presentation and relevant brain MRI findings, both of which are of low specificity. For example, in one study, pallidal T1-weighted hyperintensity was observed in brain MRIs in 26 of 90 cirrhotic patients on the liver transplant waiting list. Only 7 were eventually diagnosed with AHD [18]. Furthermore, in specific subtypes of AHD, the opposite neuroimaging findings can be found; that is, pallidal T2-weighted hyperintensity and T1-weighted hypointensity [19]. In our case series, all brain MRIs showed T1 hyperintensity of the globus pallidum, although in one patient a brain MRI performed in the acute phase of parkinsonian symptoms revealed T1-weighted hypointensity of basal ganglia.

In contrast to hepatic encephalopathy, no medical therapy has been proven to stunt the progression of AHD. Treatment with ammonia-reducing agents is not efficient in reducing ADH-related movement disorders [20]. The only known treatment for this devastating situation is liver transplantation [14]. However, there are some patients who failed to respond to transplantation or who experienced re-emergent neurological deficits after the hepatic transplant [20-22]. In our report, two patients underwent OLT during the follow-up period, but it seemed to lack any impact on neurological symptoms. One patient did not improve and the second patient showed marked amelioration under anti-Parkinsonian treatment even before transplantation.

Other therapeutic options included branched-chain amino acids (BCAAs) [23], manganese-chelating agents like trientine [24], and EDTA [25]. In our report, the use of anti-Parkinsonian drugs (dopicar/amantadine) proved helpful in two of the three patients treated with these agents. This finding is consistent with previous report showing that use of anti-Parkinsonian drugs can bring to a modest to dramatic improvement in AHD patients with Parkinsonian symptoms [25]. As previously described [6,25], the use of EDTA did not relieve neurological complaints.

CONCLUSIONS

We report here on five cases of AHD, all of which are related to portosystemic shunts. The combination of Parkinsonism, cerebellar signs, and MRI pallidal lesions, should alert physicians to the diagnosis. The role of liver transplantation in AHD is still controversial.

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Capsule

Tumor-infiltrating lymphocyte therapy or ipilimumab in advanced melanoma

Immune checkpoint inhibitors and targeted therapies have dramatically improved outcomes in patients with advanced melanoma, but approximately half these patients will not have a durable benefit. Phase 1–2 trials of adoptive cell therapy with tumor-infiltrating lymphocytes (TILs) have shown promising responses, but data from phase 3 trials are lacking to determine the role of TILs in treating advanced melanoma. In this phase 3, multicenter, open-label trial, **Rohaan** et al. randomly assigned patients with unresectable stage IIIC or IV melanoma in a 1:1 ratio to receive TIL or anti–cytotoxic T-lymphocyte antigen 4 therapy (ipilimumab at 3 mg per kg of body weight). Infusion of at least 5×10^9 TILs was preceded by nonmyeloablative, lymphodepleting chemotherapy (cyclophosphamide plus fludarabine) and followed by high-dose interleukin-2. The primary end point was progression-free survival. A total of 168 patients (86% with disease refractory to anti–programmed death 1 treatment) were assigned to receive TILs (84 patients) or ipilimumab (84 patients). In the intention-to-treat population, median progression-free survival was 7.2 months (95% confidence interval [95%CI] 4.2–13.1) in the TIL group and 3.1 months (95%CI 3.0–4.3) in the ipilimumab group (hazard ratio for progression or death 0.50, 95%CI 0.35–0.72; $P < 0.001$); 49% (95%CI 38–60) and 21% (95%CI 13–32) of the patients, respectively, had an objective response. Median overall survival was 25.8 months (95%CI, 18.2 to not reached) in the TIL group and 18.9 months (95%CI 13.8–32.6) in the ipilimumab group. Treatment-related adverse events of grade 3 or higher occurred in all patients who received TILs and in 57% of those who received ipilimumab; in the TIL group, these events were mainly chemotherapy-related myelosuppression.

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