Single Case – General Neurology

Hepatic Encephalopathy Mimicking Acute Dominant Middle Cerebral Artery Ischemic Stroke: A Case Report

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Keywords

Stroke · Hepatic encephalopathy · Hyperammonemia · Transaminitis · Stroke mimic · Digital subtraction angiography

Abstract

Hepatic encephalopathy and hyperammonemia are common in the setting of liver disease and have been associated with both generalized and focal neurological deficits. We report a case of hepatic encephalopathy with transaminitis in the setting of hyperammonemia clinically mimicking acute dominant middle cerebral artery (MCA) syndrome. A 59-year-old right-handed woman had new-onset expressive aphasia, left gaze deviation, and right hemiparesis consistent with MCA stroke. Her symptoms began 12 h after transarterial chemoembolization, a procedure to embolize blood supply and provide cytotoxic agents to a hepatocellular carcinoma tumor. Thrombocytopenia and age-indeterminate hypodensities on brain CT precluded intravenous thrombolytic administration. MRI revealed predominantly dominant hemisphere

subcortical restricted diffusion with no cortical involvement. Due to a mismatch between the MRI findings and the neurological symptoms, she underwent digital subtraction cerebral angiography to assess candidacy for intra-arterial thrombectomy, which revealed completely patent MCAs with intact filling of the distal branches. Liver enzymes and ammonia were elevated. The patient was treated with lactulose and intravenous fluids. After normalization of liver enzymes, the patient's neurological deficits resolved. Reversal of this patient's focal symptoms with medical management could potentially be explained by the recovery of blood flow-metabolic demand mismatch caused by worsening liver dysfunction and hyperammonemia. As acute stroke therapies and interventions increase in utility for large artery acute ischemic stroke, it is vital to recognize hepatic encephalopathy and liver failure as part of the differential diagnosis for patients presenting with MCA syndrome.

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Introduction

Hepatic encephalopathy and liver failure have been associated with significant neurological disorders including asterixis, delirium, and coma [1, 2]. However, focal neurological deficits in a specific vascular distribution are rarely attributed to hepatic dysfunction [3–6]. Transarterial chemoembolization (TACE) is a nonsurgical treatment for hepatocellular carcinoma (HCC) involving intra-arterial chemotherapy infusion and arterial embolization with the purpose of exhibiting cytotoxic and ischemic effects on a hepatic tumor [7]. Neurological complications can include encephalopathy and cerebral lipiodol embolism (CLE) [8–12]. We describe a case of hepatic encephalopathy associated with worsening liver function in the setting of hyperammonemia after TACE presenting with acute dominant middle cerebral artery (MCA) syndrome. MRI revealed asymmetric diffusion-weighted imaging (DWI) restricted diffusion subcortically, and the patient had an unremarkable diagnostic evaluation for ischemic stroke.

Case Description

A 59-year-old right-handed Caucasian woman without a history of clinical stroke and with a medical history of non-insulin-dependent diabetes, hypertension, hepatitis C virus resistant to prior treatment with interferon and ribavirin, and cirrhosis (MELD-Na score 13), complicated by hepatic hydrothorax, ascites, nonbleeding esophageal varices, and HCC, underwent a first-time and elective TACE. Prior to TACE, her HCC consisted of a single 5.4-cm left liver mass. Her TACE entailed arterial embolization with 100- to 300- μ m microspheres mixed with doxorubicin, and an uncomplicated procedure was documented after completion. Due to a transient elevation in her blood pressure (165/72 mm Hg or 22.0/9.6 kPa) she was admitted for observation, after which she became normotensive gradually with administration of oral furosemide 40 mg and oral metoprolol 25 mg. There were no recorded episodes of hypotension. She remained otherwise in her normal state of health with no focal weakness or language impairment for 12 h after the end of her procedure. Then, she developed new-

onset neurological symptoms. Her National Institutes of Health Stroke Scale score was 17. Points were given for drowsiness, expressive greater than receptive aphasia, left gaze deviation, right homonymous hemianopsia, and right hemiplegia consistent with left MCA syndrome. The patient's temperature was 97.1°F (36.2°C), heart rate 66 beats per minute sinus rhythm, blood pressure 117/58 mm Hg (15.6/7.7 kPa), and respiratory rate 14 breaths per minute.

Initial venous labs revealed acute transaminitis, acute kidney injury, hyperammonemia, and thrombocytopenia (see Table 1, including reference ranges). Aspartate transaminase (AST) had increased from 61 U/L before TACE to 250 U/L afterward, and alanine transaminase (ALT) had increased from 51 to 61 U/L. Her creatinine had increased from 1.4 to 2.3 mg/dL and BUN from 22 to 36 mg/dL. Her platelet count had increased from 61 to $84 \times 10^3/\text{cm}^3$. International normalized ratio was 1.29 initially (but subsequently increased to 1.48 the next day), blood glucose 137 mg/dL, and ammonia level 81 $\mu\text{Mol/L}$ at the time of neurological evaluation.

Brain CT revealed multiple subcortical patchy hypodensities concerning for age-indeterminate ischemic stroke (Fig. 1a). She was not eligible for intravenous tissue plasminogen activator due to thrombocytopenia and the age-indeterminate hypodensities on brain CT [13]. Hence, an MRI brain stroke protocol was obtained which demonstrated left greater than right subcortical restricted diffusion, particularly in the left putamen and caudate. Fluid-attenuated inversion recovery (FLAIR) sequence revealed chronic microvascular findings bilaterally, with age-indeterminate changes in some of the area of restricted diffusion, although to a lesser degree. The patient continued to exhibit disabling unilateral cortical symptoms despite the absence of cortical ischemic injury on the DWI and FLAIR sequences (Fig. 1b). Due to this marked mismatch between the patient's neurological examination and the DWI changes on MRI, she underwent digital subtraction angiography to evaluate for large vessel occlusion and consider intra-arterial therapy, which revealed completely patent vessels with an intact filling of the distal branches (Fig. 1c).

Afterward, medical resuscitation with intravenous fluids and lactulose were continued. EEG demonstrated mild diffuse slowing without epileptiform discharges. Additional diagnostic evaluation included unremarkable lipid panel, hemoglobin A1c, and telemetry. Two-dimensional echocardiography was also unremarkable and without interatrial shunt. The patient developed upper and lower gastrointestinal bleeding and required banding of multiple esophageal varices. Twenty-four hours after symptom onset her ALT had decreased to 44 U/L and her AST to 150 U/L. Over 48 h after symptom onset, the patient regained movement of her right hemi-body, and her aphasia and gaze deviation resolved. Seventy-two hours after symptom onset her AST had further decreased to 85 U/L. Ammonia remained elevated at 72 h (82 $\mu\text{Mol/L}$). She returned to her neurological baseline by the 7th day of hospitalization.

Discussion

Neurological deficits have been reported with hepatic encephalopathy and liver failure, including focal neurological findings [1–6]. It is, however, rare for focal deficits limited to a single vascular territory to be attributed to liver decompensation. In one study with prospectively collected data, 8 out of 46 hospitalizations (17.4%) for hepatic encephalopathy were for

patients who exhibited focal neurological signs. Six of these 32 patients had hemiplegia or hemiparesis. Other focal neurological symptoms described were hemianosia, limb monoplegia, and seizures. None of these patients had MRI changes and all focal symptoms resolved on subsequent examination [3]. In another study, 5 out of 170 inpatients (3%) admitted for hepatic decompensation presented with focal neurological deficits. These 5 patients comprised 15% of the 33 patients who were diagnosed with hepatic encephalopathy in this cohort. One patient demonstrated cortical blindness and agnosia and another hemiplegia, the remainder had asymmetric tone and reflexes, but not hemiparesis. This cohort of patients predated CT and MRI scans [6]. While hepatic decompensation and subsequent encephalopathy only occasionally present with symptoms consistent with stroke, it is important to include them in the differential diagnosis as acute stroke treatments such as thrombolytic and intra-arterial therapies expand.

The patient had an elevated ammonia level. Unfortunately, a baseline ammonia level was not available to us. While monitoring of ammonia levels is not recommended to diagnose or monitor hepatic encephalopathy [14], there may be some role of hyperammonemia in the patient's presentation. When elevated, ammonia is converted to glutamine by glutamine synthetase, an enzyme found in the astrocytes in the gray matter. Glutamine accumulation leads to astrocytic swelling and cerebral edema in the acutely affected brain [15–18]. Ott et al. [19] proposed that elevated ammonia levels inhibit the tricarboxylic acid cycle enzyme alpha ketoglutarate dehydrogenase, disrupting astrocytic mitochondrial energy metabolism and leading to significant cerebral protein degradation. Furthermore, restricted diffusion in the insular cortex and cingulate gyrus has been noted in patients with hyperammonemia secondary to genetically inherited errors of urea cycle metabolism [20, 21]. Unlike our patient's presentation, the bilateral MRI findings in these inherited cases of hyperammonemia tended to be symmetric, and the serum ammonia levels tended to be much higher.

Several factors may have contributed to our patient's neurological symptoms. For instance, reduced MCA blood velocity has been characterized in advanced cirrhotic patients with Child-Pugh scores B or C [22]. Moreover, in a cohort study comparing cirrhotic patients with hepatic encephalopathy to both healthy subjects and cirrhotic patients without hepatic encephalopathy, patients with hepatic encephalopathy had impaired oxygen consumption and blood perfusion when comparing PET findings. Interestingly, the authors found a correlation between these findings and ammonia levels [23]. Another study utilized transcranial Doppler ultrasound to demonstrate reduced cerebral autoregulation in patients with liver failure with hepatic encephalopathy compared to those without hepatic encephalopathy [24]. MRI findings in hepatic encephalopathy can include T2 hyperintensity and even restricted diffusion in the globus pallidus; however, these are typically bilateral [25].

We make the assumption that the mismatch between the clinical examination and imaging findings could be explained by a metabolic and perfusion demand failure due to hepatic encephalopathy and decompensation in the setting of hyperammonemia, which led to transient neurological impairment of the dominant hemisphere in the absence of vascular compromise.

Additional differential diagnoses should be considered in a patient after TACE with focal neurological deficits. CLE is a rare but well-characterized complication of TACE, in which embolization of chemical agents used for TACE, but not the actual embolization microspheres, are suspected to cause brain injury [8–12]. One study estimated a CLE frequency of 1:1,000

TACE procures [12]. CLE can present with nonspecific symptoms such as headache and confusion, but also with focal neurological symptoms [8–12]. However, in contrast to this patient's MRI findings, CLE appears to more commonly present with disseminated restricted diffusion, at or near the cortex, although also involving areas supplied by the posterior circulation [9, 11]. Another important differential is symptomatic cerebral hypoperfusion, as the patient was treated for hypertension after TACE. However, on chart review she had no recorded hypotension and she was normotensive while symptomatic. Poststroke recrudescence in the setting of metabolic derangements could also explain the patient's symptoms, especially given the chronic microvascular and ischemic changes on MRI; however, she had never had aphasia or left-sided weakness in the past [26].

We are unfortunately limited in that we do not have diagnostic studies showing oxygen metabolism or perfusion at the time of onset nor after normalization of her neurological symptoms. We are also limited as a repeat MRI after symptom resolution was not obtained for comparison purposes. Given a diagnostic evaluation negative for thrombotic and embolic source of stroke as well as normalization of neurological examination in the setting of improved liver function and resolving encephalopathy, we inferred that the patient's focal clinical presentation was related to metabolic demand rather than a thrombotic event, which is essential with the rising evidence of increased risk for ischemic stroke in cirrhotic, hepatitis C, and fatty liver patients [27–29]. How hyperammonemia and acute liver failure lead to lateralized neurological symptoms is unclear and warrants further investigation.

In summary, we discuss a case of hepatic encephalopathy in the setting of hyperammonemia and liver decompensation presenting as reversible acute dominant MCA stroke syndrome. We infer that this stroke mimic can be explained by impaired metabolism and autoregulatory and perfusion deficits. This case demonstrates the importance of distinguishing noncerebrovascular stroke mimics from actual ischemic stroke and highlights the need to carefully consider the predicted underlying pathophysiology when evaluating patients exhibiting stroke-like symptoms. In this patient population, we suggest testing for ammonia level, liver enzymes, and coagulopathy as part of the acute stroke evaluation, without delaying potential acute stroke therapies and interventions.

Statement of Ethics

The patient gave her informed consent and the case report was approved by the institute's committee on human research.

Disclosure Statement

The authors have no competing interests or disclosures.

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Fig. 1. **a** Brain CT revealed multiple subcortical patchy hypodensities (red arrows). **b** MRI demonstrated predominantly left-sided diffusion restriction in the basal ganglia (green arrows) without correlating fluid-attenuated inversion recovery abnormalities. **c** Patent middle cerebral artery vasculature based on cerebral angiography (blue arrow).

Table 1. Serum venous laboratory values

	Before TACE	Symptom onset (12 h after TACE)	24 h after symptom onset	48 h after symptom onset	72 h after symptom onset
ALT (ref. 0–65 U/L)	51	61	44	NA	45
AST (ref. 0–37 U/L)	61	250	150	NA	85
Direct bilirubin (ref. 0.0–0.3 mg/dL)	0.6	0.3	0.9	NA	0.9
Ammonia (ref. ≤45.0 μMol/L)	NA	81.0	NA	NA	82.0
INR (ref. 0.85–1.17)	1.29	1.29	1.48	NA	1.48
PT (ref. 12.0–14.7 s)	16.2	16.2	18.2	NA	18.2
Platelets (ref. 133–450 × 10 ³ /cm ³)	61	84	53	41	44
Lactic acid (ref. 0.5–2.2 mMol/L)	NA	1.4	NA	NA	1.3
Creatinine (ref. 0.5–1.4 mg/dL)	1.4	2.3	2.3	1.8	1.5
Blood sugar (ref. 70–99 mg/dL)	144	137	92	137	170

ALT, alanine transaminase; AST, aspartate transaminase; INR, international normalized ratio; NA, not available; PT, prothrombin time; ref., reference range; TACE, transarterial chemoembolization.