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Unusual Case of Hyperammonemic Encephalopathy in Elderly Patient Without Liver Disease

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Abstract

Here we describe a case of an 87-year-old man who was admitted to the hospital with clinical evidence of encephalopathy and was found to have hyperammonemia. Abdominal ultrasound (US) with color doppler showed a rare vascular anomaly consisting in a shunting of portal blood flow directly into the systemic circulation. Abdominal computed tomography scan with contrast injection was performed and revealed a spontaneous intrahepatic porto-systemic shunt (SIHPSS). Portosystemic shunts are rare and often detected in adulthood but should be considered an important cause of unexplained encephalopathy in the absence of cirrhotic liver disease or hepatic trauma. This case illustrates that, albeit rare, SIHPSS may express themselves for the first time in the elderly, a patient population that is frequently affected by many more common causes of altered mental status. Our patient was treated with medical conservative therapy which led to an impressive amelioration of his symptoms.

Keywords: Intrahepatic Porto-Systemic Shunting (IHPSS); Hepatic Encephalopathy (HE); Hyperammonemia; Non-Cirrhotic Liver; Elderly

Introduction

In clinical practice, metabolic encephalopathy secondary to hyperammonemia in the absence of hepatic cirrhosis is an uncommon condition and represents an event that rapidly compromises a patient's cerebral and systemic integrity and can lead to cerebral oedema and herniation. Readily identifying the causes is always a challenge for clinicians, as there is a wide etiopathogetic range. In this case report, through clinical investigation and laboratory testing, we describe an unusual episode of encephalopathy secondary to hyperammonemia caused by a spontaneous intrahepatic porto-systemic shunting (SIHPSS) in an elderly male patient; it was detected through an abdominal ultrasonography color doppler and confirmed with an angio-TC scan before being treated with conservative medical therapy.

Case Presentation

An 87-years old man presented to the emergency department with progressive confusion, disorientation, and fluctuating levels of consciousness. Medical history included a previous episode of recovery for altered mental status, chronic atrial fibrillation, moderate congestive heart failure reduced EF in medical therapy, and IPB. The patient had eaten large meals in the previous days without consuming alcohol, and difficulty with evacuations was reported by family members. A physical exam revealed an arrhythmic pulse rate, RR 18 bpm, and BP 140/90 mmHg. The patient was afebrile; stick-finger glucose was 180 mg/mol and there

were no signs of meningeal irritation; physical and neurological findings were unremarkable. The flapping tremor was detected but no other signs of cirrhosis such as gynecomastia, jaundice, and spider angioma were found. Blood tests including electrolytes, liver function, renal function, and indices of inflammation were almost normal; the CBC showed mild microcytic anemia, and the martial balance was normal. B vitamins and viral hepatitis serology panel were normal. NT-pro BNP was 266 pg/mL. Cranial TC showed a mild degree of subcortical brain atrophy and ruled out acute events. However, EEG demonstrated non epileptiform triphasic wave patterns compatible with metabolic encephalopathy. Consequentially, to evaluate the metabolic cause of the neurological presentation, serum ammonia was measured; an amount of 378 µg/dL made the situation compatible with acute hyperammonemic encephalopathy. On blood tests, the patient had anemia, and it is well known that hyperammonemia can be triggered by profuse bleeding. For this reason, EGDS was performed, which showed no upper digestive bleeding and no esophageal varices. Abdominal US showed the liver features as follows: increased dimension due to hypertrophy of the right lobe, quadrate lobe, and caudate lobe, with smooth hepatic margins and no diffuse echo structural alterations. There were no signs of ascites and splenomegaly. The portal vein showed a hepatopetal flow and slightly increased caliber. The suprahepatic veins and inferior vena cava were dilated, which is compatible with a stasis of the liver. Color doppler imaging showed a spontaneous intrahepatic portosystemic shunting between a right portal branch of VIII lobe and the middle suvrahepatic vein. Liver elastography showed mild fibrosis (F2 according to Metavir score). A subsequent abdominal contrast-enhanced CT scan confirmed no signs of cirrhosis and showed a large intrahepatic porto-systemic shunt draining portal blood directly in systemic circulation. Given the patient's age and comorbidities, no indication for surgery was given, so medical therapy including lactulose 20 g three times daily and rifaximine 550 mg twice daily was initiated; in addition, a low protein diet was prescribed. With this treatment regimen, at follow-up, the patient had no further episodes of altered consciousness and the QoL improved progressively.

Discussion

Hepatic encephalopathy (HE) is a complication of liver disease, consisting of brain dysfunction with altered mental status and clinical symptoms of neurological and neuropsychiatric abnormalities, usually secondary to shunting of portal blood flow directly into the systemic circulation bypassing the liver [1]. Up to 30 to 45% of patients with decompensated cirrhosis experience symptomatic hepatic encephalopathy and as high as up to 60 to 80% of patients with compensated cirrhosis have evidence of minimal hepatic encephalopathy without clinical symptoms [2]. Mostly, encephalopathy is recognized by hyperammonemia in patients with chronic hepatitis, but in other rare cases such as ours, it can be secondary to hyperammonemia in the absence of hepatic dysfunction and can be categorized in type B of hepatic encephalopathy according to the International Society for Hepatic Encephalopathy and Nitrogen Metabolism (ISHEN) practice guidelines [3,4]. Non-cirrhotic portal-systemic encephalopathy is therefore a settling entity that may be due to the presence of a vascular shunt (one of the causes of decreased elimination of the ammonia), that is a vascular malformation in which abnormal communications are created between the portal veins and the hepatic veins or the inferior vena cava system; consequently, venous blood from the bowel and spleen that is rich in metabolism breakdown products, bypasses the liver and returns into systemic circulation triggering encephalopathy, which may initially manifest with symptoms such as altered mental status, disorientation, dysphasia, and fluctuations in consciousness. The overall prevalence of Portosystemic shunt is assessed to be 1:30,000. The origin of these vascular anomalies is the matter of differing opinions. When a portal vein-hepatic vein communication is seen in a patient without liver disease or a history of trauma, it is presumed to be spontaneous or congenital in origin. Some authors have speculated that these shunts represent persistent embryonic venous anastomoses, caused by the failure of regression of connections among tributaries of the vitelline vein (the precursor of the portal and hepatic veins and portions of the inferior vena cava). Others suggest that rupture of a portal vein aneurysm into the hepatic vein is the cause of the shunting [5]. They may be single or multiple and of different sizes and can be identified, according to the Watanabe classification, into extra-hepatic or intra-hepatic shunts. Summarily, the extrahepatic shunts are further divided into type 1, which is associated with the absence of intrahepatic portal flow, and type 2 in which the intrahepatic portal flow is preserved. While the natural history of extrahepatic portosystemic shunts involves complications such as hepatic encephalopathy, pulmonary hypertension, hepatopulmonary syndrome and tumors, as well as being associated with cardiac defects or musculoskeletal abnormalities, the characteristics and natural history of intrahepatic portosystemic shunts are less defined. Many patients remain asymptomatic for most of their lives, while others do not develop hepatic encephalopathy until an advanced age, probably because of the irregular susceptibility of the brain to ammonia by aging. The most common kind of intrahepatic shunt is type 1, where a large solitary vessel connects the right portal vein with the inferior vena cava. These are naturally smaller in size and blood flow; hence they are expected to have fewer complications and better chances of spontaneous closure. However, complications might exist, such as cholestasis and hypoglycemia associated with hyperinsulinemia. Furthermore, while spontaneous closure occurs more often in extrahepatic shunts, it does not always occur in intrahepatic ones. Nevertheless, the natural course of the intrahepatic malformations varies from

the spontaneous, self-resolution of small shunts, to persisting intrahepatic or patent ductus venosus [6]. The gold standard for the diagnosis of these vascular abnormalities is a liver biopsy, but it is not always possible to perform it. The patient's age, comorbidities, poor cooperation (often due to altered level of consciousness during hyperammonaemia), increase the peri- and intra-procedural risk, making this route unfeasible [7]. Consequently, these malformations remain poorly understood. However, the number of reported cases of SIHPSS has increased in recent years, probably due to the improvement of imaging techniques. As neither clinical nor biologic presentations are specific, imaging is key for the diagnosis of SIHPSS. Ultrasonography with a Doppler study (Figure 1) is usually the firstline exam that shows abnormal communication between the portal and the systemic vein, as well as the consequences on liver morphology, the presence of liver nodules, and the association with other malformations.

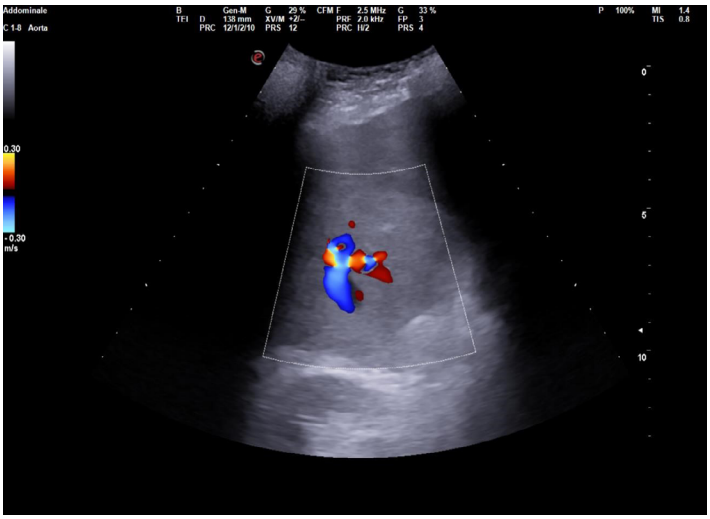

Figure 1: Abdominal Ultrasound (US) image of liver acquired using Eco-Color-Doppler showing an intrahepatic porto-systemic shunt presenting with anomalous connection between a branch of the portal vein and a branch of the hepatic vein.

It is also very useful for the follow-up of SIHPSS before and after treatment. In addition, the quantification of hepatic stiffness by means of fibro scan elastography is a valuable tool for determining the presence or absence of underlying liver disease. A decisive role in the characterization of these malformations is also played by CT (Figure 2) and MRI scans, which are used to confirm the diagnosis and to provide a precise vascular map; these can be done with or without contrast injection at the arterial and portal phase [8]. In support of how crucial it is for the correct characterization and to establish the severity of the malformation, today, thanks to a procedure called Per-rectal scintigraphy, it is possible to estimate the shunt ratio, which is the amount of portal blood that has shunted away from the liver directly into the systemic circulation [7]. Additionally, the improvement of interventional radiology techniques such as intravascular embolization using plugs or coils, have been described in several cases of SIHPSS surgery management [9]. In this case and in support of imaging, the electroencephalography (EEG) showed triphasic non-epileptiform wave patterns, that we defined as generalized, bilaterally synchronous, bifrontal periodic waves, such as dyssynchronization of fast activity, with increased dysrhythmicity, and slower delta activity followed by mixtures of slow-with-fast frequencies. These are an expression of metabolic brain distress and are seen more often in patients with encephalopathy and subcortical brain atrophy, as with our patient, than in patients with encephalopathy and no subcortical atrophy, as has already reported by several works in the literature [10,11]. The traditional treatment of hepatic encephalopathy first aims to identify and resolve the impacting agents/etiologies such as infection, gastro- intestinal bleeding, dehydration, and electrolyte disturbance. In this case report, clinical and laboratory assessment allowed us to rule out these precipitating factors, and we consequentially adopted measures that target the reduction of the nitrogenous load and other toxins, both in the gut and the brain. Therefore, the pillars of this conservative medical therapy were respectively: cathartics, such as lactulose and lactilol-non-absorbable disaccharides, which are often administered as treatments to inhibit ammoniagenic coliform bacteria, which leads to increased levels of nonammoniagenic lactobacilli. Specifically, lactulose is converted into lactic and acetic acids inside the gut, which decreases pH and thus converts ammonia to ammonium, which is less permeable to the membrane. This process ultimately leads to the retention of ammonia in the colon, as ammonium and prevents its absorption. Rifaximin is a minimally absorbed oral antibiotic administered to suppress the intestinal bacterial flora and to reduce the production of ammonia and other toxins, because it has a low risk of inducing bacterial resistance and is superior to treatment with lactulose alone. Probiotics can decrease the total amount of ammonia found in the portal blood by decreasing intestinal bacterial urease activity, decreasing pH, and thus reducing the absorption of ammonia. In addition, probiotics decrease intestinal permeability and therefore improve the nutritional status of the gut epithelium, which is known to reduce the absorption of ammonia. "Lastly, [the patient's protein intake was limited]". Dietary protein restriction is the mainstay conservative medical management of acute hepatic encephalopathy, even though restrictive diets can often result in protein malnutrition. These treatments lead to an impressive amelioration of our patient's symptoms.

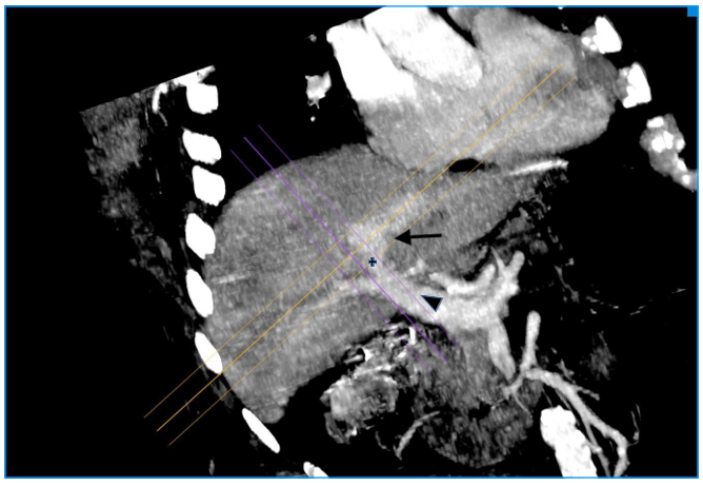

Figure 2: CT scan, MIP reconstruction from the portal venous phase scan showing the intrahepatic porto-systemic shunt (arrow), portal vein (arrowhead) and hepatic vein (plus).

Conclusions

Altered mental status in elderly patients is a common daily challenge for caregivers. When a clinical presentation with hepatic encephalopathy occurs, in the absence of any radiological and biochemical sign of chronic liver disease, regardless the age of the patient, a portosystemic shunt must be suspected, despite this being it is extremely rare in the elderly because it can remain undetected late into adulthood [6]. In this case report, clinical laboratory assessment allowed us to rule out factors precipitating hyperammonemia, such as infection, trauma, drug abuse and gastrointestinal bleeding, enabling us to consider the shunt as spontaneous. It is well known that the size of these shunts increases with age and that the brain tissue of the elderly is more susceptible to toxic metabolites; this age-associated increase in shunt size and the vulnerability of the elderly brain may help explain why our 87-year-old patient remained asymptomatic for most of his life. However, in view of the comorbidities and the senescence of the body's metabolic homeostasis in relation to our patient's age, we can say that his protein intake and the constipation reported in the days preceding hospitalization played a decisive role in increasing serum ammonia levels. Furthermore, we cannot exclude the possibility of a small shunt that has gradually enlarged due to hepatic stasis caused by a flare-up of chronic heart failure. Ultrasonography with a Doppler study as the first line of exams played a decisive role in confirming our suspicions of an underlying vascular malformation in the absence of frank cirrhotic liver disease; a subsequent abdominal CT scan with contrast injection characterized the anomaly anatomically as a spontaneous intrahepatic portosystemic shunting (SIHPSS) between a right portal branch of VIII lobe and the middle suvrahepatic vein. In order to regularly move the patient's bowel and treat the portosystemic encephalopathy, medical therapy alone has proven to be an effective strategy for improving the patient's clinical and general condition; he had a good response, episodes of neurological impairment decreased, and no other related complications occurred.

Disclosure

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Conflicts of Interest: None declared.

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