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LETTER TO THE EDITOR

Hyperammonemic encephalopathy associated with hereditary hemorrhagic telangiectasia

KEYWORDS
Liver transplantation;
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Hyperammonemia;
Encephalopathy

Hereditary hemorrhagic telangiectasia (HHT) is an autosomal dominant disorder characterized by recurrent epistaxis, cutaneous telangiectasia, and visceral arteriovenous malformations. Hepatic involvement is much more frequent in HHT type 2, and its complications, such as biliary ischemia, portal hypertension and high-output cardiac failure can be severe [1]. Hyperammoniemic encephalopathy is a very rare complication of HHT with liver vascular malformations [1,2] and we report here 2 new cases.

Cases description

The first patient was a 53-year-old caucasian woman, presenting a HHT with family history (her mother, one of her daughter). She was referred to our hospital in January 2008 because CT scan revealed multiple hepatic arteriovenous malformations. Complementary investigations disclosed significant cardiac impact of liver involvement, with high cardiac index (4.7 L/min/m^2). Initial treatment consisted in bevacizumab, from March to June 2009, which induced a reduction of cardiac output to 3.3 l/min/m^2. In April 2012, the patient was referred again because of appearance of dyspnea, related to majoration of cardiac index to 4.9 L/min/m^2. A second course of bevacizumab was performed from July to October 2012. In addition, the patient presented neurological symptoms including fluctuating confusion and somnolence. Hemoglobin, aspartate transaminase, alanine transaminase, gamma-glutamyl transpeptidase, alkaline phosphatase, and ammonemia were 12.2 g/dL (range 12—16), 22 IU/L (range, 8—30), 28 IU/L (range, 4—45), 99 IU/L (range, 9—32), 319 IU/L (range, 80—260), and 98 μmol/L (range, —50), respectively; albumin, total bilirubin and prothrombin rate were normal. Cerebral MRI was normal and the diagnosis of hyperammonemic encephalopathy was made. Lactulose had no significant impact on neurological symptoms or hyperammonemia. In March 2013, the cardiac index remained high and the patient was listed for a liver transplantation. An abdominal CT scan was performed showing multiple hepatic vascular malformations with diffuse shunts between hepatic artery, portal vein and supra hepatic veins branches. The diameter of the hepatic artery was increased and the aspect was typical of liver HHT. No extra hepatic shunts were identified. There was no arterial pulmonary hypertension. A liver transplantation was performed in July 2015, at the age of 60, with favorable outcome; the patient is going well 30 months after transplantation; hyperammonemia never reappeared.

The second patient was a 22-year old Caucasian woman with no familial history of HHT and no history of epistaxis who was referred in April 2016 for abdominal pain. An abdominal CT scan was performed showing multiple hepatic vascular malformations with diffuse shunts between hepatic artery, portal vein and supra hepatic veins branches. The diameter of the hepatic artery was increased and the aspect was typical of liver HHT. No extra hepatic shunts were identified. Liver function tests were normal. The patient also complained of deep asthenia, memory disorders, poor concentration and mild motor deficit involving the left arm. Asterixis was observed in the left hand but not the right hand. Brain imaging (CT scan and angio-MRI) did not disclose any focal lesion or cerebral vascular malformation. Bilateral Pallidal hyperintensity in T1 weighted MRI consistent with accumulation of manganese was observed. Ammonemia was slightly increased (85 μmol/L). A diagnosis of atypical hyperammonemic encephalopathy related to large intra-hepatic portosystemic shunts was made. Rifaximin (550 mg twice a day) was started and neurological manifestations resolved within a few weeks.

Abbreviations: HHT, hereditary hemorrhagic telangiectasia.

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Table 1 Summary of reported cases of hyperammonemic encephalopathy in the context of HHT.

Sex/age (Ref., year of publication)	Country	Intra-hepatic portosystemic shunts	Extra-hepatic portosystemic shunts	Treatment	Outcome
F/47 [4], (1968)	Israel	unk	unk	None	Chronic encephalopathy (Died from gastrointestinal hemorrhage)
M/57 [5], (1987)	Japan	yes	No	Branched-chain-amino-acids Lactulose	Favorable
unk [2], (2000)	Japan	unk	unk	unk	unk
unk [2], (2000)	Japan	unk	unk	unk	unk
unk [2] (2000)	Japan	unk	unk	unk	unk
unk [2], (2000)	Japan	unk	unk	unk	unk
F/55 [6], (2011)	Japan	unk	unk	unk	unk
F/66 [7], (2014)	China	yes	no	Branched-chain-amino-acids Arterial Embolization	Favorable
F/53, our case 1(2018)	France	yes	no	Lactulose	Chronic encephalopathy [Favorable after liver transplantation (indicated because of associated cardiac complications of hepatic involvement)]
F/22, our case 2(2018)	France	yes	no	Rifaximin	Favorable

Discussion

Arteriovenous malformations in the context of HHT occur in a variety of organs including the skin, brain, nose, lungs, gastrointestinal tract and liver. In most patients, liver involvement remains clinically asymptomatic, but diffuse hepatic telangiectasias and intra-hepatic shunts between portal vein, hepatic artery and hepatic vein are able to induce high-output cardiac failure, portal hypertension and/or biliary ischemia [1].

Less frequent clinical presentations include portosystemic hyperammonemic encephalopathy and abdominal angina [1]. Encephalopathy is probably the consequence of direct derivation of blood flow from the portal system to the systemic venous circulation through the portal vein *h*epatic vein shunts, and can be considered as a non-cirrhotic cause of portosystemic encephalopathy, even if HHT can induce a nodular transformation of the liver [3]. Before our cases, hyperammonemic encephalopathy has been reported only in less than 10 patients in the literature (Table 1) [2,3,4,5,6,7]. Differential diagnosis in case of neurological symptoms in the setting of HHT includes of course cerebral arteriovenous malformations which need to be ruled out by imaging, as reported in our cases, especially in case of one side asterixis. Finally, data on specific treatment of hyperammonemic encephalopathy in the particular context of HHT are lacking but it can be hypothesized that usual therapies, such as lactulose and rifaximin should be useful.

In conclusion, the two present cases emphasizes that hyperammoniemic encephalopathy is a possible complication of HHT with liver vascular malformations and the diagnosis must be suspected in case of compatible neurological symptoms.

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Disclosure of interest

The authors declare that they have no competing interest.

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