Osler-Weber-Rendu Disease Presenting as Recurrent Portosystemic Encephalopathy in a 75-year-old Female Patient

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Osler-Weber-Rendu disease is a rare autosomal dominant disorder of fibrovascular tissues, characterized by a classic triad of mucocutaneous telangiectasias, recurrent hemorrhages, and a familial occurrence. Portosystemic encephalopathy in a patient with Osler-Weber-Rendu disease is rare, but we experienced a case presenting with recurrent portosystemic encephalopathy in Osler-Weber-Rendu disease. We report on a case of a 75-year-old female presenting with an altered mentality. Initial studies including brain imaging study did not reveal any specific cause for her mental status. She was diagnosed with the rare disease after a series of tests and received conservative treatment. Her neurological status recovered fully without complication after conservative treatment and she was discharged after 18 hospital days. This case demonstrated an extremely rare case of Osler-Weber-Rendu disease presenting as portosystemic encephalopathy treated successfully with conservative treatment. For patients who have shown hepatic encephalopathy without a definite cause, we recommend evaluation for the possibility of Osler-Weber-Rendu disease. Conservative treatment based on treatment of advanced liver cirrhosis could be an alternative solution. (Korean J Gastroenterol 2015;65:57-61)

Key Words: Hereditary hemorrhagic telangiectasia; Hepatic encephalopathy

INTRODUCTION

Osler-Weber-Rendu disease, also known as hereditary hemorrhagic telangiectasia (HHT), is a rare autosomal dominant disorder of the fibrovascular tissue, characterized by hemorrhagic manifestations.1 The disease was first reported by Babinton in 1865, then Rendu in 1896, Osler in 1901, and Weber in 1907; each reported the disease, which was named Osler-Weber-Rendu disease. Then Hanes2 used the term hereditary hemorrhagic telangiectasia and so called since then. It is characterized by the classic triad of mucocutaneous telangiectasias, recurrent hemorrhages, and familial occurrence.1,3 Hemorrhage often manifests as epistaxis, or gastrointestinal bleeding (GIB), and it could be fatal in some cases. Arteriovenous malformations (AVM) could occur at any organs, including the skin, lung, brain, nose, gastrointestinal tract, and liver. Although hepatic involvements remain clinically asymptomatic in most patients, AVM of the liver is often associated with high-risk bleeding. AVM of the liver is often associated with high-risk bleeding.
hepatic vascular system causing portohepatic shunt may cause hepatic encephalopathy.4

Although there are some case reports of GIB in Osler-Weber-Rendu disease, cases reporting hepatic encephalopathy and Osler-Weber-Rendu disease are rare world-wide. We experienced a case presenting with hepatic encephalopathy and diagnosed with Osler-Weber-Rendu disease, and report it with the literature.

CASE REPORT

A 75-year-old female visited the emergency department with an altered mentality that had started about 10 hours ago. Initial vital signs measured at the emergency department were as follows: body temperature, 36°C; pulse rate, 87 beats per minute; respiration rate, 20 times per minute; and blood pressure, 129/74 mmHg. Neurological exam revealed grade II alteration according to West Haven Criteria. She was diagnosed with valvular heart disease and underwent aortic valve replacement and mitral valvuloplasty in 2005. She had been taking warfarin since then and maintaining INR between 1.2 and 1.7. She had recurrent epistaxis for more than ten years and had received coagulotherapy a few times. However, she did not show evidence of epistaxis or GIB at this time.

Familial history showed that her mother and one of her four children had died of massive GIB, and one of her children suffers from recurrent epistaxis. Two of her three living children underwent screening tests and all of them had been diagnosed with vascular malformations (Fig. 1).

Results of the initial laboratory work-up showed the following: white blood cell, 4,030 counts/μL; hemoglobin, 11.7 g/dL; platelet count, 132,000 counts/μL; aspartate aminotransferase, 39 IU/L; alanine aminotransferase, 22 IU/L; total bilirubin, 3.3 mg/dL; direct bilirubin, 1.5 mg/dL; alkaline phosphatase, 126 IU/L; ammonia, 137 μg/dL (normal value 15-45 μg/dL); INR, 1.23; albumin, 3.7 g/dL; sodium, 137 mEq/L; potassium, 4.0 mEq/L; chloride, 104 mEq/L, and C-reactive protein, 0.08 mg/dL. Cerebrospinal fluid analysis was normal.

She was admitted to the department of neurology for further investigation and treatment of the altered mental status. Electroencephalography and brain MRI were performed. Electroencephalography showed a large amount of triphasic activities on all leads, and brain MRI showed high signal intensity in the bilateral globus pallidus area in a T1-weighted image, indicating the possibility of metabolic encephalopathy. Because of hyperbilirubinemia, possibility of liver disease needed to be checked. At this point she was consulted to the department of gastroenterology for investigation of the possibility of liver disease. CT showed no signs of parenchymal abnormality or any signs of obstruction in the bile duct system. CT showed telangiectasia in liver with multiple aneurysms of the intraparenchymal branch of hepatic arteries, consistent with HHT (Fig. 2). CT also showed a small lesion suspicious of pulmonary AVM, although she did not have any respiratory symptoms (Fig. 3).

The patient had undergone transthoracic echocardiography, which showed mild pulmonary hypertension with right ventricular pressure of 42 mmHg and a well-functioning prosthetic valve with normal left ventricular systolic function.

Clinical symptoms, familial history, and CT findings strongly suggested Osler-Weber-Rendu disease and the patient took the genetic test to confirm the diagnosis. The result of the genetic test showed mutation of activin receptor-like kinase-1 (ALK-1) in chromosome 12.

Supportive care for the hepatic encephalopathy, including restriction of dietary protein, lactulose enema, and feeding was administered as a treatment, and her symptoms improved after two days of treatment. No abnormal activities were observed on follow-up electroencephalography taken after 5 days of admission. To prevent hepatic encephalopathy, she was advised not to consume a large amount of protein. She was discharged home with a full recovery after 18 days of admission; however, she revisited the emergency department only two weeks after being discharged because of a loss of consciousness. Even though she did not take a high

[Fig. 1. Familial pedigree of a patient. Pedigree shows an autosomal-dominant pattern of Osler-Weber-Rendu disease affecting a family member in every generation.]
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**Fig. 2.** Abdominal CT findings. (A) Axial CT scan shows early opacification of portal and hepatic veins on arterial phase suggestive of presence of hepatic shunts (arrow). (B) Axial 3 phase CT scan image shows a dilated, tortuous hepatic artery with multiple aneurysmal dilatations consistent with findings of hereditary hemorrhagic telangiectasia (arrow). (C) Maximum intensity projection reconstructed image of axial CT scan shows multiple aneurysmal dilatations and dilatations of the hepatic artery, which are typical finding of hereditary hemorrhagic telangiectasia (arrow).

**Fig. 3.** Chest CT findings. Axial CT scan shows suspected arteriovenous malformation (arrow) in pulmonary vasculature suggesting pulmonary involvement in a patient.

protein diet this time, she had swallowed a considerable amount of blood from epistaxis. The patient’s hepatic encephalopathy was considered to be caused by nitrogen overload from swallowing nosebleed. Fortunately, her mental status recovered without sequelae with conservative treatment including lactulose feeding and enema. The patient has not experienced any event since then.

**DISCUSSION**

HHT is an autosomal dominant disorder characterized by hemorrhagic manifestations.1 Few studies have reported on the prevalence of the disease. The reported incidence is approximately between 2.5 and 19.4 per 100,000.5-7 HHT is caused by mutation of the genes related to the transforming growth factor beta (TGF-β) signaling pathway, which has an important role in the formation of vascular endothelium.8 Two major types of HHT, type 1 and type 2, are related to the mutation of endoglin (ENG) and activin A receptor type II-like 1 (ACVRL1), respectively. The ENG gene, located on the long arm of chromosome 9 (9q34.1), codes for endoglin, a receptor of TGF-β1 and TGF-β. The ACVRL1 gene, located on the long arm of chromosome 12 (12q13), codes for ALK-1. The relation between the genotype and the phenotype is not yet fully defined. However, type I shows relatively severe manifestations, with an earlier age of onset of symptoms such as epistaxis and appearance of telangiectasia, and a higher incidence of pulmonary AVM, while type II tends to show more hepatic involvements.5,8

This patient took the genotyping test to confirm the diagnosis. The result was ALK-1 mutation in chromosome 12 suggesting type II HHT. Her family members, including two children who had been diagnosed with Osler-Weber-Rendu disease have not yet taken the genetic test. Genetic testing can identify the presence of mutation and may confirm the diagnosis in patients with limited symptoms. Therefore, genetic testing is usually recommended for family members of patients when another member of the family is suspected of Osler-Weber-Rendu disease. However, if there are confirmed HHT patients in every generation in a family, the diagnosis could be made by clinicians without the genetic confirmations.

Diagnosis is made according to Curacao criteria published in 2000, when at least three of the following four criteria are present: 1) Recurrent spontaneous epistaxis; 2) cutaneous telangiectasia of lips, oral cavity, nose, and finger and toes; 3) visceral telangiectasia of gastrointestinal tract; and 4)
AVM of lungs, liver, and brain.3
Lesions can affect the nasopharynx, central nervous system, liver, lung, spleen, urinary tract, and gastrointestinal tract, as well as arms and fingers. Various symptoms may appear, although epistaxis is the most common manifestation.9 Onset of symptoms may be delayed so that approximately 90% of patients with Osler-Weber-Rendu disease manifest symptoms by age 40 years or older.6,7 It involves any vascular system of any organs in the body and usually shows hemorrhagic features. The most common symptom is epistaxis in approximately 80% of patients, and more than 30% of cases have AVM in either the liver or the lung. Hepatic involvement is found in 8-35% of patients with Osler-Weber-Rendu disease.4,6,9 Hepatic involvement could remain asymptomatic in most patients with HHT. Hepatic symptoms appear in approximately 8% of patients with HHT with hepatic involvement. It could present as a high-output cardiac failure, portal hypertension, liver fibrosis, and liver failure.4 Hepatic artery and venous malformations result in left to right shunt, resulting in heart failure.3,10,11 Shunt between portal vein and hepatic vein could result in hepatic encephalopathy or esophageal varices and GIB. In such a case, therapeutic options include hepatic artery embolization, hepatic artery ligation, and liver transplantation, both with a risk of liver failure and death.10 Liver involvement is diagnosed with Doppler ultrasonography, CT, MRI or invasive procedures such as angiography. Hepatic arteriography can be the best method of screening vascular malformations of the liver.12 Some cases of HHT presenting as hepatic encephalopathy have been reported, however, except one case reported by Fagel et al.,13 all cases had portohepatic venous shunts.

In reports by Matsumoto et al.,14 the shunts were not detected by CT, but detectable by angiography when shunts are too small and multiple to be seen by contrast. Such a case could be more detectable by thin section, a greater amount of contrast dye and faster dye injection. In general, the degree of shunt is in close relation to clinical symptoms.

In this case, the patient visited with encephalopathy two times within two weeks, so that there should be large shunts from portal vein to hepatic vein or multiple small shunts are present. However, 3 phase liver CT showed no definite portohepatic venous shunts. This might be due to multiple small shunts too small to be detected by CT. Angiographic portogram might reveal small shunts, but our patient did not undergo the test.

Some articles have emphasized the various manifestations of Osler-Weber-Rendu disease among patients and even within the same family.14-16 Family members of our patient who are suspected of Osler-Weber-Rendu disease or had been diagnosed with HHT show a diverse range of symptoms. The patient’s mother had died of massive GIB, and the patient’s oldest daughter had a history of recurrent epistaxis. Her son has no definite symptoms, even though he also has multiple aneurysmal dilatations of hepatic arteries and veins. The patient had a recurrent epistaxis and GIB, and hepatic encephalopathy. This diversity in symptoms even within members of the same family may be due to the fact that different symptoms may appear according to the organs or sites involved.

Treatment strategy for Osler-Weber-Rendu disease is mainly symptomatic and some therapeutic plans are focused on preventing development of severe complications. In the case of epistaxis, treatment options usually include iron supplement, humidification, packing, transfusion, electrocautery, and laser ablation. In some cases, surgical transplantation of nasal septum skin could be considered for control of recurrent epistaxis refractory to ablative treatment.17 Control of intermittent GIB may be managed medically but endoscopic treatment or surgical resection may be required in severe cases.

Treatment and prevention plan for patients with Osler-Weber-Rendu disease presenting as hepatic encephalopathy are complex. As for hepatic involvement, there are no recommended treatments for patients with Osler-Weber-Rendu disease with asymptomatic liver involvement. In HHT patients with symptomatic liver involvement, the treatment strategy is mainly symptomatic treatment and management aimed at reducing shunts, such as surgical ligation and transarterial embolization.18 To date, there is no ultimate treatment that ensures a complete recovery from Osler-Weber-Rendu disease. The only proposed definitive curative treatment option for hepatic involvement in HHT is the liver transplantation. However, there is one case report on recurrence of vascular malformation in a liver-transplanted patient with Osler-Weber-Rendu disease.19 Thus, even liver transplantation is not a definitive cure, but it is currently the best option when other symptomatic treatment fails. In this patient, liver transplantation would be the best option for treatment of her recurrent portosystemic encephalopathy. However, it was very difficult to recommend liver trans-
plantation because her cardiac disease and severe pulmonary hypertension make surgical risk too high. Therefore, we attempted to administer conservative treatment instead of surgical treatment.

It was reasoned that nitrogen overload in her gastrointestinal tract would be the most probable cause of her recurrent portosystemic encephalopathy. Actually, her first documented portosystemic encephalopathy was after eating a large amount of high protein foods as encouraged by her family as a way of recovering from general weakness. Nasal bleeding dripping into the patient’s gastrointestinal tract was believed to be another major source of nitrogen overload and the contributing cause of portosystemic encephalopathy. Supportive care for hepatic encephalopathy including lactulose enema and feeding, protein-restricted diet worked as expected. A low-protein diet and a medium and short branch chain amino acid supplement for nutritional support were recommended.

She has been taking warfarin since valve replacement surgery, which is a high risk factor for bleeding complications such as gastrointestinal bleeding or epistaxis. Blood can enter the gastrointestinal tract and cause nitrogen overload, causing hepatic encephalopathy. Thus, careful monitoring for such bleeding and early management is crucial. Also, it is important that patients be instructed not to swallow nosebleed. To prevent nitrogen overload, the patient was advised to take a protein-restricted diet and lactulose ingestion together with making sure the patient had at least two to three defecations per day. The patient received the above mentioned treatments and patient education, and is being followed up at the outpatient clinic with no recurrence of portosystemic encephalopathy.

In conclusion, hepatic encephalopathy is a very rare manifestation in Osler-Weber-Rendu disease. However, patients without definite cause for a hepatic encephalopathy such as decompensated liver cirrhosis should undergo thorough evaluation for the possibility of Osler-Weber-Rendu disease with hepatic involvement. Conservative management based on treatment for advanced liver cirrhosis could be an alternative solution in patients with Osler-Weber-Rendu disease presenting as hepatic encephalopathy.

REFERENCES