Hepatic sonography in patients with hereditary hemorrhagic telangiectasia hospitalized for epistaxis

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KEYWORDS

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Abstract Hereditary hemorrhagic telangiectasia (HHT) is an autosomal dominant disorder characterized by the presence of telangiectasias and arteriovenous malformations in various organs and organ systems, including the liver. The most frequent clinical manifestation of HHT is epistaxis.

In 2010 (January–December inclusive) 51 patients with HHT were admitted to the ENT ward of our hospital for epistaxis, and in accordance with routine protocols, all 51 underwent abdominal ultrasonography in our department to detect hepatovascular lesions. They included 27 males (53%) and 24 (47%) females ranging in age from 11 to 86 years (mean 48.5 years). The sample was selected in an arbitrary manner to take maximum advantage of the hospital stay and monitor patients from regions other than our own.

Retrospective analysis of the findings from these sonographic examinations revealed hepatic HHT in 27 (53%) of the 51 patients. Nineteen (70%) of these (age range 40–86 years, mean 63) had vascular malformations of various dimensions but no portal hypertension; the other eight (30%) (age range 39–81 years, mean 60) had vascular malformations plus *portal hypertension*.

Our retrospective analysis indicates that a significant number of patients can have unrecognized hepatic involvement; that the appearance of hepatic lesions can be fairly unpredictable, even when the HHT has been diagnosed for years and the patients are already symptomatic; and that the hepatic lesions are frequently progressive. Therefore, regular sonographic follow-up is advisable for patients with HHT.

The limitations of this study are related to the small number of patients examined and to the fact that all of them were symptomatic. Further study is therefore needed (especially in asymptomatic patients) to define the indications for hepatic sonography and the optimum examination schedule.

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Sommario La telangectasia emorragica ereditaria è una malattia autosomica dominante caratterizzata dalla presenza di telangectasie e di malformazioni artero-venose in vari organi e apparati. La sua manifestazione clinica più frequente è l'epistassi.

Nel 2010 (gennaio-dicembre inclusi) 51 pazienti sono stati ricoverati nel reparto di otorinolaringoiatria (ORL) del nostro ospedale per epistassi e, secondo la loro prassi, tutti i 51 pazienti sono stati sottoposti a ecografia dell'addome nel nostro reparto per la ricerca di lesioni epatiche. Il campione era costituito da 27 maschi (53%) e 24 (47%) femmine, di età compresa tra 11 e 86 anni (media 48,5).

È stato scelto questo campione in maniera arbitraria per sfruttare al meglio il tempo del ricovero e per monitorare pazienti provenienti anche da altre regioni.

L'analisi retrospettiva dei reperti emersi all'ecografia ha mostrato lesioni epatiche da telangectasia emorragica ereditaria (HHT) in 27 (53%) dei 51 pazienti. Diciannove di questi (70%), con età compresa tra 40 e 86 anni (media di 63), avevano solo malformazioni vascolari di varia entità, senza ipertensione portale, gli altri 8 (30%) (con età compresa tra 39 e 81 anni, età media di 60 anni) avevano anche ipertensione portale.

L'analisi retrospettiva da noi effettuata evidenzia come vi possa essere un numero significativo di pazienti con lesioni epatiche misconosciute, come queste possano presentarsi in maniera abbastanza imprevedibile, anche in pazienti con HHT diagnosticata anni prima e già sintomatici, come vi sia, frequentemente, una progressione delle lesioni epatiche e sia quindi opportuno un follow-up ecografico dei pazienti con HHT.

Il limite del lavoro è legato alla relativa esiguità del numero di pazienti e al fatto che tutti erano sintomatici, ulteriori studi, in particolare su pazienti asintomatici, sono necessari per stabilire l'indicazione all'ecografia epatica e la frequenza dei controlli.

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Introduction

Hereditary hemorrhagic telangiectasia (HHT), also known as the Rendu-Osler-Weber syndrome, is an autosomal dominant disorder characterized by the presence of telangiectasia and arteriovenous malformations (MAV) in various organs and systems. The most common sites of involvement are the skin, the mucous membranes of the head and upper extremities, the respiratory tract, and the gastrointestinal tract. The reported prevalence of hepatic lesions varies widely, in part because not all patients with HHT undergo testing aimed at evaluation of the abdominal organs.

At the level of the liver (which has a dual blood supply and dual system of venous drainage) [1], all types of vessels can be affected, regardless of their caliber, and the alterations take various forms: dilatation and/or complex alterations involving the hepatic artery (Figs. 1–4), arteriovenous fistulas (i.e., between the hepatic artery and suprahepatic veins) (Fig. 5), arterioportal fistulas, portal-venous fistulas (Fig. 6), and portal hypertension (Fig. 7).

All of these lesions can be assessed sonographically. Four stages are distinguished on the basis of the structures involved and the size of the lesions [2] (Table 1).

In the presence of a fistula, color-Doppler imaging of the hepatic artery and its branches reveals increased flow velocity, aliasing, and turbulence (Figs. 2B, 3B and 4B). In the presence of a fistula, turbulent flow is seen (Fig. 5); arterioportal fistulas are also associated with phasic or continuous inversion of flow. In the presence of arteriovenous fistulas at the level of the suprahepatic veins, flow alterations are detected only in stage IV. Venoportal and venovenous fistulas are less common.

Figure 1 Patient with Rendu-Osler-Weber syndrome with sonographic stage 1 liver involvement. Ultrasonography (A) and subsequent color Doppler imaging (B) reveal enlargement of the hepatic artery (HA) at the extrahepatic level with a diameter that is comparable to that of the portal vein (PV).

Figure 2 Patient with Rendu-Osler-Weber syndrome with sonographic stage 2 liver involvement. Ultrasonography (A) and subsequent color Doppler imaging (B) reveal dilatation and tortuosity of the hepatic artery (arrows) at the intrahepatic level.

In patients with HHT, focal nodular hyperplasia (FNH) (Fig. 8) is observed with an increased frequency (prevalence 2.9% versus 0.3% in the general population). These lesions are the result of an anomalous increase in blood flow to a specific portion of the parenchyma, which triggers a focal hyperplastic reaction in the liver cells. In HHT patients, arteriovenous shunts are probably the cause of this process since the hepatic artery seems to play a direct role in the development of FNH [3]. The combination of fibrosis around the anomalous vessels, FNH, and portal hypertension can lead to an erroneous diagnosis of cirrhosis.

Occasionally, patients with HHT do actually have cirrhosis (secondary to extensive necrotizing cholangitis),

Figure 3 Patient with Rendu-Osler-Weber syndrome with sonographic stage 3 liver involvement. Ultrasonography (A) and subsequent color Doppler imaging (B) reveal complex alterations of the hepatic artery (HA): the dilated, tortuous branches form variceal clusters around the suprahepatic veins and portal-vein branches.

hepatocellular carcinoma or hemobilia secondary to rupture of arteriovenous malformations (AVMs) in the biliary tree [4].

Our staff performs abdominal sonography on a large number of patients with HHT. In fact, in January of 2010, this examination became part of the routine diagnostic work-up for HHT patients admitted to the ENT ward of our hospital for epistaxis. For this reason, we decided to conduct a retrospective review of the cases of this type examined in 2010 and assess the relation between the sonographic data obtained and the natural history of hepatic HHT involvement in an attempt to improve the clinicotherapeutic management of these cases.

Materials and methods

Between 1 January and 31 December 2010, 51 patients with HHT-related epistaxis were admitted to the ENT ward of our medical center. They included 27 males (53%) and 24 (47%) females; ages ranged from 11 to 86 years (mean 48.5 years). The sample was selected in an arbitrary manner to take maximum advantage of the hospital stay and monitor

Figure 4 Patient with Rendu-Osler-Weber syndrome with sonographic stage 3 liver involvement. Ultrasonography (A) and subsequent color Doppler imaging (B) reveal complex alterations of the hepatic artery, which presents markedly dilated, tortuous intrahepatic branches that form variceal clusters around the suprahepatic veins and portal vein branches.

patients from regions other than our own. In accordance with standard protocol in the ENT ward, all 51 patients underwent abdominal sonography in our department to identify any HHT-related lesions and/or monitor the progress of lesions that had already been identified.

For most of the patients (38/51), the 2010 examination was the first hepatic imaging study ever performed; the other 13 had already had one or more abdominal sonographic or computed tomographic (CT) examinations, and ten of these had previous findings of hepatovascular alterations. In the latter cases, we compared findings from the 2010 study with those of earlier imaging studies to characterize the evolution of the hepatic involvement over time. Our analysis was based on the original findings reported by the radiologists who had performed the sonographic examinations (i.e., the images themselves were not reviewed).

The examinations were performed with a Philips IU22 or GE LOGIC® E9 scanner and a convex 3.5–5.0 MHz transducer. They began with a B-mode scan of the entire hepatic parenchyma with at least two scans in planes that were perpendicular to one another and the patient lying in various positions. This was followed-in all cases-by color-

Figure 5 Patient with Rendu-Osler-Weber syndrome with sonographic stage 3 liver involvement. Color Doppler imaging reveals an arteriovenous fistula (arrow) (A) With turbulent flow (B).

Doppler imaging of the hilar vessels and of any images that were suggestive of vascular anomalies.

Results

Twenty-seven (53%) of the 51 patients presented hepatic HHT lesions on the scans performed in 2010 (16 of the 38 undergoing US for the first time and 11 of the 13 undergoing repeat scans). On the whole, the 27 patients with positive findings included 19 (70%) (aged 40–86 years; mean 63) with a solitary vascular malformation of variable dimensions and no sign of portal hypertension (Figs. 1–6) and eight (30%) (aged 39–81 years; mean 60) with one or more

Figure 6 Patient with Rendu-Osler-Weber syndrome with sonographic stage 3 liver involvement. Ultrasonography (A,B) and subsequent color Doppler imaging (C,D) reveal arteriovenous malformations (arrows) in segment V.

Figure 7 Patient with Rendu-Osler-Weber syndrome with sonographic stage 4 liver involvement. Color-Doppler imaging reveals portal hypertension with flow velocity at the hilum of 29 cm/s.

vascular malformations plus some degree of portal hypertension (Fig. 7).

The 13 patients who had already been examined with US or CT (1 to 6 years earlier) included 11 with positive findings in the 2010 study. Compared with the earlier studies, the sonographic examination performed in 2010 revealed alterations that were essentially unchanged ($n = 5$); extension of the lesions ($n = 3$); and new onset portal hypertension in 2 patients previously known to have only fistulas of various types, indicating progression of the hepatic involvement. In these latter two cases, the previous imaging examination had been performed 18 and 28 months before the 2010 study. In one patient with negative findings on all previous scans (74, 57, and 11 months before the study examination), the 2010 examination revealed hepatovascular changes, with no evidence of portal hypertension.

In the remaining 24 (47%) patients (aged 7–79 years; mean 43), the 2010 examination did not reveal any hepatovascular changes, but one of these presented a hepatic lesion compatible with FNH (Fig. 8).

Table 1 Sonographic staging of hereditary hemorrhagic telangiectasia.

Stage I	Dilatation of the common hepatic artery (>7 mm)
Stage II	Intrahepatic and extrahepatic dilatation of the hepatic artery
Stage III	Complex alterations of the hepatic artery with marked dilatation (sometimes aneurysmal) with dilated, tortuous intrahepatic branches, that form variceal clusters around the suprahepatic veins and/or portal vein. Arteriovenous fistulas (between the hepatic artery and suprahepatic veins) and arterioportal fistulas (between the hepatic artery and branches of the portal vein) associated with dilatation of the suprahepatic veins or portal vein, respectively. Arteriovenous fistulas are the more common. Arteriovenous anastomoses and hypertrophic arterial networks can be seen at the hilum of the liver. The echo structure of the liver may be coarse and hyperechoic
Stage IV	Sonographic evidence of heart failure or portal hypertension (depending on whether the fistulas are arteriovenous or arterioportal) At this stage, too, the echo structure of the liver may also be coarse and hyperechoic

Discussion

Hereditary hemorrhagic telangiectasia (HHT) or Rendu-Osler-Weber syndrome is an autosomal dominant genetic disorder that affects multiple organs. It is characterized by vascular dysplasia, which results in the presence of multiple telangiectasias and AVMs involving the skin, mucous membranes, gastrointestinal tract, lungs, and other organs. These alterations are frequently associated with bleeding [4].

Figure 8 Patient with Rendu-Osler-Weber syndrome. Ultrasonography reveals a solid formation in the left lobe of the liver with well-defined margins (A) and typical vascular patterns (wagon-wheel or star patterns) at color Doppler imaging (B).

HHT occurs throughout the world with a prevalence in the general population ranging from 1 in every 5000 to 10,000 inhabitants. The prevalence displays geographic variability with very low values in some areas (1/39,216 in the north of England) and extremely high rates in others (1 in 1331 in the Afro-Caribbean population of the Netherlands Antilles). The frequency of HHT is similar in men and women [5].

The syndrome also displays enormous phenotypic variability at both the inter- and intrafamily levels. For this reason, the prevalence of the disorder is usually underestimated [6].

HHT is associated with mutations involving genes that encode proteins implicated as mediators of the effects of transforming growth factor beta β (TGF β) on endothelial cells.

The syndrome is classified as HHT type 1 or HHT type 2 depending on the specific mutation responsible for the disorder (Table 2). A new locus for HHT (HHT type 3) has recently been mapped to chromosome 5, although the specific gene has not been identified. There is also a subgroup of patients, whose HHT is associated with juvenile polyposis (JP-HT) and mutations of the *MADH4* gene [7,8].

The most common clinical manifestation of HHT is epistaxis (which occurs in 90% of all cases). It usually develops during infancy, and it can be mild (requiring no therapy) or severe (requiring transfusions) [6]. Multiple telangiectasias involving the skin and mucous membranes of the face, lips, mouth, conjunctiva, and ears are common. Involvement of the lingual mucosa is particularly important because bleeding from this site is difficult to control. The skin of the arms and fingers is also frequently involved. In older patients, the presence of telangiectasias at the level of the gastrointestinal tract causes bleeding with the risk of severe anemia in 15%–45% of all patients, depending on the series [9]. Larger AVMs are found mainly in the lungs (15–35% of patients), where they can cause hypoxia, hemothorax, and thrombotic or septic embolism. Cerebral lesions are less common (15–30% of patients), probably because they are often misdiagnosed. They can cause migraines, convulsions, ischemia, hemorrhages, and abscesses [4,9]. The incidence of AVMs involving the kidneys, ureters, bladder, and/or urethra is very low [10].

Hepatic involvement ranges from the presence of telangiectasias to malformations involving larger-caliber vessels. As reported in the literature, this type of involvement is found in anywhere from 30% to 73%, and the high variability may be

Table 2 Genetic types of hereditary hemorrhagic telangiectasia.

Type 1	Mutation of the <i>ENG</i> (endoglin) gene on chromosome 9
Type 2	Mutation of the <i>ALK-1</i> (or <i>ACVRL1</i> = activin receptor-like kinase 1) gene on chromosome 12
Type 3	Mutation of a currently unidentified gene on chromosome 5

due to the fact that in many studies participants are not screened for hepatic AVMs [5,9,10]. In rare cases, simple telangiectasias can cause symptoms such as right hypochondrial pain and/or moderate elevation of markers of cholestasis (GGT). Arterioportal shunts can produce pain, alterations liver function indices (especially the indices of cholestasis secondary to bile duct ischemia), portal hypertension, ascites, encephalopathy, and hematemesis, and arteriovenous shunts are occasionally the cause of high-output heart failure and necrotizing cholangitis resulting from arterial steal. (Perfusion of the bile ducts depends exclusively on blood supplied by the hepatic artery.) [4]. The clinical diagnosis is based on the so-called Curacao criteria [11], which consist in epistaxis, mucocutaneous telangiectasias, visceral manifestations, and a positive family history.

The natural evolution of hepatic telangiectasias is directed toward shunt formation. Transcatheter embolization via the femoral vein has been proposed to treat hepatic arteriovenous shunts, but evidence suggests that this approach can be associated with serious complications, including liver necrosis, bile duct ischemia with necrotizing cholangitis, liver abscesses, hemorrhages leading to hemobilia, and sepsis. For this reason, liver transplant is advised for patients with severe symptoms of hepatic insufficiency and/or heart failure. In some cases, AVMs have been documented in the transplanted liver several months after the procedure, in patients whose liver function parameters are within normal limits, and this highlights the importance of protracted follow-up, even after the patient has received a liver transplant [12].

Conclusions

There are currently no diagnostic protocols that provide for sonographic assessment of the liver in HHT patients at a specified frequency. In our facility, for example, these patients undergo sonography only when they are hospitalized for the treatment of epistaxis.

Our retrospective analysis of the 51 cases of this type examined in 2010 shows that a significant number of patients with HHT may have unrecognized hepatic involvement; that the development of such involvement is fairly unpredictable, even in patients whose HHT was diagnosed many years ago and who are already symptomatic; and that progression of these lesions is frequent. Sonographic follow-up of HHT patients is thus advisable.

The limitations of this study are related to the small number of patients examined and the fact that all of them had symptomatic HHT. Therefore, further study—particularly of asymptomatic patients is needed to establish the indications for hepatic sonography and the frequency of such

examinations, also on the basis of possible indications for treatment.

Conflicts of interest

The authors have no conflicts of interest to disclose.

Appendix A. Supplementary material

Supplementary material related to this article can be found online at [doi:10.1016/j.jus.2012.04.001](https://doi.org/10.1016/j.jus.2012.04.001).

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