Hepatic vascular malformations in hereditary hemorrhagic telangiectasia: Doppler sonographic screening in a large family

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Background/Aims: The prevalence of hepatic vascular malformations in hereditary hemorrhagic telangiectasia has been estimated in the literature on clinical criteria, thus giving unreliable data. In our study the presence of hepatic vascular malformations in hereditary hemorrhagic telangiectasia was evaluated in a large Italian family by using Doppler sonography as screening technique. Doppler sonographic findings were compared to computed tomography and angiography results. Clinical features were related to the severity of hepatic vascular malformations.

Methods: Seventy-three relatives were checked for the presence of signs of hereditary hemorrhagic telangiectasia. Abdominal Doppler ultrasonography was performed in all of them. Every subject with a positive Doppler ultrasonography for hepatic vascular malformations underwent abdominal computed tomography and celiac angiography.

Results: Forty family members proved to be affected by hereditary hemorrhagic telangiectasia. Of these, hepatic vascular malformations were evidenced by Doppler ultrasonography in 13 females. Doppler ultrasonography demonstrated minimal hepatic vascular abnormalities in three subjects, moderate in three, and severe in seven. Doppler study was diagnostic for arteriovenous shunt with hepatic veins in seven cases and with portal vein in two. Computed tomography failed to demonstrate hepatic vascular malformations in two cases, while angiography confirmed the Doppler sonographic findings in all cases. Cardiac failure was present in only one case. Cholestasis was present in subjects with moderate and severe hepatic vascular malformations.

Conclusions: Doppler sonography is the ideal imaging technique to screen hereditary hemorrhagic telangiectasia affected families for hepatic vascular malformations. These malformations do not appear to be age-dependent, but sex-dependent. Cholestasis is the main clinical sign, and it seems to correlate with the severity of hepatic vascular derangement.

Key words: Cholestasis; Doppler sonography; Hereditary hemorrhagic telangiectasia; Liver vascular malformations; Screening.
Nevertheless, the detection of hepatic VMs is important, because, as in most of the reported cases, they can induce life-threatening complications (15–17).

We screened a large family affected by HHT for hepatic VMs using Doppler sonography. We have recently described the corresponding imaging findings (18).

The aims of this study were: 1) to detect hepatic involvement in HHT by using Doppler US as screening technique; 2) to relate Doppler US findings to CT and angiography; and 3) to relate clinical and biological features to the stages of hepatic vascular derangement.

Patients and Methods

We began the family study in April 1992, when the index case, a 61-year-old woman, was admitted to our department. She presented with several mucocutaneous telangiectases and suffered from severe high-output heart failure due to intrahepatic arteriovenous shunts. Her large, six-generation family was investigated.

Ninety-five of 120 relatives (non consort) were alive. Seventy-three of them (27 males, 46 females, mean age 41.3, range 4–89) were studied. Informed consent to the study was obtained from each subject. Clinical records or history was available for 17 deceased family members.

Two out of three major criteria (epistaxis, telangiectasia, autosomal dominant inheritance) had been the criteria for a diagnosis of HHT in an extended epidemiological study. Well-documented visceral involvement was also accepted instead of one of these criteria (4).

Affection status of subjects with only minimal signs (less than five angiectases and/or less than ten epistaxes per year) was retrospectively classified as unknown in performing linkage analysis, which is a safe assumption to avoid spurious lod scores (19).

We collected the clinical history of each subject, with particular attention to: self-reported epistaxis occurring at any time in life; gastrointestinal hemorrhages; hepatic and cardiopulmonary diseases. Each subject underwent a complete physical examination, looking in particular for: mucocutaneous telangiectases, presence of thrill on abdominal palpation and murmur on abdominal auscultation.

A blood sample for DNA extraction was drawn from each examined subject.

Each subject underwent a Doppler sonographic examination of the abdomen. Every examination was performed after overnight fasting with a duplex-type Aloka SSD-650 (Aloka, Co. Ltd., Tokyo, Japan) with a 3.5 MHz convex probe, provided by a pulsed Doppler device operating at a frequency of 2.5 MHz. The high-pass filter was maintained at 100 Hz. The angle between the ultrasonic beam and the blood flow direction was kept at below 60°. Pulse repetition frequency and sample volume were set so as to optimize Doppler signals from the vessels. Subjects were asked to hold their breath during the Doppler examination. The following were recorded: liver and spleen size, liver echo structure and margins. We studied caliber, course and abnormalities of the hepatic artery, portal vein and hepatic veins. In particular, we searched for dilation of the hepatic artery (extra- or both extra- and intrahepatic). The common hepatic artery caliber was measured about 2 cm after its origin from celiac trunk; normal values were considered to be 5 mm±1 (20). The presence of hypertrophic collaterals at porta hepatis was also recorded. We studied flow patterns of hepatic vessels with qualitative (direction, turbulence) and quantitative (peak flow velocity in the common hepatic artery, mean velocity in the portal vein, diastolic peak flow velocity in hepatic veins) Doppler parameters. The mean value of three consistent values of blood velocity was recorded. We regarded the following as normal values (according to the data of our Doppler sonographic laboratory): peak flow velocity in the hepatic artery (at hilus) 70±10 cm/s, mean velocity in the portal vein (portal vein trunk) 18±2 cm/s, diastolic peak flow velocity in hepatic veins (2–3 cm proximal to their entrance into vena cava) 25±10 cm/s. For the diagnosis of arteriovenous shunt we required the association of abnormalities of the hepatic artery with abnormality of hepatic and/or portal veins. Depending on the number and degree of abnormalities, we classified hepatic VMs as minimal (abnormality of the hepatic artery only in the extrahepatic part), moderate (abnormality of both extra- and intrahepatic arteries, with possible moderate dilation of hepatic and/or portal veins), and severe (complex changes of the hepatic artery, associated with marked dilation of hepatic and/or portal veins) (18).

In the second part of our study, each subject with Doppler US study positive for hepatic involvement underwent a predefined series of tests.

To exclude other hepatic diseases, the following were evaluated: bilirubin, transaminases, alkaline phosphatase, gammaglutamyl transferase, biliary acids, prothrombin, serum albumin, antinuclear, anti-smooth muscle and antimitochondrial antibodies, ferritin, markers for hepatitis B and C viruses. Chest X-ray and upper digestive tract endoscopy were per-
formed to search for other visceral involvement. Echocardiography was also performed to show cardiac hyperkinesia or failure, and to calculate cardiac output.

Abdominal CT and celiac angiography were performed as a confirmatory test for hepatic involvement. CT was performed with Tomoscan LX (Philips, The Netherlands); CT scan was performed dynamically with two intravenous bolus of contrast: one with focus on the hepatic hilus and one with focus on hepatic veins. CT studied the presence of dilation of the hepatic artery, associated possibly with dilated hepatic veins and/or portal vein, and filling kinetics of the hepatic artery, portal vein and hepatic veins.

Celiac angiography (with aortography and selective arteriography of the hepatic artery) was done with an infusion of iopamidole (Iopamiro, Bracco, Milan, Italy) at a concentration of 300 mg/ml, with infusion volume ranging between 10 and 18 ml, at infusion rate of 3–8 ml/min. Angiography searched for at least one of the features of hepatic involvement in HHT: prominence of the hepatic artery, intrahepatic angiectases, early filling of hepatic veins and/or portal vein.

**Results**

The family studied, as a whole, completely fulfils the requirements for the diagnosis of HHT, as autosomal dominant inheritance is clearly observed in the pedigree with several instances of male to male transmission, and with telangiectases, epistaxis and visceral involvement being present in various combinations.

Forty subjects (10 males, 30 females, mean age 53.9, range 17–89) out of 73 living family members were diagnosed to be affected by HHT (10 subjects had only minimal signs: 1–4 angiectases or 3–4 epistaxes per year or epistaxis only in childhood). We classified as probably affected by HHT 9 subjects among the deceased family members (6 males, 3 females). Among the 40 affected living subjects, hepatic VMs were found at Doppler US in 13 females (32.5% of the 40 affected subjects, and 43.3% of the affected females) (Fig. 1). The results of US examinations are shown in Table 1.

At US, dilation of the hepatic artery was found only in the extrahepatic tract in three cases (Fig. 2) and in both the extra- and intrahepatic tract in three

**TABLE 1**

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Case 8 is index case
+ presence, / absence ↑, increased. extra, dilation only in extrahepatic tract. extra-intra, dilation of both extra- and intrahepatic tract. n, normal. inhomog, inhomogeneous. hyperec, hyperechogenic.
Fig. 2. Transverse sonogram of upper abdomen shows celiac trunk (arrowhead) below left lobe of the liver (l); hepatic artery (arrow) is dilated (diameter 8 mm), without normal tapering.

Fig. 3. Oblique subcostal sonogram of the liver shows multiple tangle branches of hepatic artery (arrows) surrounding the gallbladder (g). c. = vena cava.

Fig. 4. Longitudinal duplex sonogram of left lobe of liver demonstrates a prominent hepatic artery below liver margin, with spectrally broadened, high-velocity flow (peak flow velocity: 197 cm/s).

cases. In the remaining seven cases, the hepatic artery (both extra- and intrahepatic) was markedly altered (Fig. 3), prominent and even aneurysmal, tortuous, with hypertrophic collaterals at the porta hepatis. The caliber of the hepatic artery ranged from 7 to 22 mm. The portal vein was dilated in one case and hepatic veins in seven. In cases 8, 9 and 12, an arteriovenous anastomosis was detectable at US. Increased liver size was found in seven cases, while no irregularity of liver margins was detected in any case. Inhomogeneous or coarse pattern was found in four cases. The only hepatic focal lesion we detected was an angioma in case 9. Spleen size was moderately enlarged in five cases.

The pulsed Doppler study showed high-velocity flow, even aliased or turbulent in the hepatic artery, extra- or both extra- and intrahepatic, in all 13 subjects (Fig. 4, 5). Peak flow velocity in the common hepatic artery ranged from 95 to 210 cm/s. Portal flow pulsatility with continuous or phasic reversal was demonstrated in case 4 (mean velocity within normal limits) and 8, respectively. In case 8 we found biphasic flow in hepatic veins with high antegrade diastolic peak (56 cm/s). In the remaining subjects, the flow pattern of hepatic veins proved normal.

Doppler US indicated arteriovenous shunt with hepatic veins in cases 1, 5, 8, 9, 10, 11 and 12, and with the portal vein in cases 4 and 8.

Altogether, Doppler US findings were consistent with minimal vascular abnormalities in cases 2, 7 and 13, moderate in cases 3, 6 and 11, and severe in cases 1, 4, 5, 8, 9, 10 and 12.

Abdominal CT and celiac angiography were performed in 12/13 subjects with Doppler US diagnosis of hepatic involvement (patient 1 refused CT and angiography). CT diagnosed hepatic vascular malformations in 10 cases, but failed to demonstrate hepatic VMs in cases 2, 13. CT demonstrated the following: prominence of the hepatic artery in all the remaining cases, early filling of hepatic veins (in cases 5, 8, 9, 10, 11, 12), early filling of the portal vein (in case 4) and diffuse telangiectases in hepatic parenchyma (in cases 5, 8, 9, 10, 12).

Angiography showed prominence of the hepatic artery in the extrahepatic tract (cases 2, 7, 13), in both extra- and intrahepatic tracts (cases 3, 6, 11), diffuse parenchymal telangiectases (cases 5, 8, 9, 10, 12), early filling of hepatic veins (cases 5, 6, 8, 9, 10, 11,
Fig. 5. Pulsed Doppler sonogram of tortuous intrahepatic branches of hepatic artery shows high-velocity flow, both systolic and diastolic.

12), early filling of portal vein (cases 4 and 8.) The presence of arteriovenous shunt was therefore demonstrated in eight subjects (in six with hepatic veins, in one with portal vein, in one with both portal and hepatic veins). Additional findings with angiography were: the presence of an arterial stenosis (celiac trunk in cases 5, 9, 10, 12, splenic artery in case 8); the presence of an aneurysm (hepatic artery in case 8, splenic artery in case 10); the presence of arteriovenous malformations of collateral vessels (cases 5, 11), of the superior mesentery artery (case 12), and of the right renal artery (case 9).

The main clinical features of these subjects are shown in Table 2.

Of these 13 subjects, three reported epistaxis (in case 2, three to four nose bleeds when adolescent, and in case 12, minimal nose bleed once a year), and 10 subjects had mucocutaneous telangiectases (in five subjects, one to four telangiectases). Three patients with severe liver involvement were symptomatic: case 8, our index case (cardiac failure), case 12 (mild exertional dyspnea) and case 4 (repeated digestive hemorrhages due to bleeding gastric angiectases). All 10 remaining patients were asymptomatic. None of the subjects who had had children complained of symptoms related to cardiac failure while pregnant.

Physical examination disclosed the signs of cardiac failure in case 8 (ascites, edema, pleural effusion), cardiac murmur in four cases, murmur at epigastrium or at right hypochondrium in nine cases, and palpable thrill in these areas in one case.

Cholestasis was found in cases 1, 8 and 12 with severe vascular malformations, as alkaline phosphatase and gammaglutamyl transferase were elevated between two and seven times the normal values, and serum biliary acids between five and 15 times the normal values. Bilirubin proved to be two to three times the normal values in case 8. In cases 4, 5, 6, 10 and 11 we found only an increase of serum biliary acids three to five times the normal values. Serum transaminases and liver function tests (prothrombin, serum albumin) were normal in all cases.

By chest X-ray we detected pulmonary av fistula in one case. Upper digestive tract angiectases were found in 10 cases; in no case did we find signs of portal hypertension in the upper digestive tract. Echocardiogram showed dilation of all four chambers, severe tricuspid regurgitation and cardiac output of 16 liters/min in case 8. In cases 1, 5, 9 and 12, cardiac output was shown to have increased but did not exceed 7 liters/min.

### Table 2

Clinical features of 13 females with hepatic VMs

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+, presence. /, absence. UDT, upper digestive tract. CO, cardiac output. ND, not done.
Discussion

Until the end of 1960s the only reliable diagnoses of hepatic VMs in HHT were by biopsy or necropsy (6). There have since been many reports of one or more sporadic cases of hepatic involvement, well documented by imaging techniques such as angiography, and, in the last decade, by Doppler US, CT and magnetic resonance imaging (10–14). In some recent retrospective studies (4,5) liver involvement could only be suspected by clinical criteria such as hepatomegaly or jaundice. These criteria are equivocal in patients with HHT, who may have a variety of liver abnormalities or diseases such as iron overload or acute and chronic viral hepatitis or cirrhosis because of multiple transfusion for recurrent bleeding (21). Hepatic VMs in HHT were detected in one third of the affected members of our family, more frequently than clinically suspected in a very large series of patients (4).

A locus for HHT was mapped to chromosome 9 (3), and endoglin has been identified as the HHT gene mapping to this chromosome (22). In other families the disease does not segregate with marker loci mapping on chromosome 9 (23–25). A second locus has recently been mapped to chromosome 12 (26). In our family, linkage analysis demonstrated that the disease does not segregate with marker loci mapping on chromosomes 9 or 12 (27). The genetic heterogeneity of this disease could imply clinical heterogeneity, as already noticed with the familial clustering of pulmonary arteriovenous fistulas (23–25,28). Liver involvement could be the hallmark of a distinct subtype of HHT, or its frequency could be different in the different subtypes of HHT. In any case, since hepatic involvement can not be ruled out on a purely clinical basis, it is important to screen every member of HHT-affected families for the presence and severity of hepatic VMs (4,21), especially because they could be the most relevant, though clinically silent, HHT sign, as in our cases 2 and 12. There are several reasons why hepatic VMs must be detected.

Even if in almost all our cases neither quality of life nor longevity are impaired, hepatic VMs can induce life-threatening complications, as in our index case and in other described reports (15–17,29). A correct diagnosis enables the physician to inform the affected persons about the natural history of hepatic VMs, and to warn them about the potential complications and their symptoms. This is especially important when the vascular abnormalities are detected in young persons, as in our cases 7, 10, 11, 12 and 13. Genetic counseling is relevant to identify people at risk of having affected children and to help in active medical management. Young women should be warned about the risk of cardiac failure during the pregnancy (7).

According to the age of the affected subject, and the degree of his/her hepatic vascular derangement, the follow-up should be scheduled to detect possible worsening of vascular abnormalities (30). Accurate diagnosis of hepatic VMs is crucial to treat the complications correctly and in time. In fact, even if diffuse liver involvement usually precludes radical cure (21), transarterial embolization of liver arteriovenous fistulas can be an effective and repeatable therapy (29,31). Orthotopic liver transplantation will be reserved for the patients who are otherwise unmanageable (17). It is thus possible to improve the prognosis even in severe hepatic vascular derangement.

Even though the necessity of family investigation and follow-up of affected subjects has already been affirmed by other authors (4,6,21), an effective screening test for hepatic vascular malformation has not yet been defined.

Imaging techniques can effectively document the hepatic vascular abnormalities (7,13,14), but not all of them are suitable for screening. CT and angiography cannot be extensively used in family investigations as they are invasive and more expensive than sonography. On the other hand, in our cases, angiography gave the complete picture of liver vascular derangement, confirming the sonographic findings and also defining the abnormalities of the hepatic artery collaterals and other vessels near the liver.

Doppler US, being non-invasive, easily available and cost-effective, is the ideal imaging technique for the screening of HHT-affected families. We emphasize that the dilation of the hepatic artery represents a very sensitive diagnostic parameter for hepatic vascular malformations in HHT, present in all our cases. The vascular lesion consists of dilated post-capillary venules that progressively enlarge and create direct arteriovenous communication (32). Therefore, hepatic artery dilation is probably the earliest sign of liver involvement in HHT, due to the increased hepatic blood flow through arteriovenous fistulas (33), even when they are microscopic. If dilation of the hepatic artery is accurately searched for, US can reveal the liver involvement even in the early stages, when only this abnormality is detectable, as in our cases 2, 7 and 13. Our Doppler finding of increased flow velocity in the hepatic artery in all 13 cases, even in the absence of angiographically demonstrable shunt, can be explained by the pathophysiology of hepatic VMs. In more severe stages of liver involve-
ment it is not difficult to diagnose the nature of dilated abnormal tubular structures within the liver, and to differentiate them from dilated bile ducts (11,18,34). When associated with Doppler studies, US yields a reliable picture of liver VMs, giving the analysis of flow patterns, and the shunt's hemodynamic significance (18). Therefore, Doppler US should be considered sufficient for diagnosis in asymptomatic subjects, who will undergo follow-up, while angiography should be reserved for symptomatic subjects to plan the treatment.

Neither case reports nor clinical studies can relate clinical to imaging features of hepatic vascular abnormalities, because almost all the reported cases have been detected when symptomatic because of severe vascular derangement. On the other hand, in our familial investigation, hepatic vessel malformations were detected even in early or clinically silent stages: we can therefore describe the wide spectrum of clinical, biological and radiological features related to hepatic vascular abnormalities.

In spite of the age-related penetrance of the HHT gene (4) we found hepatic VMs even in young subjects (5/13 were premenopausal women), and the stages of liver vascular derangement appeared independent of age, as mild or moderate abnormalities were also detected in old people.

A striking finding of our study is the presence of hepatic vascular malformations only in women; the preponderance of women among HHT-affected people with liver involvement has been also noticed in the literature (6). We can not explain this finding, but sex-dependent expressivity is well known in other genetic disorders.

Liver involvement in HHT is almost always asymptomatic in our cases, and, as shown by case 1, it can remain clinically silent until old age, independent of the severity of hepatic vascular derangement. On the other hand, hepatic VMs can induce two kinds of complications, depending on the venous side of liver arteriovenous fistulas: high-output cardiac failure in the case of hepatopetal fistulas (16,35) and portal hypertension in the case of hepatopetal fistulas (6,13). In our subjects, pregnancy was not a precipitating factor for cardiac failure, as reported by others (7). Echocardiography proved useful in our study to determine cardiac index and its variations depending on the treatment, as in our index case (29), and during the follow-up, thus avoiding the need for more invasive procedures, such as heart catheterization (7).

In our family, pulmonary av fistulas seem to be rare; we do not intend to have the family screened for these anomalies, as chest X-ray is not the best method to diagnose them.

The only biological abnormality detected in our subjects with liver involvement was cholestasis, as already reported (6–8,13,17). We found a correlation between the importance of cholestasis and the severity of vascular abnormalities, supporting the hypothesis that the impaired arterial supply to bile ducts due to VMs results in bile duct damage and thus cholestasis (17).

The results of our study should alert physicians to the importance of the screening in all HHT-affected families for hepatic VMs. Doppler US is the ideal diagnostic tool, and the dilation of the hepatic artery is a very reliable US parameter for the presence of liver VMs.

Hepatic VMs appear independent of age, but are sex-dependent. Cardiac failure and, moreover, complications of portal hypertension are rare. Cholestasis is frequent and its degree seems dependent on the severity of hepatic vascular derangement.

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