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Liver involvement in a large cohort of patients with hereditary hemorrhagic telangiectasia: Echo-color-Doppler vs multislice computed tomography study☆

Paolo Buonamico[1,†], Patrizia Suppressa[1,†], Gennaro M. Lenato[1], Giovanna Pasculli[1], Francesco D'Ovidio[2], Maurizio Memeo[3], Arnaldo Scardapane[3], Carlo Sabbà[1,*]

[1]*Unit of Internal Medicine, Department of Internal Medicine and Public Health, Interdepartmental HHT Centre, University of Bari – Policlinico, Piazza Giulio Cesare 11, Bari 70124, Italy*

[2]*Department of Statistics, Department of Internal Medicine and Public Health, Interdepartmental HHT Centre, University of Bari, Bari, Italy*

[3]*Unit of Radiology, Interdepartmental HHT Centre, University of Bari, Bari, Italy*

***Background/Aims*: Hepatic arterio-venous malformations (HAVMs) have been found in 74% of hereditary hemorrhagic telangiectasia (HHT) patients with multislice CT (MSCT). This single-blind study aimed to compare the diagnostic accuracy of echo-color-Doppler with MSCT and identify the most sensitive ultrasound criteria indicating hepatic shunts.**

***Methods*: One hundred and fifty-three HHT patients were systematically screened for HAVMs by biological tests, abdominal MSCT and echo-color-Doppler. Twenty-five normal subjects and 15 cirrhotic patients were also included as control groups. Both intrahepatic ("color spots" and hypervascularization) and extrahepatic parameters (diameter, flow velocity and tortuosity of hepatic artery and diameter and flow velocity of portal/hepatic vein) were utilized. "Color-spots" are defined as subcapsular vascular spots with a high-velocity arterial blood flow and low resistivity index and can identify extremely small HAVMs.**

***Results*: CT was positive in 128/153 (84%) patients and Doppler color spots were found in 131/153 (86%) patients. The sensitivity, specificity and diagnostic accuracy of "color spots" compared to MSCT were 95.3%, 68.0% and 91.8%, respectively. The "color-spot" showed a greater correlation to CT (V_{index} = 0.655; $p < 0.0001$) than extrahepatic criteria (V = 0.317). In 20/29 (69%) subjects, echo-color-Doppler, confirmed by CT, identified the third criterion for definite HHT diagnosis.**

***Conclusions*: Intrahepatic criteria was superior to extrahepatic criteria for identification of HAVMs. A new Doppler parameter ("color-spots") with an optimal accuracy for detecting HAVMs is proposed for easy periodic screening of HHT patients.**

***Keywords*: HHT; Arterio-venous malformations; Liver shunts; Multislice CT; Echo-color-Doppler; Color spots; Hypervascularization**

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* Corresponding author. Tel./fax: +39 080 5478708.
E-mail address: c.sabba@dimimp.uniba.it (C. Sabbà).

† These authors contributed equally to this work.

Abbreviations: HHT, hereditary hemorrhagic telangiectasia; AVMs, arterio-venous malformations; MSCT, multislice CT; ECD, echo-color-Doppler; RI, resistivity index; PV, portal vein; HA, hepatic artery; RI, resistance index; V_{max}, maximum velocity; THADS, transient hepatic attenuation differences.

1. Introduction

Hereditary hemorrhagic telangiectasia (HHT) or Rendu–Osler–Weber disease is a predominantly inherited disorder involving structural abnormalities of small veins involving the skin, mucosa and internal organs, determining frequent bleeding episodes. Its prevalence has been estimated at 1/8000 [1]. Mutations in two different genes, ENG located on chromosome 9q33–q34 [2] and ALK-1 or ACVRL1 on chromosome 12q13 [3], characterize HHT1 and HHT2, respectively. The two

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genes, known to modulate the endothelial response to the TGF-β superfamily of ligands, are involved in the process of angiogenesis [4,5]. Mutations in a third gene, MADH4, have been reported in a subgroup of HHT individuals with or without signs of juvenile polyposis [6]. Additional HHT-causing genes have also recently been mapped to chromosomes 5 [7] and 7 [8]. At present, the clinical diagnosis is based on the presence of at least three of the following criteria: family history, recurrent epistaxis, presence of muco-cutaneous telangiectases and/or visceral arterio-venous malformations (AVMs), which can involve the brain, lung and liver and other organs [9].

Conventional angiography has been established as the gold standard for almost all vascular territories. However, in the last few years, advances in new techniques, such as multislice spiral CT (MSCT) technology and angio-MRI, have provided an anatomical visualization of the vascular tree comparable to that of conventional angiography. In our previous paper, MSCT scan was performed on a large sample of unselected HHT patients, demonstrating a good diagnostic accuracy and a high percentage of liver involvement (74%) in the investigated population [10].

For several years there has been much debate concerning the need to screen for hepatic AVMs which are generally asymptomatic and have scarce therapeutic options [11]. This controversial issue has been discussed in a recent paper which reported the general guidelines for hepatic screening in HHT patients, formulated by a panel of high-expertise members of the HHT community [12].

According to these consensus guidelines, extensive high-sensitivity liver screening in all HHT patients, independent of the presence of clinical signs, is indicated as a research tool in order to clarify different aspects of liver involvement.

The echo-color-Doppler (ECD) is a non-invasive method which has been proposed for the study of liver involvement in HHT patients [13,14]. To date, liver involvement identified with this technique has been confirmed with computed tomography (CT) but only in Doppler-positive patients; in fact, Doppler-negative HHT patients have never been systematically evaluated with CT scan. Therefore, even though ECD has been previously utilized, its real accuracy for diagnosis of hepatic shunts still remains to be clarified in the absence of controlled studies including an accepted gold-standard. Moreover, as liver involvement is frequent in these patients, the capability of ECD to detect even asymptomatic shunts would be extremely useful to reach a definite diagnosis of HHT.

Thus, the aims of the present study were: (1) to establish the diagnostic accuracy of ECD compared to MSCT scan in order to evaluate its efficacy as a screening procedure for the study of the liver involvement in HHT; (2) to identify the most sensitive ultrasound parameters to diagnose HHT liver shunts.

2. Materials and methods

2.1. HHT patients

Our initial sample included 156 patients (82 males and 74 females) who referred to our University Interdepartmental Centre for the study and research on HHT over a four-year period (2003–2007); three were excluded because of concomitant liver cirrhosis (two with hepatitis C virus, one with siderosis). Thus, the study population consisted of 153 patients, 80 males and 73 females (mean age 47 ± 15; range 15–75 yrs) including 124 subjects with definite diagnosis (presence of 3 Curaçao criteria: spontaneous recurrent epistaxis, mucocutaneous telangiectases, positive family history) and 29 with suspected diagnosis (2 positive criteria) for HHT. In particular, 10/29 patients had epistaxis and telangiectases, 11 patients showed a positive family history and telangiectases, eight had positive family history and recurrent epistaxis.

All individuals were subjected to clinical screening and biological tests to identify the presence of symptoms and signs of liver involvement, including serum transaminase activity, γ-glutamyl transferase activity, bilirubin, alkaline phosphatase, albumin, prothrombin time and ammonia; particular attention was focused on an eventual history of digestive hemorrhage, abdominal pain, hepatomegaly, ascites, symptoms and signs of heart failure [15,16]. According to the clinical features of Garcia-Tsao [15], patients were classified according to high output heart failure, portal hypertension and biliary disease. Moreover, screening for the detection of pulmonary, cerebral and gastrointestinal AVMs was performed by chest MSCT, cerebral MRI, endoscopy, respectively. In addition, genetic testing for the identification of gene mutations was carried out for all patients, according to techniques published elsewhere [17,18]. Other visceral AVMs (brain, lung, GI tract), providing the fourth criterion for HHT diagnosis, were found in 89/124 (72%) patients with definite HHT diagnosis, whereas the third criterion for definite diagnosis was provided for 26/29 patients with suspected diagnosis.

All 153 patients with and without HAVMs at ECD were subjected to liver MSCT scan which was considered the gold standard.

2.2. Non-HHT healthy controls

A total of 25 non-HHT healthy individuals without liver disease were utilized as a negative control group to further investigate the accuracy of ECD parameters, including seven members of HHT families and 18 healthy volunteers. The former referred to our HHT Center because of epistaxis and, due to a suspected diagnosis, were instrumentally evaluated to confirm/exclude the diagnosis of HHT and subjected to the single-(operator)-blind MSCT/ECD liver screening, as for all study patients; once the disease-causing mutation was identified in the family proband, subsequent genetic testing excluded their status as carriers of the familial HHT mutations. The 18 control volunteers were healthy subjects recruited among hospital personnel and subjected to the non-invasive ECD analysis. (However, the MSCT-based HAVM screening, a procedure involving radiation exposure, was considered unethical and thus avoided for this control subgroup).

2.3. Non-HHT cirrhotic patients

Fifteen hospitalized patients with non-HHT-related liver diseases were clinically diagnosed with liver cirrhosis based on liver biopsy in five cases and on clinical, laboratory and endoscopic findings in the remaining cases.

All HHT patients and controls (normal and cirrhotic patients) provided informed written consent to participate in this prospective study which was approved by the local Ethics Committee.