Research Article

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Identifying the presence of clinically significant hepatic involvement in hereditary haemorrhagic telangiectasia using a simple clinical scoring index

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Background & Aims: Though hepatic involvement is common in patients with hereditary haemorrhagic telangiectasia (HHT), symptomatic liver disease is rare but potentially fatal without liver transplantation. Factors associated with clinically significant liver disease in patients with HHT are unknown.

Methods: In this prospective cohort study, we included consecutive patients from 2001 to 2011 with definite HHT, who underwent systematic protocol screening including contrast-enhanced hepatic CT and/or abdominal ultrasound. Using a multivariable logistic regression model, we developed a simple clinical scoring index to identify the presence of symptomatic liver disease (cardiac failure, portal hypertension, or biliary disease) or 'at-risk' liver disease (asymptomatic patients, with hepatic bruit, abnormal liver biochemistry, or elevated cardiac index).

Results: Of 316 patients with definite HHT, 171 patients (54.1%; age 53.4 ± 15.2 y, 101 females) had hepatic involvement on imaging. Twenty-nine patients had symptomatic liver disease (22 patients with high-output heart failure); 45 patients were 'at-risk' for liver disease. Using multivariable logistic regression analysis, we derived a score using age, gender, hemoglobin and alkaline phosphatase at presentation which could accurately distinguish patients with clinically significant liver involvement from patients with no or incidental liver lesions (c-statistic = 0.80). A score <3 indicated low risk (<5%) and score >6 indicated high risk (>80%) of harboring clinically significant liver disease in HHT.

Conclusions: A simple scoring system can distinguish patients at low, moderate, and high risk of harboring clinically significant liver disease. With validation, this score may be used to identify patients for individualized screening and enrollment in clinical trials.

Introduction

Hereditary haemorrhagic telangiectasia (HHT) is an autosomal dominant genetic disease with high penetrance, and a prevalence of 1–2 cases per 10,000 population [1]. HHT is related to mutations in genes encoding proteins of the transforming growth factor-β pathways involved in vasculogenesis, resulting in formation of telangiectasias and vascular malformations (VMs) affecting the skin, mucous membranes, and multiple visceral organs, including the liver.

Hepatic involvement with VMs is observed in 41–84% of patients with HHT on doppler ultrasound or multiple slice computed tomography (CT) [2–5]. However, most of these patients are asymptomatic; symptoms attributed to liver VMs secondary to abnormal shunting between the hepatic artery, hepatic vein, and portal veins are observed in as few as 5–8% of patients [3,4,6]. In a recent prospective cohort study of 154 unselected HHT patients with hepatic involvement identified on screening, 5.2% died and 25.3% experienced complications due to liver VMs over a median follow-up of 44 months [7]. High-output heart failure, portal hypertension, and ischemic biliary disease are the most common manifestations [8]. Besides supportive management of high-output heart failure and portal hypertension, liver transplantation may be the only effective therapy for advanced disease, with excellent graft and patient survival [9,10]. More recently, bevacizumab, a vascular endothelial growth factor antagonist, has been shown to reduce cardiac output and induce regression of VMs in patients with high-output heart failure [11], serving as a bridge to liver transplantation and may also be effective in patients with severe ischemic cholangiopathy due to HHT [12].

Routine screening for hepatic involvement is not recommended by the HHT Foundation International, due to the small

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Abbreviations: AVMs, arteriovenous malformations; CT, computed tomography; HHT, hereditary haemorrhagic telangiectasia; VMs, vascular malformations.

proportion of symptomatic patients and lack of effective therapy which could modify disease course with early identification [13,14]. There is a great need, however, for early identification of patients with HHT with clinically significant liver disease to enable individualized and cost-effective screening as well as to identify patients who could participate in trials of potentially disease-modifying therapy [15].

Thus, the aims of the current study were: (a) to describe the pattern of hepatic involvement in a large cohort of patients with HHT and (b) to identify risk factors associated with the presence of clinically significant liver disease. From these data, we derived a simple clinical scoring index, which may be useful for distinguishing patients at low or high risk of harboring significant liver disease.

Patients and methods

Patients

After approval from the Institutional Review Board, in this prospective cohort study, we included consecutive adult patients ($\geqslant$18 years) from 2001 to 2011, referred to our HHT center. Patients with HHT were classified as 'definite', 'possible' or 'unlikely' based on presence of $\geqslant$3/4, 2/4 or <2/4 standard clinical Curacao criteria, respectively [spontaneous and recurrent epistaxis; multiple mucocutaneous telangiectasias; presence of visceral AVMs (pulmonary, gastrointestinal, hepatic, cerebral or other visceral organ involvement); family history of HHT in a first-degree relative] [16]. Patients with 'possible' HHT and characteristic mutations in the endoglin (ENG), activin receptor-like kinase type 1 (ALK1) or SMAD4 genes were classified as having 'definite' HHT. Using these criteria, out of 359 patients seen in the HHT clinic, 316 were identified as having 'definite' HHT and included in the study.

Evaluation

All patients with HHT underwent systematic screening for visceral arteriovenous malformations (AVMs).

(1) Pulmonary AVMs: All patients underwent transthoracic contrast echocardiography and pulmonary AVMs (PAVMs) were diagnosed if bubbles were seen in the left atrium after 4–6 cardiac cycles. Patients with a positive contrast echocardiogram bubble study then underwent computed tomography (CT) of the chest to confirm and measure the size of pulmonary AVMs, advised prophylactic use of antibiotics for dental procedures, and embolization was recommended if the feeding artery was >3 mm and/or accessible for intervention. Cardiac output (L/min) and cardiac index (L/min/m^2) were routinely reported on contrast echocardiography, calculated using the formula: Qc = $\prod \times d^2/4 \times VTI \times Qf$ (Qc: cardiac output, d: diameter of the left ventricular outflow tract; VTI: sub-aortic velocity time integral; Qf: cardiac frequency), and measured when hemoglobin was >9 mg/dl.
(2) Cerebral AVMs: All patients underwent magnetic resonance imaging of the brain to identify intra-cranial AVMs and/or capillary telangiectasia.
(3) Hepatic AVMs: All patients underwent multiphasic, multi-detector hepatic CT (n = 309 patients) or doppler ultrasound (n = 8 patients) to identify hepatic VMs, along with clinical evaluation for signs of hepatic involvement (audible bruit, palpable thrill, pulsatile liver and/or hepatomegaly) and liver biochemical panel (serum alanine and aspartate aminotransferase, alkaline phosphatase, bilirubin).
(4) Gastrointestinal AVMs: Routine screening for gastrointestinal AVMs in asymptomatic patients with HHT was not performed. If clinically indicated (for example, for severe anemia unexplained by epistaxis), patients underwent upper endoscopy and colonoscopy. A small minority of patients were identified as having gastrointestinal AVMs at time of hepatic CT and/or screening endoscopy for non-HHT indications. Additionally, on hepatic CT, pancreatic/splenic AVMs were also diagnosed based on presence of pancreatic telangiectasias or high-flow pancreatic VMs.

Genetic counseling and screening was offered to all patients with HHT. A subset of patients (n = 131), particularly those with 'possible' HHT, underwent genetic screening for mutations in endoglin and ALK1 genes (and if these were negative, then in SMAD4 gene) [17].

Definitions

Hepatic disease
The patterns of liver disease were defined as follows:

(1) Symptomatic liver disease: Patients with HHT with hepatic involvement were classified as having symptomatic disease if they had high-output heart failure (symptoms of heart failure with echocardiographic evidence of high cardiac index [$\geqslant$4 L/min/m^2]), portal hypertension (presence of esophageal varices/ascites), hepatic encephalopathy, or symptomatic biliary disease (history of recurrent cholangitis or abscess with imaging evidence of biliary abnormalities).
(2) 'At-risk' liver disease: Patients were classified as having 'at-risk' liver disease if they had imaging evidence of hepatic involvement due to HHT but without symptoms listed above, but with abnormal physical examination of the liver (audible bruit, palpable thrill, pulsatile liver and/or hepatomegaly); abnormal liver biochemistry (elevated serum alanine aminotransferase [>45 U/L] and aspartate aminotransferase [>43 U/L], alkaline phosphatase [>118 U/L] and/or bilirubin [>1 mg/dl]); and/or elevated cardiac index on echocardiography [15]. Patients with abnormal liver enzymes underwent clinically indicated evaluation for other causes of liver diseases by an experienced hepatologist (P.S.K.) before attributing disease to HHT.
(3) Incidental liver disease: Patients with normal liver physical examination and liver biochemistry with normal cardiac index in the presence of hepatic telangiectasias or VMs were classified as having incidental liver disease.

Patients with symptomatic liver disease or 'at-risk' liver lesions were classified as having clinically significant liver disease [15]. Based on imaging findings, hepatic involvement was classified as 'early' (liver VMs or telangiectasias or hepatic artery dilation) or 'advanced' (portal vein or hepatic vein dilation or abnormal flow, or large AV fistulae, or presence of focal nodular hyperplasia [FNH]), derived from criteria suggested by Gincul *et al.* [18].

Extra-hepatic disease
Definitions of severe epistaxis, symptomatic pulmonary and gastrointestinal VMs are reported in the Supplementary data.

Follow-up
All patients were prospectively followed-up clinically with or without imaging depending on severity of disease, at intervals of 6 months to 3 years at the discretion of the treating physicians.

Statistical analysis
Statistical analysis was performed using SAS, version 9.1 software (Cary, NC). Data are presented as mean (and standard deviation [SD]) or median (and inter-quartile range [IQR]). Proportions and categorical variables were compared using χ^2 or Fisher's exact tests as appropriate. Continuous variables were compared using Student's *t* test.

Multivariable logistic regression analysis was used to identify factors associated with the presence of clinically significant liver disease (symptomatic liver disease or 'at-risk' liver disease). These included demographic (age, sex), clinical (other visceral organ AVMs including lung, brain, gastrointestinal tract or pancreas; presence of severe epistaxis, transfusion-dependent anemia; symptomatic pulmonary involvement), and laboratory features (hemoglobin, AST, ALT, alkaline phosphatase, bilirubin at presentation). From this multivariable logistic regression model, we developed a simple clinical scoring index to identify clinically significant liver disease in this cohort of patients with HHT. Time-to-event analysis using Kaplan-Meier curves and log-rank test was performed to estimate transplant free-survival in patients with different patterns of liver involvement.

Results

Three hundred and sixteen patients (age 46.3 ± 17.4 years, 179 females) were identified as having 'definite' HHT. Genotype information was available for 131 patients – 64 (48.9%) patients were noted to have a mutation of the *ENG* gene (HHT type 1) and 45 (34.4%) were identified as having a mutation of the *ALK1* gene