Respiratory Medicine (2015) 109, 768–777

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/rmed

Prevalence and nature of dyspnea in patients with hereditary hemorrhagic telangiectasia (HHT)

Dmitry Rozenberg [a], Eva Leek [b], Marie E. Faughnan [b,c,*]

[a] Division of Respirology, Department of Medicine, University of Toronto, Toronto General Hospital, Canada
[b] Toronto HHT Centre, Division of Respirology, Department of Medicine, University of Toronto, St. Michael's Hospital, Toronto, Canada
[c] Li Ka Shing Knowledge Institute of St. Michael's Hospital, Toronto, Canada

Received 31 October 2014; accepted 7 April 2015
Available online 15 April 2015

KEYWORDS
Hereditary hemorrhagic telangiectasia;
Pulmonary arteriovenous malformation;
Dyspnea

Summary
Background: Hereditary hemorrhagic telangiectasia (HHT) is a vascular disorder associated with pulmonary AVMs (PAVMs), present in about 30–50% of patients. Dyspnea is frequently reported by about one-half of patients with PAVMs and has been related to the degree of right to left shunting. However, many HHT patients with PAVMs remain asymptomatic and those without PAVMs have been observed to have dyspnea, the cause of which has not been characterized. The study objectives were to determine the prevalence of dyspnea and its etiology in the HHT population.
Methods: Retrospective review of over 1000 patients at an HHT Center of Excellence from 1997 to 2010. Patients were categorized as definite HHT if they met $\geq$3 clinical diagnostic criteria or had a positive genetic diagnosis. Patients were unlikely to have HHT (non-HHT) if they had 1 or fewer diagnostic criteria. Data on dyspnea prevalence (MMRC $\geq$ 1), PAVMs, underlying cardiopulmonary disease, symptomatic liver venous malformations, anemia and obesity was reviewed.
Results: 506 patients were categorized as having HHT, of which 202 (40%) had confirmed PAVMs. Dyspnea prevalence was 35% (178/506) vs. 18% (50/284, $p < 0.0001$) in the HHT and non-HHT patients, respectively. With multivariable logistic regression, the odds of dyspnea (MMRC $\geq$1) was 3.45 (95% CI 2.08–5.71) with the presence of PAVMs in HHT patients. Other independent predictors of dyspnea were older age, underlying cardio-pulmonary disease, anemia, and obesity.

* Corresponding author. St. Michael's Hospital, University of Toronto, 30 Bond Street, Suite 6049, Toronto, Ontario, M5B 1W8, Canada. Tel.: +1 416 864 5412; fax: +1 416 864 5922.
E-mail address: Faughnanm@smh.ca (M.E. Faughnan).

http://dx.doi.org/10.1016/j.rmed.2015.04.003

Conclusion: Prevalence of dyspnea is significant, evident in about one-third of HHT patients, often associated with PAVMs. It is important to consider other etiologies for dyspnea when assessing patients with HHT.

Abbreviations

AVMs	Arterio-venous Malformations
BMI	Body Mass Index
CAVMs	Cerebral Arterio-venous Malformations
CT	Computed Tomography
DLCO	Diffusion Capacity
FEV_1	Forced Expiratory Flow in 1 second
FVC	Forced Vital Capacity
GI	Gastrointestinal
HHT	Hereditary Hemorrhagic Telangiectasia
IQR	Interquartile Range
LVMs	Liver Vascular Malformations
MMRC	Modified Medical Research Council Dyspnea Scale
PAH	Pulmonary Arterial Hypertension
PAVMs	Pulmonary Arterio-venous Malformations
PFT	Pulmonary Function Test
RVSP	Right Ventricular Systolic Pressure
TLC	Total Lung Capacity
TTCE	Trans-thoracic Contrast Echocardiogram

Introduction

Hereditary hemorrhagic telangiectasia (HHT) is an autosomal dominant disorder, with an estimated prevalence of 1 in 5000 [1]. It is characterized by vascular dysplasia in the form of muco-cutaneous telangiectases and arterio-venous malformations (AVMs) in the lungs, brain, liver and gastrointestinal (GI) tract.

Patients with HHT often report dyspnea with the etiology generally attributed to pulmonary AVMs (PAVMs), which are present in 30—50% of HHT patients [1—3]. Dyspnea has been reported in about one-half of patients with PAVMs [1,2,4,5] and felt to be related to the degree of right to left shunting [5]. However, many patients with PAVMs remain asymptomatic during exercise due to reduced pulmonary vascular resistance and increased cardiac output adaptation [6]. Furthermore, most patients with PAVMs undergo transcatheter embolotherapy to prevent future complications with excellent procedural success (close to 100%) and long-term efficacy (>83%) in several long term series [7,8]. Despite the high procedural success of embolotherapy, a large proportion of patients remained dyspneic in one case series of 39 patients with bilateral PAVMs despite successful embolotherapy [9].

There are other known causes of dyspnea which have been investigated in HHT. High output heart failure from liver vascular malformations (LVMs) has been suggested as another potential etiology for dyspnea, but represents only a small proportion of patients [10,11]. Similarly, idiopathic pulmonary hypertension has been described in HHT, but is also uncommon [12]. However, other more common causes of dyspnea such as anemia and non-HHT related cardiopulmonary diseases have not been investigated in HHT patients.

Given the clinical and diagnostic implications of dyspnea in the general HHT population, we proposed to study the prevalence of dyspnea in an unselected group of HHT patients and to characterize the etiology of dyspnea in this population.

Methods

Study design

Retrospective chart and database review of 1015 consecutive patients evaluated at the Toronto HHT Centre of Excellence, from January 1997 to December 2010. The Toronto HHT Centre is based at St. Michael's Hospital (SMH), a tertiary care facility affiliated with the University of Toronto, which receives referrals from across Canada (80% from Ontario). The study was approved by SMH's Research Ethics Board (#10—108) and all patients had consented to be included in the Toronto HHT Database for research purposes.

Toronto HHT database

The HHT Database is a File-Maker Pro relational database (Filemaker Inc., Santa Clara, CA) which includes patients assessed at the Toronto HHT Centre from 1997 to present. All patients have undergone a comprehensive history and physical examination by an HHT physician/pulmonologist (M.E.F.) and routine screening for PAVMs and CAVMs. Patients are not routinely screened for other vascular malformations (liver, spinal, gastrointestinal) unless symptomatic. Data from the initial clinical assessment and follow-up visits is entered into the database on past medical history, medications, laboratory and imaging investigations, genetic testing and family history.

Definition of HHT and patient selection

Consecutive patients were categorized as HHT or non-HHT. Patients were classified as HHT if they met 3 or more clinical diagnostic criteria (epistaxis, muco-cutaneous telangiectases, visceral lesions, first degree relative) or had a positive genetic diagnosis. Patients were categorized unlikely to have HHT (non-HHT) if they had 1 or fewer