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EDITORIAL

Pulmonary hypertension in hereditary haemorrhagic telangiectasia

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Abstract

Hereditary haemorrhagic telangiectasia (HHT) is an autosomal dominant inherited disorder characterised by vascular malformations in predominantly the brain, liver and lungs. Pulmonary hypertension (PH) is increasingly recognised as a severe complication of HHT. PH may be categorised into two distinct types in patients with HHT. Post-capillary PH most often results from a high pulmonary blood flow that accompanies the high cardiac output state associated with liver arteriovenous malformations. Less frequently, the HHT-related gene mutations in ENG or ACVRL1 appear to predispose patients with HHT to develop pre-capillary pulmonary arterial hypertension. Differentiation between both forms of PH by right heart catheterisation is essential, since both entities are associated with severe morbidity and mortality with different treatment options. Therefore all HHT patients should be referred to an HHT centre.

Key words: Hereditary haemorrhagic telangiectasia; High cardiac output; Pulmonary arterial hypertension; ENG; ACRVL1; Pulmonary hypertension

Core tip: Pulmonary hypertension (PH) is increasingly recognised as a severe complication of hereditary haemorrhagic telangiectasia (HHT), but the true prevalence of PH in HHT is not known. Post-capillary PH most often results from the high cardiac output associated with hepatic arteriovenous malformations. More rarely the HHT gene mutations (ACRVL1 or ENG) result in pre-capillary pulmonary arterial hypertension (PAH). Differentiation between post-capillary PH en pre-capillary PAH can be done by right heart catheterisation, and is of importance since both entities are associated with severe morbidity and mortality and have different options for treatments.

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HEREDITARY HAEMORRHAGIC TELANGIECTASIA

Hereditary haemorrhagic telangiectasia (HHT), also known as Rendu-Osler-Weber syndrome, is an autosomal dominant inherited disorder with late onset penetrance (nearly 97% at the age of 60 years) characterised by vascular malformations with an estimated prevalence of 1:5000 individuals[1,2]. The abnormal vascular structures in HHT range from small telangiectasia of the skin and mucosal membranes to arteriovenous malformations (AVMs) in predominantly the brain, liver and lungs[3,4].

Genetics and pathogenesis

HHT consist of two main subtypes, HHT type 1 and HHT type 2, which results from mutations in the ENG gene on chromosome 9, encoding the protein endoglin and from mutations in the activin receptor-like kinase (ACVRL1) gene on chromosome 12, encoding the protein ALK-1 respectively[5,6]. A third disease-causing mutation has been found in the *SMAD4* gene, causing a combination of the juvenile polyposis syndrome and HHT[7] . Most HHT families have a unique mutation and many types of mutations have been described.

The exact pathogenesis of HHT is still unclear. However, hypoxia or local hemodynamic changes could act as a possible trigger promoting tissue inflammation or endothelial cell injury[8,9]. Both endoglin, ALK-1 and SMAD4 proteins are endothelial receptors of the transforming growth factor β (TGF-β) superfamily. All three proteins cooperate in the TGF-β/ALK-1 signalling pathway, which is involved in angiogenesis. In HHT, most vessels are normal, but the mutations in ACVRL1 and ENG result in abnormal angiogenetic responses and lead to the formation of abnormal arteriovenous connections, ranging from small telangiectases that bleed easily, to large arteriovenous malformations, that can occur in every organ, but especially in the lungs, liver and brain[10,11].

Diagnosis

The clinical diagnosis can be based on the four Curaçao criteria[1], which consist of: (1) Spontaneous, recurrent epistaxis; (2) Multiple telangiectasia at characteristic sites (lips, oral cavity, fingers, nose); (3) Visceral lesions (gastrointestinal telangiectasia, pulmonary, hepatic, cerebral or spinal AVMs); and (4) A first degree relative with HHT.

Three criteria suffice for a definitive diagnosis of HHT, two criteria are considered as "possible" HHT, and one or no criterion makes the diagnosis "unlikely". The positive predictive value for a definite clinical diagnosis and the negative predictive value for an unlikely diagnosis are excellent (100% and 97.7% respectively), when compared with DNA testing[12]. However, HHT has an age dependent penetrance and the clinical presentation varies among patients[1]. Therefore genetic testing has emerged as an important tool to help make the diagnosis in paediatric patients and younger adults with a "possible" clinical diagnosis[12].

PULMONARY HYPERTENSION

Pulmonary hypertension (PH) is a haemodynamic and pathophysiological condition defined as an increase in mean pulmonary arterial pressure (mPAP) of equal to or more than 25 mmHg as assessed by right heart catheterisation (RHC)[13]. PH is a progressive disease of many origins, affecting more than 100 million people world wide[14]. The elevated pressure in the pulmonary circulation can lead to various symptoms including limited exercise capacity and dyspnoea on exertion. The chronic elevated pressure may ultimately result in right-sided heart failure and premature death[13].

Depending on the origin, PH can be divided into two main groups; pre- and post capillary PH. Patients with pre-capillary PH are characterised by a mPAP $\geqslant$ 25 mmHg, pulmonary artery wedge pressure (PAWP) $\leqslant$ 15 mmHg, and elevated pulmonary vascular resistance (PVR) (> 3 Wood units)[15]. Pre-capillary PH can be further divided in different clinical groups, based on pathophysiological mechanisms, clinical presentation and therapeutic options (Table 1)[13].

Transthoracic echocardiography is the cornerstone for screening in all patients suspected of PH. Typically, a dilatation of the right ventricle with septal flattening (also called D-sign) and an increase in right ventricular systolic pressure (RVSP) (sum of right ventricle-right atrium pressure gradient and estimated pressure in the right atrium based on the dimension and collapse of the inferior caval vein) (Figure 1)[13,16].

PH and hereditary haemorrhagic telangiectasia

PH is increasingly recognised as an important complication of HHT. HHT associated PH can occur by several mechanisms. Most often, post-capillary PH may develop as a consequence of a hyperkinetic state resulting in heart failure associated with high cardiac output (CO) due to hepatic arteriovenous malformations (HAVMs) (Figure 2)[17], while less frequently, precapillary PH can be related to pulmonary arterial hypertension (PAH) characterised by remodeling of small pulmonary arteries with broadly similar histologic lesions than observed in idiopathic PAH[17]. The HHT-related gene mutations (ENG or ACVRL1) appear to predispose for the development of PAH[18-22]. Various studies found a high estimated prevalence of PH in HHT when screening with echocardiography[23,24]. An elevated RVSP on echocardiography was found in 9 (20.5%) out of 44 HHT patients (22 ACVRL1, 3 ENG, 19 unknown mutation), in 7 out of these 9 subjects an *ACVRL1* gene was found[23]. Sopeña *et al*[24] found a high estimated prevalence of PH (31%) in 29 hospitalised patients with HHT with a mean estimated RVSP of 73 ± 17.0 mmHg measured with echocardiography. HAVMs were

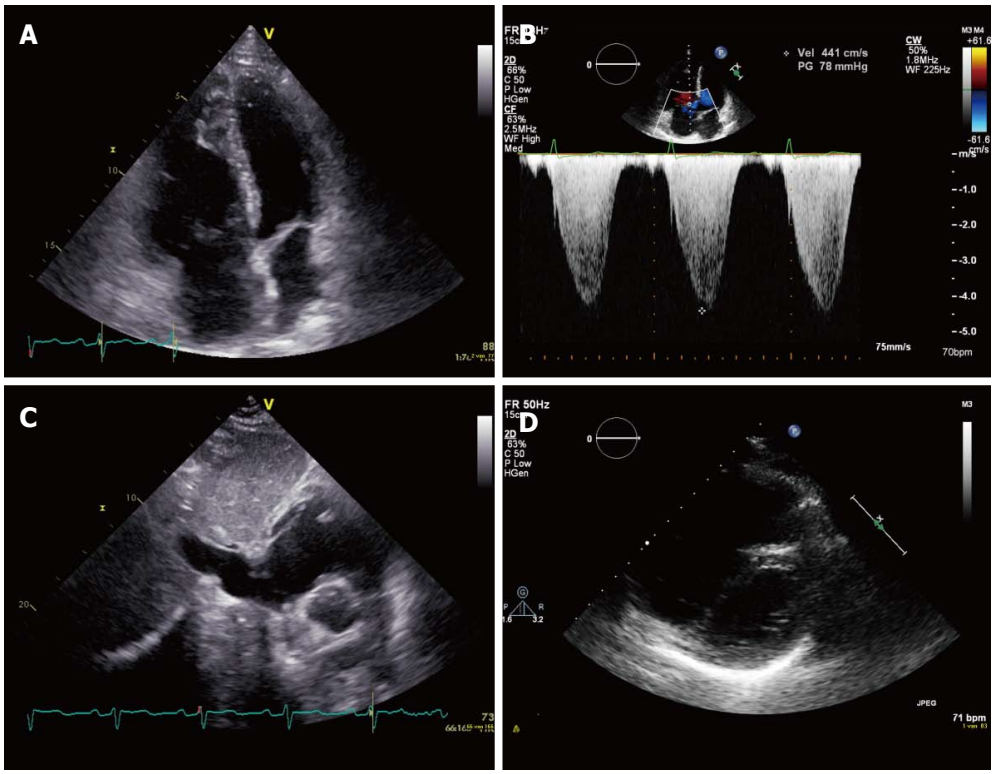

Figure 1 Characteristic echocardiogram of a patient with pulmonary hypertension. A: Apical 4-chamber view showing dilatation of the right ventricle; B: Apical 4-chamber view with Doppler signal (continuous wave) showing an increased right ventricular- right atrial pressure gradient (4.4 m/s); C: Subcostal view showing dilatation of the inferior caval vein corresponding with an increased pressure in the right atrium; D: Parasternal short axis view showing flattening of the interventricular septum (D-sign) and dilatation of the right ventricle.

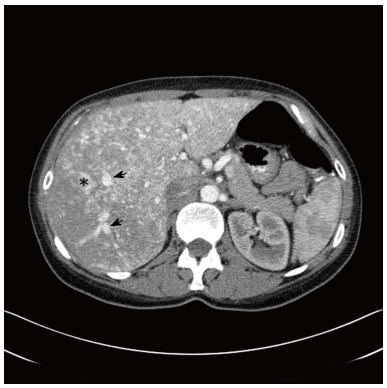

Figure 2 Hepatic arteriovenous malformations. Computed tomography with contrast in arterial fase showing extensive filling of the hepatic veins (arrows), and diffuse hepatic arteriovenous malformations (asterix).

documented in 67% of these patients. However, large observational studies including consecutive HHT patients are lacking.

Since the treatment strategies differ between post-capillary high-output PH and pre-capillary PAH, it is important to differentiate between these two different entities. RHC is the gold standard for making the diagnosis of both high-output PH and PAH[13,17,25].

In PAH, the mPAP is usually higher with an increase in PVR and transpulmonary gradient due to arteriopathy. Most often a normal or decreased CO and PAWP is seen. In high-output PH on the other hand, there is only a moderate increase in mPAP, with a normal PVR, elevated PAWP and most importantly, an increased CO (Table 2)[13,17].

High output PH

High-output heart failure is the most common initial presentation of HAVMs in HHT. Liver involvement is present in 32%-78% of the HHT patients and is predominantly seen in HHT type 2[1,26-28]. The presence of symptoms is directly associated with significant morbidity and mortality and therefore, screening for liver AVMs with Doppler ultrasound is warranted in all patients who are symptomatic or have abnormal liver enzymes[1,25]. In the majority of cases, only small telangiectasia are seen, which do not lead to symptoms. However, large HAVMs exist in typically three different and often concurrent types of intrahepatic shunting; from the hepatic arteries to hepatic veins, from the hepatic arteries to portal veins, and from the portal veins to hepatic veins[17,25]. These hepatic shunts can lead to high-output cardiac failure, portal hypertension, biliary ischaemia or encephalopathy with a wide range of symptoms[25]. Overall, symptoms due to HAVMs occur in 8% of HHT patients and predominantly in females[29]. Symptoms of high-output cardiac failure usually develop in females between 50 and 70 years of age and are characterised by dyspnoea on exertion,

Table 1 Updated classification of pulmonary hypertension

Pulmonary arterial hypertension
Idiopathic PAH
Hereditable PAH
BMPR2
ALK1, endoglin (with or without hereditary haemorrhagic telangiectasia), SMAD9, CAV1, KCNK3
Unknown
Drug and toxin induced
Associated with:
Connective tissue diseases
HIV infection
Portal hypertension
Congenital heart diseases
Schistosomiasis
Pulmonary veno-occlusive disease and/or pulmonary capillary haemangiomatosis
Persistent pulmonary hypertension of the newborn
Pulmonary hypertension due to left heart disease
Left ventricular systolic dysfunction
Left ventricular diastolic dysfunction
Valvular disease
Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies
Pulmonary hypertension due to lung diseases and/or hypoxia
Chronic obstructive pulmonary disease
Interstitial lung disease
Other pulmonary diseases with mixed restrictive and obstructive pattern
Sleep-disordered breathing
Alveolar hypoventilation disorders
Chronic exposure to high altitude
Developmental abnormalities
Chronic thromboembolic pulmonary hypertension
PH with unclear and/or multifactorial mechanisms
Haematological disorders: chronic haemolytic anaemia, myeloproliferative disorders, splenectomy
Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis
Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
Others: tumoural obstruction, fibrosing mediastinitis, chronic renal failure, segmental PH

PH: Pulmonary hypertension; BMPR2: Bone morphogenetic protein receptor, type 2; CAV1: Caveolin-1; HIV: Human immunodeficiency virus. Adapted from Simonneau *et al*[46], with permission of the publisher.

fatigue, orthopnoea, ascites and/or oedema[17,29].

Pathophysiology of high output PH: Exercise testing in healthy persons revealed that an increase in CO leads to an elevation in pulmonary artery pressure (increase in mPAP up to 0.5 to 3.0 mmHg/L per minute)[30].

In patients with HAVMs, shunting of blood from the hepatic arteries and/or portal veins to the hepatic veins results in a hyperdynamic state, in which the CO can be elevated two-to-three fold[31]. Besides this cause of high cardiac output, severe epistaxis or gastro-intestinal bleeding in patients with HHT may lead to anaemia with a compensatory increase in CO as well.

In HHT, a multifactorial cascade will eventually lead to high-output cardiac failure. At first, the increase in CO will be compensated by dilatation of the pulmonary arteries and thereby pulmonary pressure will still be maintained. An increase in left atrial (LA) pressure will predispose patients for atrial fibrillation (due to enlargement of the LA) and diastolic dysfunction of the left ventricle. Increased LA pressure and impaired pulmonary vasodilatation will eventually result in PH. The combination of volume and pressure overload leads to right ventricular (RV) dilatation, decreased systolic function of the RV and subsequent right heart failure. Severe bleeding (*e.g.*, epistaxis or gastro-intestinal bleeding) may trigger the cascade because of the subsequent increase in CO[17,29,31].

Table 2 Haemodynamics in pulmonary hypertension associated with hereditary haemorrhagic telangiectasia

	High output PH	PAH
mPAP (mmHg)	+	++
PAWP (mmHg)	=/+	=
PVR (Wood units)	=	++
CO (L/min)	++	-

PH: Pulmonary hypertension; PAH: Pulmonary arterial hypertension; mPAP: Mean pulmonary artery pressure; PAWP: Pulmonary artery wedge pressure; PVR: Pulmonary vascular resistance; CO: Cardiac output. +: Increase; =: Normal; -: Decrease. Adapted from Faughnan *et al*[17], with permission of the publisher.

Treatment of high output PH: The first-line treatment of PH associated with a high-output state consists of intensive medical treatment including salt restriction and diuretics, correction of anaemia, antihypertensive and antiarrhythmic agents and digoxin if necessary[9]. In patients refractory to medical-therapy, liver transplantation is the best option, with a 5-year survival of 83% in a series of 40 patients[29]. However, a high post-operative morbidity is seen[25,32].

Recently, Dupuis-Girod *et al*[33] treated 25 patients with severe HAVMs and a high CO [median cardiac index (CI) 5.1 L/min per square meters (range 4.1-6.2 L/min per square meters)] with bevacizumab, a vascular endothelial growth factor inhibitor. This treatment resulted in a significant decrease in CO [median CI at 6 mo 4.1 L/min per square meters (range 3.0-5.1 L/min per square meters)], normalisation of the pulmonary pressure in 5 out of 8 patients with PH at baseline and clinical improvement of dyspnoea[33]. Other invasive treatments such as surgical hepatic artery ligation or transcatheter therapeutic embolisation of the hepatic artery are associated with a high morbidity and mortality and therefore not recommended[1,17].

PAH

PAH is a clinical condition characterised by the presence of pre-capillary PH due to arteriopathy with media hypertrophy and intima proliferation. It is increasingly recognised as a severe complication of HHT.

There have been a few case series that describe the association between PAH and HHT, however these series all included patients with PH in which HHT

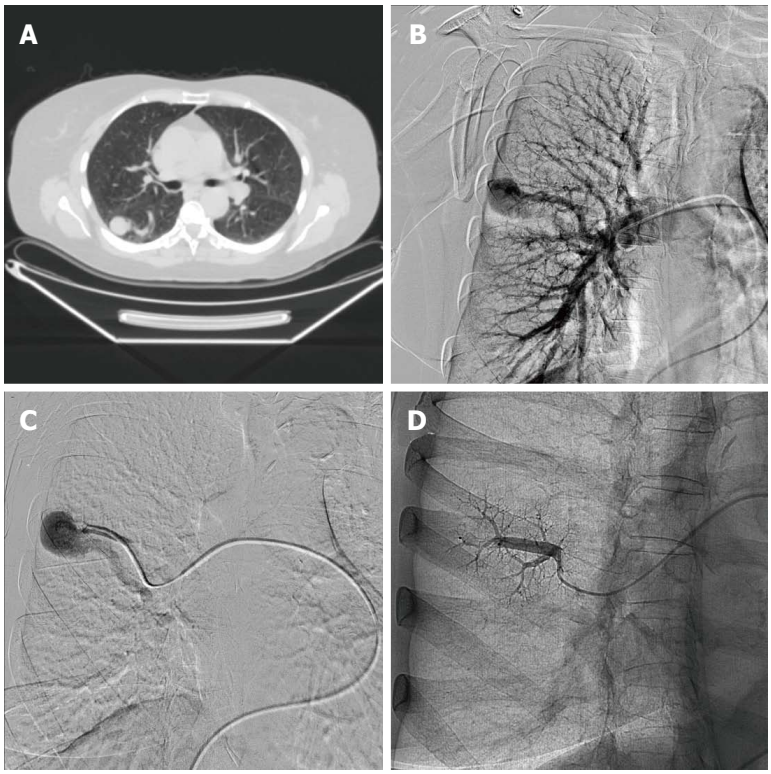

Figure 3 Pulmonary arteriovenous malformations. A: Computed tomography of the chest with large pulmonary arteriovenous malformation (PAVM) in the lower lobe of the right lung; B: Pulmonary angiogram of the PAVM in the same patient; C: Selective pulmonary angiogram of the PAVM in the apex of the lower lobe of the right lung; D: Repeat angiogram after transcatheter embolisation of the PAVM with a vascular plug.

symptoms were also present[18-22].

Pathophysiology and genetics of PAH: In 2001, it was demonstrated for the first time that different mutations in ACVRL1 predispose patients for the development of PAH[18]. This was confirmed in a few case series describing the presence of PAH in patients with an *ACVRL1* mutation and clinical features of HHT[19,21,22]. Trembath *et al*[18] described that mutations in *ACVRL1* may lead to both occlusion of the pulmonary arteries together with vascular dilatation, manifested as AVMs in HHT. Although less frequently, ENG mutations have also been identified in patients with both HHT and PAH, suggesting a less potent association between endoglin and PAH[18,19]. Mutations in the bone morphogenic protein receptor type 2 gene, which is another gene encoding the endothelial surface protein components of the TGF-β receptor that is detected in approximately 70% of the patients with hereditable PAH, were not found in HHT associated PAH[34].

Prognosis: The clinical outcomes of patients with PAH caused by an ACVRL1 mutation have been analysed in 32 patients and compared to other PAH patients without this mutation. PAH caused by an *ACVRL1* mutation was found in significantly younger patients (mean age 21.8 ± 16.7 years) and had a significantly shorter survival, despite similar therapy[34]. No data exist about the prognosis of patients with *PAH* and *ENG* mutations. The overall prognosis of PAH in general ranges from 6 mo to several years based on the underlying disease[13].

It is noteworthy that *ACVRL1* mutation carriers may develop severe PAH without any clinical evidence of HHT because of the early development of PAH in these patients and the late-onset penetrance of ACVRL1 mutation for HHT manifestations[34].

Treatment of PAH in HHT: No systematic evidence exists for treatment of HHT patients with PAH. It seems rational to treat patients according to the guidelines for PAH, with PAH-specific medication and supporting therapy (diuretics, oxygen, and digoxin)[13].

Today there are three different groups of PAH specific medication; endothelin receptor antagonists (ERA), phosphodiesterase inhibitors (PD5I) and prostacyclins. There are two case-reports that describe successful treatment of PAH in HHT patients with the ERA bosentan. After treatment, improvement of symptoms, exercise capacity and laboratory findings and a decrease in mPAP were found[35,36].

There are no reports describing the treatment with other PAH specific medication in patients with PAH and HHT. Since there was no response to acute vasodilator challenge in 32 patients with HHT and PAH, there is probably no role for the use of calcium channel blockers in this population[17,34]. And due to an increase in bleeding complications regular treatment with oral anticoagulation is not advised[1]. However, based on recent literature, treatment with anticoagulation could be considered on a case by case basis[37].

Pulmonary arteriovenous malformations in PH: The coexistence of PH and pulmonary arteriovenous malformations (PAVMs) has specific clinical and therapeutic implications. PAVMs are low-resistance, high-flow abnormal vascular structures that bypass the

normal capillary filter and thereby result in permanent pulmonary right-to-left shunting (Figure 3A-C)[38-40]. Paradoxical embolisation through these PAVMs can lead to severe neurological complications, such as a stroke or brain abscess[1,40]. Contrast echocardiography is the screening test of choice (sensitivity up to 98.6%), with a direct relationship between shunt grade and prevalence of cerebral manifestations in patients screened for HHT[40-42]. To avoid neurologic and bleeding complications, PAVMs can be treated with transcatheter embolisation with coils or plugs (Figure 3D)[1,43]. It may be expected that closing this low resistance system will result in a rise in mPAP. Measuring the pulmonary pressure before and after embolisation of PAVMs in 43 patients, Shovlin *et al*[44] found no significant found no significant increase in mPAP after embolisation, even in patients with pre-existing mild to moderate PH.

A possible explanation is a decrease in CO after embolisation which has a greater effect on the PVR than occlusion of the PAVMs. This fall in CO immediately after PAVM closure was recently described in 29 HHT patients by Vorselaars *et al*[45]. Furthermore, PAVM-related hypoxemia can induce vasoconstriction with a concomitant increase in PVR. Both studies described an increase in saturation after embolisation which may result in a decrease in pulmonary vasoconstriction and thereby PVR[44,45]. One case report described a fatal rupture of a PAVM in a patients with severe PAH. Although patients with severe PH were excluded from the above studies, it would be prudent to consider that the higher the mPAP and PVR at baseline and the larger the PAVM, the greater likelihood of worsening PH after embolisation[44].

Further research and recommendations

Although a number of studies described patients with PH and HHT, no data are available about the exact prevalence of PH in the overall HHT population. Most studies used a small sample size of highly selected patients and data from RHC are lacking. Therefore we recommend to perform a systematic screening to reveal the true prevalence of both forms of PH with their different aetiologies in a HHT population.

Because of the non-specific symptoms and potentially fatal prognosis, all HHT patients should be referred to an HHT centre of excellence.

CONCLUSION

PH is increasingly recognised as a severe complication of HHT, but the true prevalence of PH in HHT is still unknown. PH in HHT is mostly post-capillary in origin and results from high cardiac output due to HAVMs and anaemia. Rarely ACRVL-1 or ENG mutations results in pre-capillary PAH. Differentiation between both forms of PH in HHT by RHC is essential, since both entities are associated with severe morbidity and mortality with different specific treatment options. Therefore all HHT patients should be referred to an HHT centre.

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