Early-life pulmonary arterial hypertension with subsequent development of diffuse pulmonary arteriovenous malformations in hereditary haemorrhagic telangiectasia type 1

C J Mache,1 A Gamillscheg,1 H H Popper,2 S G Haworth3

ABSTRACT
The case history is presented of a male infant who was thought to have idiopathic pulmonary arterial hypertension (PAH) at 3 months of age. Subsequently the PAH decreased unexpectedly and diffuse pulmonary arteriovenous malformations (PAVMs) were seen at 6.9 years of age for the first time. Hereditary haemorrhagic telangiectasia type 1 (HHT1) related to an endoglin mutation was diagnosed. At 10.3 years of age a lung biopsy showed diffuse PAVMs as well as pulmonary arteriopathy with medial hypertrophy. This is the first case of HHT1 presenting with PAH at such a young age. The subsequent decrease in pulmonary arterial pressure (PAP) was probably caused by the development of PAVMs. In the presence of PAVMs, measurement of the PAP may underestimate the extent of PAH-related vasculopathy.

Pulmonary arterial hypertension (PAH) is defined as a mean pulmonary artery pressure (mPAP) of >25 mm Hg at rest or >30 mm Hg during exercise, with an increased pulmonary vascular resistance index (PVR) of >5 Wood units (WU).m2 and a normal pulmonary artery wedge pressure (PAWP) of ≤15 mm Hg. The currently used clinical classification of PAH (Venice, 2005) distinguishes between idiopathic sporadic and familial PAH and PAH related to cardiac or systemic disease, and a number of risk factors and associated conditions for PAH have been identified.1 In the past, the idiopathic form of PAH in childhood had a particularly poor prognosis with a median survival of <1 year.2 Mutations in genes encoding members of the transforming growth factor (TGF)-β receptor have been identified in some of these patients, indicating an aetiological role for the TGF-β pathway.3

DISCUSSION
Familial PAH and HHT are autosomal dominant disorders of the vascular system caused by mutations of genes encoding TGF-β receptor components including bone morphogenetic protein receptor type 2 (BMPR2), activin receptor-like kinase 1 (ALK1) and endoglin (ENG).4 Heterozygous mutations in BMPR2 have been identified in the majority of familial PAH cases and up to 26% of patients with sporadic PAH.7 HHT1 is related to mutations in ENG.8 In HHT2, mutations in ALK1 are seen.9 The association between PAH and HHT occurs predominantly in HHT2.10 HHT1-related PAH has been reported in three adults.9 However, these patients had conditions or risk factors that might have contributed to the development of PAH, such as pulmonary embolism, extensive liver arteriovenous malformations with increased cardiac output and a raised PAWP, or a history of dexfenfluramine intake.9 In contrast, our patient with early-life PAH in HHT1 provides evidence that defective

1 Department of Pediatrics, Medical University Graz, Graz, Austria; 2 Institute of Pathology, Medical University Graz, Graz, Austria; 3 Institute of Child Health, London, UK

Correspondence to: Dr C J Mache, Department of Pediatrics, Medical University Graz, Auenbruggerplatz 30, A-8036 Graz, Austria; christoph.mache@meduni-graz.at

Accepted 4 April 2007

Received 4 December 2006

Thorax 2008;63:85–86. doi:10.1136/thx.2007.076109
endoglin signalling by itself may lead to PAH. The parental observation of recurrent cyanosis since birth is in accordance with the hypothesis that FVR may not decrease normally after birth in some neonates with PAH being diagnosed at a later date as the pulmonary vascular disease progresses. In our patient PAH preceded the diagnosis of PAVMs. This clinical course raises the issue whether PAH promoted the early development of PAVMs in this patient with a genetic susceptibility.

HHT is characterised clinically by recurrent epistaxis, mucocutaneous telangiectases and visceral arteriovenous malformations. More than 20% of patients with HHT develop PAVMs, ranging from diffuse PAVMs to large complex structures. In our patient the decrease in mPAP was associated with the development of PAVMs. It is probable that PAVMs were present before the age of 6.9 years because microscopic PAVMs cannot be excluded by pulmonary angiography. An unexpected decrease in mPAP in a patient with PAH should therefore alert the clinician to screen for PAVMs with highly sensitive contrast echocardiography. Conversely, in PAVMs pulmonary haemodynamics may not reflect the extent of PAH-related vasculopathy. In PAVMs and borderline PAH, histological examination may help to assess the severity of the pulmonary arteriopathy.

Competing interests: None.

REFERENCES
Early-life pulmonary arterial hypertension with subsequent development of diffuse pulmonary arteriovenous malformations in hereditary haemorrhagic telangiectasia type 1

C J Mache, A Gamillscheg, H H Popper and S G Haworth

Thorax 2008 63: 85-86
doi: 10.1136/thx.2007.076109