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Research letter

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PULMONARY HYPERTENSION IN HEREDITARY HEMORRHAGIC TELANGIECTASIA IS ASSOCIATED WITH MULTIPLE CLINICAL CONDITIONS

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Hereditary hemorrhagic telangiectasia (HHT) is a rare autosomal dominant vascular disorder. The prevalence of pulmonary hypertension (PH), in the course of the disease, is considered lower than 10% [1-4]. As previously reported, the increase of pulmonary arterial pressure, in this sitting, may result from different mechanisms: isolated high flow state, PH due to left heart disease secondary to high cardiac output in the presence of hepatic arteriovenous malformations (post-capillary PH, clinical classification group 2) or can result from pulmonary vascular remodeling (pre-capillary PH) [1-3]. For this last case, the diagnosis of heritable PAH (group 1.2) could be applicable, as genetic mutations in the transforming growth factor-beta (TGF-β) signaling pathway (*ALK1, ENG*) are always found [5].

Here, we hypothesized that several causes or risk factors may be associated in this genetically susceptible population to promote the occurrence of pre-capillary PH. Therefore, a study was conducted in HHT patients from a large single-center cohort. During the study period (1995 to 2018), all consecutive patients with a definite diagnosis of HHT referred to the French National Reference Center for HHT (Lyon, France) were invited to participate to a prospective cohort study. In a second time, pre capillary pulmonary hypertension cases have been studied retrospectively. This registry was set up in agreement with French bioethics laws.

Patients who underwent a right heart catheterization (RHC) has been classified into 3 hemodynamic profile sub-groups according to current definitions of PH [6]: pre-capillary PH (mean pulmonary arterial pressure [mPAP] >20mmHg, pulmonary artery wedge pressure [PAWP] ≤15mmHg, pulmonary vascular resistance [PVR] ≥3WU), isolated post-capillary PH (mPAP >20mmHg, PAWP >15mmHg, PVR <3WU) and combined pre- and post-capillary PH (mPAP >20mmHg, PAWP >15mmHg and PVR ≥3WU). Clinical data of patients with pre-capillary and combined PH have been reviewed with a focus on etiological evaluation (pulmonary function tests, arterial blood gases, ventilation/perfusion lung scan, computed tomography, abdominal ultrasound scan and genetic testing).

Out of 901 consecutive patients with HHT, 313 underwent echocardiography for arteriovenous malformation screening or for dyspnea. Depending on the echographic outcomes, 31 RHC were performed at baseline. Among the 23 patients who had mPAP >20mmHg, 1 had isolated high pulmonary blood flow, 8/31 (25.8%) had isolated post-capillary PH, 8/31 (25.8%) had combined

pre- and post-capillary PH and 6/31 (19.3%) had isolated pre-capillary PH (figure 1). Of 14 patients with pre-capillary and combined PH, 12 were female (male-to-female ratio 0.17) versus 0.68 in HHT patients without PH (p=0.047). The mean (SD) age at PH diagnosis was 66.3 (9.9) years. PH was discovered 38 (+/- 52) months after HHT diagnosis was performed.

Multiple clinical conditions that could have contributed to PH pathogenesis were identified in 12 of 14 patients with precapillary PH (86%) (Table 1): 1) Genetic mutations in the TGF-β signaling pathway (*ALK1* n= 12, *ENG* n=2) were present in all cases. Mutation ALK1, exon 8, c.1112 dup was found in 8/14 patients (57%). 2) Chronic lung disease with a forced expiratory volume in 1 second (FEV_1) <60% or a forced vital capacity (FVC) <70% was found in 6 patients (linked to 3 restrictive and 3 obstructive pulmonary diseases, associated with severe hypoxemia in 2 of them). 3) Portal hypertension related to hepatic fibrosis was present in 1 patient. 4) Four patients also had significant perfusion defects on ventilation - perfusion lung scintigraphy and thrombo embolic patterns on computed tomography. 5) A hyperkinetic state was observed in 3 patients.6) Left heart failure were further noted in 8 individuals (table 1). Overall, 6 patients (43%) had 3 or more potential risk factors for PH.

The combination of multiple potential risk factors for PH was striking, since a vast majority (86%) of patients with PH exhibited multifactorial mechanisms. Therefore a systematic etiological evaluation is required to guide management. Even if genetic mutations in the TGF-β signaling pathway can participate in PH development, additional factors might have contributed, especially frequent left heart failure (group 2 PH). Indeed, chronic increase of pulmonary flow due to left-to-right shunt may leads, as in Eisenmenger syndrome, to pulmonary vascular remodeling in the long-term [7]. Chronic lung disease and chronic thromboembolic disease may also have significantly increased the risk of PH in this HHT population (group 3 and 4 PH, respectively). It is noteworthy that HHT patients have an increased risk of thrombosis [8, 9]. It has been reported that environmental risk factor such as methamphetamine or dexfenfluramine exposure had contributed to the development of PH in HHT patients [10, 11]. In our study, exposure to drugs and toxins was not systematically assessed and may have been underestimated. These findings are reminiscent of other

etiological contexts in patients with PH, in which several comorbidities and cofactors can contribute to increase the risk of PH, patients with HIV infection, hepatitis liver disease, interferon therapy, and illicit drug intake for example [12].

The large female predominance that has been noticed here had previously been reported [4]. Epidemiologic data of both heritable PH and HHT demonstrate female predominance. In some studies, hepatic arteriovenous malformations and *ALK1* mutations were also more common in women than in men with HHT [13], leading to the hypothesis that female sex hormones may affect vascular remodeling.

Limitations in our study included the retrospective design, although the data were collected prospectively in a national HHT registry at the time of each hospitalization. The study was monocentric, but included a relatively large cohort of patients from a tertiary referral HHT center. In this large cohort, only a few subjects underwent a RHC. This has been probably due to the fact that transthoracic echocardiography was not performed systematically but only when arteriovenous malformation screening was conducted or when PH was clinically suspected. Therefore, it cannot be excluded that pre-capillary PH could have been under-estimated, although results were consistent with previous data [1-4]. Finally, the ALK1 gene mutation c.1112 dup, was frequently found due to the founder effect described in the Rhône Alpes region [14]**.**

In conclusion, multiple clinical conditions were combined with genetic mutations to contribute to the development of PH in HHT patients. This finding highlights how critical a systematic etiological evaluation could be. Various management strategies could result from it.

Abbreviations:

HHT: Hereditary hemorrhagic telangiectasia; PH : pulmonary hypertension; TGF-β: Transforming growth factor-beta; ALK1: activin receptor like kinase 1 ; ENG: endoglin; RHC: right heart catheterization; mPAP : mean pulmonary arterial pressure ; PAWP : pulmonary artery wedge pressure; CI : cardiac index; PVR : pulmonary vascular resistance; FEV1 : forced expiratory volume in 1 second ; FVC: forced vital capacity; CTED : chronic thrombo-embolic disease; AVM : arteriovenous malformation (H : hepatic, P: pulmonary); HS : hyperkinetic state.

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Figure 1: Flow chart

RHC: right heart catheterization; mPAP: mean pulmonary arterial pressure ; PAWP : pulmonary artery wedge pressure; PVR : pulmonary vascular resistance