Pulmonary arteriovenous malformations in hereditary hemorrhagic telangiectasia: A Series of 126 patients

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Pulmonary Arteriovenous Malformations in Hereditary Hemorrhagic Telangiectasia

A Series of 126 Patients

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Abstract: Hereditary hemorrhagic telangiectasia (HHT) is a genetic disorder characterized by epistaxis, telangiectasia, and visceral vascular manifestations. Infectious and ischemic central nervous system (CNS) manifestations due to embolism through pulmonary arteriovenous malformations (PAVMs) represent the main causes of morbidity. To improve the phenotypic characterization of HHT with PAVM, we conducted a retrospective multicenter study of patients with HHT and at least 1 PAVM detected by chest computed tomography (CT) and/or pulmonary angiography, with particular attention to CNS and infectious manifestations.

The study included 126 patients (47 men, 79 women), with a mean age of 43.1 ± 17.4 years; 45 patients had a mutation of the ENG gene and 16 had a mutation of ACVRL1. PAVMs were diagnosed as a result of systematic screening procedures (29%), incidental imaging findings (15%), dyspnea (22%), or CNS symptoms (13%). The PAVMs were diagnosed at a mean age of 43 ± 17 years, with a linear distribution of diagnosis between 20 and 75 years. Dyspnea on exertion was present in 56% of patients. Four patients had a hemothorax, including 1 during pregnancy.

Fifty-three CNS events directly related to HHT (excluding migraine) were observed in 35% of patients: cerebral abscess (19.0%), ischemic cerebral stroke (9.5%), transient cerebral ischemic attack (6.3%), and cerebral hemorrhage (2.4%). The median age of onset was 33 years for cerebral abscesses (range, 11–66 yr), and 53.5 years for ischemic cerebral events (range, 2–72 yr). Migraine was reported in 16% of patients. The diagnoses of PAVM and HHT were made at the time of the cerebral abscess in 13 cases (54%).

Forty-three percent of patients were hypoxemic at rest. Contrast echocardiography showed intrapulmonary right-to-left shunting in 87% of tested patients. PAVMs were seen on chest radiograph in 54% of patients, and on the CT scan in all patients. One hundred five patients (83%) underwent treatment of the PAVM, by percutaneous embolization (71%) and/or by surgical resection (23%).

A high frequency of CNS and infectious complications was observed in this large series of patients with HHT-related PAVM. Physicians may not be sufficiently aware of the clinical manifestations of this orphan disorder. Patients diagnosed with HHT should be informed by physicians and patient associations of the risk of PAVM-related complications, and systematic screening for PAVM should be proposed, regardless of a patient's symptoms, familial history, or genetic considerations.

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Abbreviations: CNS = central nervous system, CT = computed tomography, GERM"O" P = Groupe d'Etudes et de Recherche sur les Maladies "Orphelines" Pulmonaires, HHT = hereditary hemorrhagic telangiectasia, PAVM = pulmonary arteriovenous malformation, TGF = transforming growth factor.

INTRODUCTION

Hereditary hemorrhagic telangiectasia (HHT), or Rendu-Osler-Weber disease, is an orphan disorder of genetic origin, characterized by recurrent epistaxis, mucocutaneous telangiectasia, and vascular visceral involvement^{95,109} including arteriovenous communications that may develop in virtually any organ, especially in the lung. According to the Curaçao criteria, the diagnosis of HHT is considered definite when at least 3 out of 4 of the above criteria are present, and suspected when 2 criteria are present¹⁰⁹. While everyday symptoms of the patients are dominated by epistaxis that may markedly alter their quality of life⁹¹, more severe manifestations of the disease are due to the consequences of pulmonary arteriovenous malformations (PAVMs), and less often to liver or brain involvement.

The first clinical manifestations of HHT were described successively by Benjamin Guy Babington in 1865⁹ and John Wickham Legg⁷⁵ in 1876⁴¹. In 1886, Henri J. L. M. Rendu distinguished the disease¹⁰⁶ from hemophilia, and

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reported the association of epistaxis, cutaneous telangiectasia, and familial occurrence⁴¹. The disease was further described in 1901 and 1907 by William Osler^{88,89}, who demonstrated inheritance of the disease and the possibility of visceral manifestations. Frederik Parkes Weber and Frederic M. Hanes also contributed to the clinical description of HHT in 1907 and 1909, respectively^{57,120}.

HHT is one of the commonest monogenic diseases, with an estimated prevalence of 1 in 5000 to 1 in 10,000 inhabitants, with important geographic disparities^{50,110}. Particularly high frequencies have been found in areas such as the French department of Ain²¹, in Vermont⁵¹, and the Afro-Caribbean population of the Netherlands Antilles¹²¹. HHT is inherited as an autosomal dominant trait⁹⁵, with late-onset penetrance (up to 50 years of age). There is no age cut-off when apparently unaffected children of an HHT-affected parent can be told they do not have HHT, unless a mutation of the ENG or ACVRL1 genes has been excluded in them¹². Epistaxis and telangiectasia are generally not present at birth but develop with age, with epistaxis being often the earliest symptom of the disease in childhood, followed by PAVMs, then cutaneous and mucous telangiectasia developing during the second to fifth decades¹². Cutaneous telangiectases are present at the age of 30 yr in half the patients⁹⁵. The progressive onset of clinical manifestations of HHT has implications for screening.

Molecular genetic analysis has led to the identification of mutations in 2 genes, ENG on the long arm of chromosome 9 (9q33-34) coding for endoglin⁸¹, and ACVRL1 on the long arm of chromosome 12 (12q11-14) coding for the activin receptor-like kinase (ALK-1)¹⁴, with more than 100 mutations described to date⁷⁶, causing haploinsufficiency⁹². Molecular screening of ENG and ACVRL1 genes identified a germline mutation in 62.5% of patients, including 36% in the ENG gene⁷⁶. Endoglin and ALK-1 are both membrane receptors of the transforming growth factor- β (TGF- β) superfamily. Vascular abnormalities have been reproduced in animal models by inactivation of the ENG or ACVRL1 gene^{24,25,112}. Recently, germinal mutations of the gene *smad4* (coding for the protein Smad4 also involved in TGF- β signaling) have been described in patients with a syndrome of combined familial juvenile polyposis and HHT⁴². It is likely that there is at least 1 more locus involved in patients with HHT and PAVMs^{29,93,119}. Mutations of the ENG gene may be associated with an increased risk of PAVMs, and earlier and more severe epistaxis than mutations of ACVRL1, whereas mutations of ACVRL1 may more frequently cause pulmonary hypertension or hepatic arteriovenous malformations^{1,2,13,15,110} (and G. Lesca, personal communication).

Pulmonary vascular manifestations of HHT include PAVMs and less frequently pulmonary hypertension. PAVMs consist of abnormal communications between pulmonary arteries and pulmonary veins; PAVMs involving several segmental arteries or veins are designated as complex PAVMs. The prevalence of PAVM has been estimated at between 15% and 33% of patients with HHT in previous studies^{11,52,110}. PAVMs remain frequently undiagnosed, but may cause hypoxemia and dyspnea due to right-

to-left shunting. PAVMs may also result in severe complications, such as massive hemoptysis or hemothorax, central nervous system (CNS) complications including transient ischemic attack or cerebral stroke, and systemic abscess (including cerebral abscess). Infections may be related to the right-to-left shunting that facilitates the passage of septic or aseptic emboli into the cerebral circulation. Hence, stroke and cerebral abscess have been reported in up to 30% and in 5%–9% of patients with HHT and PAVM, respectively^{48,78}. Such severe complications may be the presenting manifestation leading to the diagnosis of the PAVM and even of HHT itself⁹⁵. Over two-thirds of CNS manifestations of HHT may be related to PAVMs, with the remaining third due to cerebral or spinal arteriovenous malformations that may cause subarachnoid hemorrhage or seizure¹⁰⁰. Treatment of PAVMs significantly decreases right-to-left shunting^{49,123}, and may reduce the risk of cerebral complications¹¹⁰.

To improve the clinical characterization of this disease and its complications, we conducted a retrospective multicenter study of patients with HHT and PAVM, with particular attention to CNS and infectious manifestations.

METHODS

Case Recruitment

This retrospective multicenter study was conducted by the Groupe d'Etudes et de Recherche sur les Maladies "Orphelines" Pulmonaires (GERM"O" P), a collaborative group of over 200 physicians dedicated to the study of rare (so-called orphan) pulmonary diseases. A letter was sent to physicians of 6 French departments of respiratory medicine with experience in HHT who participated in the GERM"O" P network, asking them to report any case of HHT with PAVM encountered between January 1985 and December 2004. Participating physicians were also members of a French research network on HHT coordinated by 1 of us (HP). Reports to the GERM"O" P registry were nominative for patients who gave their written consent, or anonymous otherwise. The clinical data were then collected retrospectively through a detailed questionnaire sent to each participating physician who had reported cases.

Inclusion Criteria

Inclusion criteria were a history of probable or definite HHT based on published criteria (2 or more of the following: epistaxis, telangiectases, visceral lesions, family history¹⁰⁹), and the presence of at least 1 PAVM of 5 mm or more on chest CT and/or pulmonary angiography. Cases were excluded if the diagnostic criteria for HHT were not met, especially when presence of PAVM was the only criterion for the diagnosis of HHT.

Only patients in whom CT scan of the chest and/or pulmonary angiography were available were included in this study. The diagnosis of PAVMs on CT scan of the chest was based on the presence of a mass or nodule fed by an enlarged artery, with characteristic enhancement after contrast medium injection when performed¹⁰³.

Diagnostic Tests

All patients (or parents for patients younger than 18 yr) gave oral consent before tests were performed as part of the routine diagnostic and therapeutic procedures. Standard chest radiographs (anteroposterior and lateral views) were taken in standing position and at maximum inspiration, and were interpreted by the chest physician. Pulmonary angiography was performed in patients with PAVMs on chest CT and in whom embolization therapy was indicated.

Pulmonary function tests were performed according to the European Respiratory Society guidelines¹⁰². The alveolar-arterial oxygen difference $AaPO_2$ while breathing room air was estimated as the difference between PAO_2 and PaO_2 , where $PAO_2 = (\text{mean barometric pressure } \{101.3 \text{ kPa}\} - 6.3) \times 0.21 - PaCO_2/0.8$. The alveolar-arterial oxygen difference $AaPO_2$ while breathing 100% O_2 was performed as described elsewhere³⁰; briefly, PaO_2 was measured after the patient had been breathing 100% O_2 for at least 15 minutes, with a deep inspiration every minute; the actual PiO_2 was measured to estimate PAO_2 , with $PAO_2 \text{ (kPa)} = PiO_2 - 6.27 - (PaCO_2/0.8)$, and $AaPO_2 = PAO_2 - PaO_2$.

Transthoracic contrast echocardiography was performed by injecting 4.5 mL of agitated modified fluid gelatin or isotonic saline solution with 0.5 mL room air into a peripheral vein while simultaneously imaging the atria with 2-D echocardiography. The test was considered positive for pulmonary right-to-left shunting when contrast was visualized in the left atrium after a delay of at least 4 cardiac cycles. Pulmonary arterial hypertension was defined by a systolic arterial pulmonary pressure 45 mm Hg or higher as estimated by the tricuspid regurgitant flow on echocardiography.

Definitions

Transient cerebral ischemic attack was defined by the abrupt onset of a nonconvulsive and focal neurologic deficit of ischemic origin, with symptoms and signs resolving in less than 24 hours; ischemic stroke was defined by similar symptoms lasting more than 24 hours⁶.

Statistical Analysis

Microsoft Excel 2003 and SPSS 12.1 were used for data analysis. Numerical data were expressed as mean $\pm$ standard deviation, unless stated otherwise. The age of onset of PAVMs was analyzed using the Kaplan-Meier method.

RESULTS

Study Population

A total of 133 patients with a diagnosis of HHT with at least 1 PAVM of 5 mm or more on chest CT and/or pulmonary angiography was registered into the GERM“O”P database. Diagnostic criteria for a definite or possible HHT were eventually not met in 7 patients, since isolated PAVM was the only criterion for the diagnosis of HHT, so 126 patients were included in the study.

At least 3 diagnostic criteria indicating a definite diagnosis of HHT were present in 97% of patients (Table 1).

According to the inclusion criteria, all patients included in the study had involvement of at least 1 visceral organ, namely PAVM. In addition, 21% of patients were diagnosed with involvement of another visceral organ. One further patient had a history of surgery of aneurysm of the splenic artery, possibly but not definitely related to HHT.

Half the patients underwent genetic screening for HHT-related mutations; 45 patients had a mutation of the ENG gene, 16 had a mutation of ACVRL1, and no mutation of either gene could be found in the remaining 15 patients (see Table 1).

Patients were predominantly women (ratio, 1.7 female: 1 male), with a mean age of 43.1 ± 17.4 years (see Table 1). There were 66 patients who never smoked (52%), 29 active smokers, and 24 exsmokers, with a mean of 15 ± 14 pack years (range, 1–60).

Epistaxis, present in 89.7% of patients, had started at a median age of 10 years (range, 2–67 yr), and had required surgical treatment in half of the patients (50.7% of cases with available information) at a median age of 29 years (range, 7–59 yr). The frequency of epistaxis was less than once a month in 21%, between once a month and once a week in 29%, once a week or more in 29%, and once a day in 21%. Telangiectases were present in 85.7% of patients and were located on the lips (64%), fingers (54%), tongue (50%), face (49%), in the mouth (45%), and occasionally on the ears or thorax. The number of telangiectases was lower than 5 in 19%, between 5 and 30 in 45%, and greater than 30 in 36%.

TABLE 1. Clinical and Genetic Characteristics of 126 Patients With HHT and PAVM*

Clinical Data	
Age, yr	43.1 ± 17.4 (10.3–79.0)
Men/women (no.)	47/79
HHT diagnostic criteria	
4 criteria present	87 (69.0)
3 criteria present	35 (27.8)
2 criteria present	4 (3.2)
Family history of HHT	114 (90.5)
Epistaxis	113 (89.7)
Telangiectasia	108 (85.7)
Visceral arteriovenous malformations	126 (100)
Lung	126 (100)
Gastrointestinal tract	21 (16.7)
Liver	13 (10.3)
CNS	2 (1.6)
Other (vertebra)	2 (1.6)
Mutation analysis available	76 (60.3)
Mutation of ENG	45 (48.4)
Mutation of ACVRL1	16 (12.7)
No mutation found	15 (11.9)

*Data for age are mean $\pm$ SD (range); other data are number of patients (percentage).

TABLE 2. Circumstances of Diagnosis of PAVM

Circumstance	No. (%)
Systematic screening for PAVM in HHT patients	37 (29.4)
Incidental imaging findings	19 (15.1)
Respiratory symptoms	28 (22.2)
Dyspnea	23 (18.3)
Hemoptysis	3 (2.4)
Hemothorax	2 (1.6)
CNS events	17 (13.5)
Cerebral abscess	13 (10.3)
Ischemic cerebral stroke	3 (0.8)
Transient cerebral ischemic attack	1 (2.4)
Unknown	25 (19.8)
Total	126 (100)

A family history of a probable or definite case of HHT was present in over 90% of patients; the median number of relatives known to be affected by the disease was 4 (range, 0–30), over a median of 3 generations (up to 5 generations were involved). In addition, 3 patients had first-degree relatives with a history of recurrent epistaxis but without a confirmed diagnosis of HHT. Epistaxis and telangiectasia were reported by the patient in at least 1 family member in 41.8% and 26.7% of the cases, respectively; 32.5% of patients reported having a family member with CNS manifestations of the disease, while 36.6% reported the existence of PAVMs in a relative, and 14.3% reported hepatic or gastrointestinal involvement of the disease in a family member.

Seventy-seven percent of the female patients had children, with a mean of 2.3 ± 1.4 children per patient; 22 were nulliparous, and information was not recorded for 9. Thirty-five percent of female patients were postmenopausal. Among patients who underwent screening procedures for PAVM, 2 patients were pregnant at the time the diagnostic tests were performed; in 2 patients the screening tests that led to the discovery of PAVM were motivated by a wish to have these done before having a child.

Circumstances of the Diagnosis of PAVM

PAVMs were diagnosed as a result of systematic screening procedures for PAVM in patients known to have HHT (29.4% of the cases), incidental imaging findings (15.1%), respiratory symptoms (22.2%) especially dyspnea, or CNS symptoms (13.5%) (Table 2). In 1 patient, dyspnea first revealed polycythemia, which was subsequently related to PAVM-associated hypoxemia. In 1 patient PAVMs were revealed by hemoptysis related to bronchial angiomatosis. In 2 patients, PAVMs were revealed by hemothorax, including 1 during pregnancy. Of note, PAVMs were revealed by the occurrence of CNS complications in 17 patients (13.5%), including cerebral abscess in 13 (10.3%) patients, and cerebral ischemic stroke or transient attack in 4 patients.

The PAVMs were diagnosed at a mean age of 43 ± 17 years (range, 10–79 yr). Analysis of the age distribution at the time of diagnosis of PAVM according to the Kaplan-Meier

method illustrates that the diagnosis of PAVM was made with a linear distribution between the ages of 20 and 75 years (Figure 1A). There was a non-statistically significant trend toward earlier diagnosis of PAVM in patients with a familial history of HHT (median age 41.0 versus 53.5 yr; log-rank 1.07, $p = 0.3$), as well as in patients in whom the PAVM was diagnosed as a consequence of a symptom or a complication of the PAVM rather than as a result of systematic screening (median age 38.0 versus 46.8 yr; log-rank 0.35, $p = 0.55$).

Respiratory Symptoms

Overall, respiratory symptoms were present in 60% of the cases, with dyspnea on exertion being the most frequent manifestation of the PAVM (55.6% of the patients with PAVM) (Table 3). Fifteen patients (12%) had hemoptysis at a median age of 33 years (range, 17–69 yr); it was severe in only 1 patient. Four patients (3%) developed hemothorax as a complication of PAVM at a median age of 45.5 years (range, 25–66 yr); in a single case the hemothorax occurred during pregnancy and revealed the PAVM. The combination of dyspnea, cyanosis, and finger clubbing was present in only 18 patients (14.3%). Fiberoptic bronchoscopy was performed

FIGURE 1. A. Plot using the Kaplan-Meier method showing the distribution of age at the time of diagnosis of PAVM in 126 patients with HHT. B. Plot using the Kaplan-Meier method showing the age of onset of severe infection including brain abscess in 126 patients with HHT.

TABLE 3. Respiratory Symptoms in 126 Patients With HHT and PAVM

Respiratory Symptom	No. (%)
Dyspnea	70 (55.6)
NYHA class I	14 (20.0)
NYHA class II	40 (57.1)
NYHA class III	8 (11.4)
NYHA class IV	1 (1.4)
Hemoptysis	15 (11.9)
Thoracic murmur	4 (3.2)
Finger clubbing	28 (22.2)
Chest pain	8 (6.3)
Cyanosis	23 (18.3)

Abbreviation: NYHA = New York Heart Association.

in 10 patients because of hemoptysis, and showed in 5 patients (4%) telangiectasia of the tracheobronchial tree that may have accounted for the hemoptysis.

Chest Imaging

An anteroposterior chest radiograph, available in 111 patients, showed abnormalities suggestive of PAVM in 68 patients (54%) and was considered normal in the remaining 43 patients (34%). The number of PAVMs visible on chest radiograph was as follows: a single PAVM (n = 47; 37% of patients); 2 PAVMs (n = 12; 10%); 3 PAVMs (n = 6; 5%); more than 3 PAVMs (n = 3; 2%).

A CT scan of the chest was performed in 115 patients (91%), and showed the presence of at least 1 PAVM in all but 7 patients who had been operated on for PAVM before the chest CT. The number of PAVMs (5 mm or more) was as follows: 1 (n = 41; 37.9% of the 108 patients with PAVMs on chest CT); 2 (n = 22; 20.4%); 3 (n = 11; 10.2%); 4–9 (n = 22; 20.4%); 10 or more (n = 12; 11.1%), with a mean of 4 PAVMs per patient. Pulmonary angiography was performed in 90 patients (including 79 patients who also had a CT scan of the chest showing PAVM).

Nonspecific micronodular opacities were also present on the CT scan of the chest in 5 patients, and may potentially represent small PAVMs not amenable to embolization therapy. In addition, small PAVMs with a feeding vessel <2 mm and not treatable by embolization therapy were present on pulmonary angiography in 5 patients.

Infectious Events

Forty-seven infectious events were observed in 34 (27%) patients with HHT-associated PAVM (Table 4). Infections likely related to the PAVM-associated right-to-left shunting included 25 cerebral abscesses (Figure 2), 4 abscesses of the soft tissues (abscess of the arm, of the calf, of the hip with septic arthritis, and *Pasteurella multocida* infection of axillary lymph nodes), and 1 hepatic abscess. Hence, 30 severe infections occurred in 25 patients (20%) at a median age of 33 years (range, 11–66 yr) and were directly related to the PAVM. Notably, 1 patient had a first episode of cerebral abscess at the age of 19 years, then a cerebral hemorrhage at age 26 years followed by generalized epilepsy, and a second episode of

TABLE 4. Infectious Events in 126 Patients With HHT and PAVM

Infectious Event	No. of Patients (%) [*]	No. of Events (%) [†]	Age of Onset, yr Median (range)
Likely related to the PAVM			
Cerebral abscess	24 (19.0) [‡]	25 (53.2)	33 (11–66)
Abscess of soft tissue	4 (3.2) [§]	4 (8.5)	25 (18–31)
Hepatic abscess	1 (0.8)	1 (2.1)	37
Not likely to be related to the PAVM or unknown relationship with PAVM			
Tuberculosis	4 (3.2)	4 (8.5)	19.5 (2–21)
Latent tuberculosis infection	2 (1.6)		10.5 (2–19)
Active tuberculosis infection	2 (1.6)		20.5 (20–21)
Acute community acquired pneumonia	3 (2.4)	6 (12.8)	20 (15–25)
Pleural empyema	1 (0.8)	1 (2.1)	NA
Acute bacterial meningitis	2 (1.6)	2 (4.3)	31.5 (30–33)
Infectious acute aortic endocarditis	1 (0.8)	1 (2.1)	22
Acute brucellosis	1 (0.8)	1 (2.1)	27
Acute peritoneal infection (complicating acute appendicitis)	1 (0.8)	1 (2.1)	NA
Acute pyelonephritis	1 (0.8)	1 (2.1)	29
Total	34 [¶] (27.0)	47	29.5 (2–66)

Abbreviation: NA = not available.

^{*}Number of patients/total number of patients (that is, 126).[†]Number of events/total number of infectious events.[‡]Including 7 cases where the cerebral abscess revealed the PAVM.[§]Including 1 patient with *Pasteurella* infection of axillary lymph nodes.[¶]Some patients had several types of infection.

FIGURE 2. CT scan of the brain of a patient with HHT who developed a brain abscess.

cerebral abscess at age 41 years (then PAVM was eventually diagnosed and treated by percutaneous embolization). Five cerebral abscesses and 1 hepatic abscess occurred in 5 patients belonging to 2 unrelated families. Bacteria responsible for the cerebral abscesses were identified in only 4 cases, including 1 with a single bacterial agent (*Capnocytophaga*), and 3 with multiple bacterial agents (*Peptostreptococcus*, *Clostridium sordelli*, *Fusobacterium nucleatum*, and *Actinomyces*; *Streptococcus intermedius*, *Haemophilus*, and *Actinomyces meyeri*; and *Haemophilus aphrophilus* and *Actinomyces meyeri*, respectively). The entry route of bacterial infection was rarely identified (sphenoidal sinusitis in 1 case; anthrax in 1 case; dental treatment without prophylactic antibiotic therapy in 1 case).

Among the 24 patients who presented with a cerebral abscess, the diagnosis of PAVM and the diagnosis of HHT were made at the time of the CNS complication in 13 cases (54%). In 6 additional cases (25%), the diagnosis of PAVM was made with a median delay of 6.5 years (range, 1–30 yr) after the occurrence of the cerebral abscess, as a result of systematic screening procedures for PAVM in patients known to have HHT (3 cases), or incidental imaging findings (3 cases). Analysis of the occurrence of severe infections using the Kaplan-Meier method indicated that infections occurred regularly between the ages of 15 and 70 years (see Figure 1B).

In 5 cases (21%), the occurrence of the cerebral abscess followed the diagnosis of PAVM by a median of 18 years (range, 3 mo–22 yr). In 3 of the 5 cases, the PAVM had not been treated because of patient denial of treatment ($n = 1$), unavailability of percutaneous embolization at the time (1979—however, surgery was not considered) ($n = 1$); and occurrence of a cerebral abscess only 3 months after the diagnosis of the PAVM while surgery was planned (percutaneous treatment was unsuccessful) ($n = 1$). In the remaining 2 cases, another PAVM had been treated 18 (right lower lobectomy) and 18.5 (combination of localized resection of PAVM of the left upper and lower lobes and percutaneous vaso-occlusion) years earlier, respectively, and residual or

recurrent right-to-left shunting after treatment had not been evaluated after the treatment procedures.

Of note, a history of infection was not significantly more frequent in patients with multiple compared with unique PAVM on chest CT (20.9% versus 12.5%, $p = 0.321$, bilateral exact Fisher test). Patients with a history of severe infection did not have significantly more PAVMs on chest CT than patients who had no history of infection (6.4 ± 13.8 versus 3.5 ± 5.0 ; 2-tailed $p = 0.369$, Student t test assuming unequal variances).

In addition to the 30 severe infections likely related to the PAVM, 17 various infections were observed whose relationships to the PAVM were either unknown (pleural empyema, bacterial meningitis, aortic endocarditis, community-acquired pneumonia) or unlikely (tuberculosis, brucellosis, peritoneal infection, pyelonephritis). Of note, 2 patients developed bacterial meningitis, 1 after acute pharyngitis, the other during pregnancy; the latter also developed cerebral abscess 18 years later.

CNS Events

Fifty-three CNS events directly related to the disease (excluding migraine) were observed in 44 (35%) patients with HHT-associated PAVM (Table 5); 51 of the 53 events were considered directly related to the PAVM, and 2 were related to intracerebral vascular malformations. The most frequent CNS complication was cerebral abscess, which occurred in almost one-fifth of the patients with PAVM, and represented 47% of CNS complications. Ischemic cerebral events (combining ischemic cerebral strokes and transient cerebral ischemic attacks) were also frequent (Figure 3), representing 40% of CNS complications and occurring in 16% of patients with PAVM. Cerebral hemorrhage accounted for only 5.7% of CNS events.

The median age of onset of CNS manifestations of the disease was 31 years for cerebral abscesses and 53.5 years for ischemic cerebral events. Intracerebral vascular malformations and cerebral hemorrhage were diagnosed at a younger age (median, 16 and 31 yr, respectively). Of note, a significant proportion of patients presented with severe complications early in life, with 4 patients aged 18 years or younger with a cerebral abscess, and 4 others with an ischemic cerebral event, including 1 with an episode of ischemic stroke and hemiplegia at the age of 2 years that resolved over a period of 3 months.

In addition, 1 patient presented with 2 acute episodes of transient unconsciousness of undetermined cause (normal CT of the brain) at the age of 22 and 28 years. Two other patients had arteriovenous malformations within vertebrae (7th dorsal vertebra in 1, 7th dorsal and 3rd lumbar vertebra in 1) revealed by vertebral pain, without abnormality of the spinal cord. One further patient had congenital right hemiplegia, which could not definitely be related to the disease.

Of 44 patients with CNS manifestations related to the disease, 10 patients (23%) had several CNS complications of HHT, including 1 with 3 complications of the disease (1 cerebral hemorrhage and 2 consecutive cerebral abscesses). For example, 1 patient had an ischemic cerebral

TABLE 5. CNS Manifestations (Excluding Migraines) in 126 Patients With HHT and PAVM

	No. of Patients (%) [*]	No. of Events (%) [†]	Age of Onset, yr Median (Range)
Cerebral abscess	24 (19.0)	25 (47.2)	33 (11–66)
Ischemic cerebral stroke	12 (9.5)	12 (22.6)	53 (2–66)
Transient cerebral ischemic attack	8 (6.3)	9 (17.0)	54 (17–72)
Cerebral hemorrhage	3 (2.4)	3 (5.7)	31 (26–44)
Intracerebral vascular malformations	2 (1.6)	2 (3.8)	16 (14–18)
Acute bacterial meningitis	2 (1.6)	2 (3.8)	31.5 (30–33)
Overall	44 (34.9)	53	35 (0–72)

^{*}Number of patients/total number of patients (that is, 126).

[†]Number of events/total number of infectious events.

stroke at age 18 years secondary to PAVM; an asymptomatic parietal cerebral arteriovenous malformation was incidentally diagnosed at that time, left untreated, and was later responsible for transient ischemic cerebral attack when venous thrombosis of the cerebral vascular malformation occurred.

A history of migraine was reported in 20 patients (15.9%), beginning at a median age of 25 years (range, 10–43 yr). The number of PAVMs was not significantly different

in patients with migraine than in patients without migraine (7.3 ± 16.2 versus 4.1 ± 4.1 , $p = 0.24$).

Venous Thromboembolic Events

Five patients (4%) had a history of venous thromboembolic disease, including 1 spontaneous deep vein thrombosis in the context of heterozygous factor V Leiden, and 4 pulmonary emboli (postoperative, $n = 1$; absence of predisposing factors, $n = 3$).

FIGURE 3. Imaging of a 35-year-old patient with HHT, PAVM, and transient cerebral ischemic attack. **A.** Nuclear resonance imaging of the brain showing increased signal in T2 of the right perioral area; **B.** Three-dimensional reconstruction of the chest CT demonstrating the anatomy of the PAVM; **C.** mediastinal and **D.** parenchymal windows of the chest CT showing a PAVM of the right lower lobe.

TABLE 6. Pulmonary Function Tests in Patients With HHT*

Test	Mean ± SD (Range)
Forced vital capacity (FVC), % predicted	97 ± 18 (38–144)
Residual volume, % predicted	103 ± 29 (38–180)
Total lung capacity, % predicted	96 ± 15 (61–128)
Forced expiratory volume in 1 s (FEV ₁), % predicted	93 ± 18 (41–129)
FEV ₁ /FVC, %	78 ± 8 (49–97)
DLco, % predicted	92 ± 29 (20–213)
DLco/VA, % predicted	89 ± 29 (27–195)
PaO ₂ at rest (supine position), kPa	9.5 ± 2.0 (4.5–15.3)
PaCO ₂ at rest (supine position), kPa	4.5 ± 0.6 (2.4–6.1)
Alveolar-arterial PaO ₂ difference (room air), kPa	4.8 ± 2.3 (0.3–10.1)
Alveolar-arterial PaO ₂ difference (100% O ₂), supine position, kPa	21.8 ± 20.8 (1.7–79.9) [†]
Alveolar-arterial PaO ₂ difference (100% O ₂), upright position, kPa	27.8 ± 24.8 (1.8–79.9) [‡]
PaO ₂ at exercise - PaO ₂ at rest (supine position), kPa	−0.3 ± 1.0 (−2.9–2.3) [§]

*Data were obtained in 109 patients unless specified.

[†]Data in 78 patients.

[‡]Data in 58 patients.

[§]Data in 66 patients.

Laboratory Results

Hemoglobin levels were highly variable, with 24 patients (19%) with hemoglobin level <120 g/L at the time of diagnosis or treatment of the PAVMs, and 24 patients (19%) with hemoglobin levels >160 g/L. Overall, the mean hemoglobin level was 140 ± 30 g/L (range, 60–221 g/L), the mean hematocrit was 0.43 ± 0.09 (range, 0.20–0.71), and the mean erythrocyte count was 4.8 ± 0.9 × 10¹²/L (range, 2.6–8.5).

Pulmonary Function Tests

Pulmonary function tests were available in 109 patients (Table 6). The mean forced expiratory volume in 1 second (FEV₁)/forced vital capacity (FVC) (78%) and FEV₁ (93% of predicted values) were normal, with 18% of patients with FEV₁ lower than 80% of predicted, and only 9% of patients with an obstructive ventilatory defect as defined by FEV₁/FVC <70% presumably due to tobacco smoking-related chronic obstructive lung disease. A restrictive ventilatory defect as shown by decrease of total lung capacity was found in 15% of patients, presumably resulting from obesity and/or lung surgery. Transfer factor for carbon monoxide was lower than 80% of predicted values in 37% of tested patients and higher than 120% in 16%, while transfer coefficient was lower than 80% of predicted in 39% patients and higher than 120% of predicted in 11%. Forty-seven patients (43%) were hypoxemic at rest (PaO₂ <10 kPa), and 52% of patients were hypoxemic at exercise (PaO₂ <10 kPa in 32/66 tested patients). The detection of right-to-left shunting by the measurement of AaPO₂ under 100% oxygen was performed in 78 patients (62%). Normal values for AaPO₂ were previously defined by a receiver-operating-characteristic curve analysis³⁰. Increased AaPO₂ suggestive of right-to-left shunting was present in 47/78 tested

patients (60%) in the supine position (AaPO₂ >9.1 kPa), with a mean AaPO₂ of 22 ± 21 kPa, and in 40/58 patients (69%) in the upright position (AaPO₂ >9.7 kPa; mean AaPO₂ 28 ± 25 kPa).

Echocardiography and Radionuclide Lung Scanning

Echocardiography was performed in 82 patients (65%) and showed criteria of pulmonary hypertension (including dilatation of the right cavities and estimated systolic pulmonary arterial pressure 45 mm Hg or higher) in none.

A contrast echocardiography was performed in supine and/or upright position in 70 patients (56%), and showed intrapulmonary right-to-left shunting suggestive of PAVM in 61 patients (87% of tested patients), whereas no shunting was observed by echocardiography in 1 patient (despite the presence of a single PAVM on the CT scan and radionuclide lung scanning showing positive activity on both renal and cerebral areas), and in the 8 patients in whom the PAVM had been treated at the time the echocardiography was performed. We note that intracardiac shunting due to patent foramen ovale and aneurysm of the interauricular septum was also found in 7 patients with PAVM and intrapulmonary shunting (that is, 10% of patients with echocardiography), showing that intracardiac and intrapulmonary right-to-left shunting may be associated.

Right-to-left shunting was assessed by the isotopic method in 57 patients (45%). Radionuclide lung scanning showed positive activity on renal and cerebral areas in 35 patients (61%).

Treatment of PAVMs

Among the population of 126 patients with PAVM related to HHT, 105 (83%) underwent treatment of the

PAVM (Table 7). Pulmonary angiography was performed as part of the therapeutic procedure in 90 patients (71%), and showed PAVMs potentially amenable to embolization therapy in all patients as follows: 1 PAVM ($n = 37$; 41%); 2 ($n = 15$; 17%); 3 ($n = 8$; 9%); 4–9 ($n = 12$; 13%); 10 or more ($n = 6$; 7%); data not available ($n = 12$; 13%). Percutaneous embolization therapy was performed in 90 patients (71%) between 1994 and 2004. Several procedures of embolization therapy were required to occlude all visible PAVMs of significant size in 28% of the patients who underwent this treatment, especially in patients with multiple PAVMs (up to 11 procedures in 1 patient). Embolization therapy was considered not feasible for technical reasons in 10 cases (8%), and was turned down by 5 patients (4%). In 16 patients (13%), embolization therapy was performed after surgical resection of another PAVM had been performed previously. In only 1 of the cases was surgery necessary after embolization therapy was performed.

Treatment consisted of surgical resection of the PAVM in 30 (23%) patients, including a majority (21/29) by lobectomy, and some by wedge resection (9/29), with a single patient who underwent combined lobectomy of the right upper lobe and segmentectomy in the middle lobe. In addition, surgery was performed as an emergency procedure for hemothorax in 1 patient, consisting of surgical exploration of the chest by thoracotomy, control of the source of bleeding, and evacuation of the hemothorax. Surgical treatment was performed as early as 1960, with the latest surgical treatment performed in 2000. Surgical treatment was performed in most cases before percutaneous embolization therapy was available, with 22 of 30 surgical procedures (73%) performed before 1990 and only 2 since 1996 (1 case because of 3 large PAVMs in the same lobe for which embolization therapy was not considered feasible; 1 case after failure of embolization therapy). Complications of surgery included late or incomplete reexpansion of the lung in 3 cases; phrenic nerve palsy in 1 case; peripheral pulmonary embolism in 1 case; postoperative seizure in 1 case.

TABLE 7. Treatment of PAVMs in 126 Patients With HHT

Method of Treatment	No. (%)
Percutaneous embolization therapy	90 (71)
1 embolization procedure	52 (58)
2 embolization procedures	11 (12)
3 embolization procedures	6 (7)
>3 embolization procedures	8 (9)
No. of procedures not available	13 (14)
Surgery	30 (23)
Wedge resection	9 (7)
Lobectomy	21 (17)
Pneumonectomy	0
Emergency treatment of hemothorax	1 (1)

DISCUSSION

Diagnosis of HHT

In the current series, the diagnosis of HHT was definite according to the so-called Curaçao criteria¹⁰⁹ in 97% of patients, and was likely in 4 additional patients. A family history of a probable or definite case of HHT was present in over 90% of patients, with a median number of 4 relatives affected by the disease. However, the proportion of patients reporting specifically epistaxis and telangiectasia in at least 1 family member was relatively low, and may be largely underestimated due to difficulties in obtaining relevant information from patients about their relatives. Cases with isolated PAVM as the only criterion of HHT were not included in the study. The mutation analysis was not taken into account to establish the diagnosis of HHT.

Since clinical manifestations of the disease become more prominent with age, and genetic penetrance of the disease is considered complete at about 50 years of age (with interindividual and interfamilial variability), it is noteworthy that the mean age of patients included in the current study was 43.1 ± 17.4 years. Epistaxis had started at a median age of 10 years, while telangiectasia appeared later in life, consistent with series from the literature^{12,96}.

PAVMs: Definitions and Epidemiology

PAVMs consist of abnormal communications between pulmonary arteries and pulmonary veins, giving rise to right-to-left shunting and causing hypoxemia; rarely, the vascular malformation may involve a systemic artery rather than pulmonary artery, with lack of consequences on hematosis⁴⁸. Complex PAVMs (65%–80%) are vascularized through several segmental pulmonary arteries, and/or drained through multiple segmental pulmonary veins^{73,123}. At least 80% of PAVMs occur in the context of HHT. Although morphologically and histologically similar to solitary PAVM⁴⁸, the PAVMs that occur in the context of HHT are more likely to be multiple (35%–65% of cases in the literature^{32,85,115,123} and 63% in the current series) and bilateral¹⁰¹ than isolated PAVM. They predominate in the lower lobes (60%–95%) on either side of the lungs^{32,35,49,73,123}. The risk of serious infection or CNS complication was not significantly higher in patients with multiple PAVMs than in patients with single PAVM (although the sizes of the PAVM and of the feeding vessels were not compared in these groups of patients); therefore similar attention must be paid to the treatment of unique and multiple PAVMs, which may evolve to serious complications in either case when left untreated.

Due to the age-related penetrance of the disease, the prevalence of PAVMs has been reported to increase with age, with a reported prevalence of up to 33% during the fifth decade^{11,52,95,110,115}. Intrapulmonary shunt as evidenced by chest CT, pulmonary angiography, and/or contrast echocardiogram may be present in 41%–65% of patients^{11,71,86}. The current study, which included only HHT patients with PAVM, does not allow estimation of the prevalence of PAVMs in HHT. However, the median age of diagnosis of PAVM was

42 years, with extreme values of 10 to 79 years, indicating that PAVM may occasionally remain clinically silent for a prolonged period of time, may be underdiagnosed, and/or may occur late in life, as previously reported^{32,33}. The current study further challenges the concept of PAVM being rare before adolescence. A major finding of our study was to demonstrate that the age of diagnosis of PAVM was equally distributed between the ages of 20 and 75 years, indicating that screening for PAVM should not be restricted to young adults. In addition, PAVM with severe CNS complications including stroke and cerebral abscess has been reported in children^{39,83} (and our unpublished observations) (see reference 46 for review); diffuse PAVMs may be more frequent in children with HHT than in adults, although this may be related to a more severe disease leading to earlier diagnosis³⁹. Since our study was conducted by chest physicians mainly caring for adult patients, it is likely that children are under-represented in our study due to referral bias.

Notably 36.6% of patients reported the existence of PAVM in a family relative, a frequency higher than the overall frequency of PAVMs in the population of HHT patients^{52,110}, in keeping with previous observations of familial heterogeneity of the expression of HHT^{63,82,97}. The risk of PAVM is higher in families with mutations of the ENG gene^{11,13,23,69,77}, who also carry a higher risk of earlier and more severe epistaxis, and more frequent cerebral AVMs^{11,15,77}, while families with mutations of the ACVRL1 gene tend to have a lesser penetrance of the disease⁶⁷, albeit a higher prevalence of hepatic AVM^{2,13}. Consistently, a majority of patients with PAVM in this series had mutations of ENG. In a series of 538 patients with HHT, the prevalence of PAVM was 47.7% in patients with ENG mutations, and only 5.3% in patients with mutations of the ACVRL1 gene⁹⁸. Results of population statistics should be interpreted with caution before applying to an individual case. Specifically, screening tests for PAVM should be performed in every HHT patient irrespective of genetic status, since PAVM may also be present in patients carrying mutations of the ACVRL1 gene^{98,110}.

Although there is no gender predominance of HHT due to its genetic autosomic inheritance, a female predominance has been reported for HHT-related PAVM. Male:female sex ratio was 1:1.7 in the current series, in agreement with previous series (sex ratio 1:1.5 to 1:1.9)^{32,33,54}. PAVMs may increase in size and number during pregnancy due to hormonal and hemodynamic factors^{32,111}, and may occasionally give rise to potentially lethal complications such as hemorrhage^{40,65,66,72,111} requiring emergency surgical treatment^{40,66,72} or embolization therapy⁴⁵. One patient had a hemothorax and another developed bacterial meningitis during pregnancy. Potential complications of PAVM during pregnancy further highlight the relevance of systematic screening of PAVM especially in women of childbearing age, and of close follow-up of HHT patients throughout pregnancy.

Respiratory Manifestations of PAVMs

Dyspnea on exertion is present in about half of the patients with PAVM (56% in the current series, 26%–86% in

older series^{12,30,110}). The lack of dyspnea does not exclude PAVM, and a majority of cases may thus be missed in the absence of systematic screening investigations for PAVM. Only 22% of PAVMs were revealed by respiratory symptoms including dyspnea. A number of patients may present with little dyspnea despite longstanding daytime hypoxemia; exercise tolerance may be maintained in patients with HHT due to low pulmonary vascular resistance allowing increase of cardiac output during exercise¹²⁵. The presence of dyspnea does not correlate with the number of PAVMs³², but has been related to the severity of right-to-left shunting^{48,115}. Platypnea (dyspnea only in erect position) is rare and considered related to the predominance of PAVM in lower lobes. Severe hemorrhagic manifestations of PAVM, present in up to 8% in a series of 143 patients with HHT and PAVM⁴⁰, may include intrabronchial or intrapleural rupture with ensuing hemoptysis or hemothorax respectively. Hemorrhage may be lethal in HHT¹¹¹. Cyanosis may be prominent in HHT patients with hypoxemia-related erythrocytosis, or absent in case of anemia in patients with chronic gastrointestinal bleeding from telangiectasia or epistaxis.

Infectious Complications of PAVMs

Since PAVMs remain frequently undiagnosed, they may be revealed by potentially severe complications such as transient ischemic attack, cerebral stroke, and cerebral abscess due to the right-to-left shunting that facilitates the passage of emboli into the cerebral circulation. Such severe complications may be the presenting manifestation leading to the diagnosis of the PAVM and even of HHT itself^{95,100}, and are considered more frequent in the context of HHT than in solitary PAVM¹⁰⁸. Indeed, the incidence of cerebral abscess was 19% in the current series, compared with 5%–9% of patients with HHT^{48,78}, and 5%–17% of patients with HHT and PAVM^{35,43,49,73,115,123} (9.1% in the largest series to date⁹⁸). It has been estimated that almost 1% of HHT patients will have a brain abscess during their lifetime^{44,100}. This incidence compares to that in the general population, estimated at 1 in 100,000 persons per year⁸⁰. Since most patients in the current series originated from chest physicians, it is unlikely that this very high incidence of brain abscess is due to referral bias. The risk of cerebral complications of PAVMs is considered significant when the feeding artery of the PAVM exceeds 3 mm in diameter⁸⁵, although most groups tend to treat smaller PAVMs when technically feasible. The risk of infectious complications of PAVMs may be increased in patients with multiple PAVMs⁸⁵; we consider that the severity of the right-to-left shunting rather than the overall number of PAVMs might influence the risk of complications. As observed in the current series, cerebral abscesses in HHT tend to form in areas supplied by the middle cerebral artery, and are due to several infectious agents including *Streptococcus*, *Actinomyces*, and anaerobic bacteria such as *Fusobacterium*, similar to metastatic abscesses developing as a complication of pyogenic lung infection⁸⁰; predisposing conditions such as paranasal sinusitis, otitis media, and dental infection⁴³ are often lacking^{37,100}.

We note that the infectious complications of PAVMs are not restricted to cerebral abscess, since abscesses of the kidney, of the knee, of the spinal cord, meningitis, *Staphylococcus aureus* septicemia and endocarditis, and bacterial spondylodiscitis have been reported^{22,31,36,52,62}. We further describe 4 cases of abscess of the soft tissue and 1 hepatic abscess that were likely related to PAVM. We consider that the fact that 4/5 of the abscesses of the soft tissues or of the liver occurred in patients who also developed a cerebral abscess earlier or later in life highlights the likelihood that these infections were indeed related to the PAVM. Of note, work is currently underway by several groups to determine whether moderate abnormalities of the immune system may contribute to infections independently of right-to-left shunting and PAVM in patients with HHT^{4,28}.

Even in patients who develop a cerebral abscess, the relationship between the infection process and the diagnosis of HHT often was not recognized by physicians, and PAVMs were often identified later in life as a result of systematic screening procedures or incidental imaging findings. Similarly, PAVMs (not recognized at the time of infection) were retrospectively identified in 2 of 126 patients who had a brain abscess⁴⁴, indicating that screening for PAVMs should be recommended in patients with brain abscess. On the other hand, 5 abscesses occurred after the diagnosis of PAVM.

It is recommended that patients with functional PAVM receive antibiotics before potentially bacteriemic procedures in order to reduce the risk of brain abscess^{30,48}; we also advocate such prophylactic treatment in patients with no visible PAVM but positive contrast echocardiography that may correspond to possible microscopic PAVMs and/or vascular dilatations³⁰. Modalities for prophylactic treatment in patients with HHT remain to be established.

CNS Complications of PAVMs

PAVMs were revealed by the occurrence of CNS complications in 17 patients (13%), including cerebral abscess in 13 (10%) patients. Cerebral strokes have been reported in 15%–19% (and even up to 30% in some series) of patients with HHT^{49,98,101,115,123}, and were similarly present in 9.5% of patients in the current series, with an additional 6% who had a history of transient ischemic attack (compared with 12%–37% in previous series)^{27,35,49,73,98,115,123}. Overall, 35% of patients had a history of CNS events directly related to the disease (excluding migraine), similar to what has been reported in the literature¹⁰⁸.

A striking feature was the early age of onset of ischemic cerebral events (mean age 41.6 ± 25 yr) in the context of HHT, more than 20 years lower than that of ischemic strokes in the general population. The mean age of ischemic stroke in a study of over 21,000 patients was 63.2 ± 10.4 years⁵. In addition, patients presented with cerebral abscess at a younger age (median, 31 yr) than patients with bacterial cerebral abscesses in the general population¹¹⁷.

A remarkable finding of the current study was the large predominance of CNS symptoms related to the PAVM over the manifestations of cerebral arteriovenous malformations, as opposed to a third of CNS manifestations related to

cerebral or spinal arteriovenous malformations causing subarachnoid hemorrhage or seizure in some series of HHT patients (regardless of the presence of PAVM)¹⁰⁰. Cerebral hemorrhage accounted for only 4% of CNS events. The occurrence of cerebral arteriovenous malformations in patients with HHT was 7.6% in a large recent series⁹⁸, and may approximate 10%–15% when systematic screening is performed⁵⁴. Inclusion bias may have influenced the nature of CNS symptoms in the current study, since only patients with PAVMs (hence more at risk of brain abscess) were included. The prevalence of cerebral arteriovenous malformations may have been underestimated, since not all patients had systematic brain imaging. In patients with PAVMs, CNS manifestations of HHT are more frequently related to the PAVM through infections and embolic stroke than to hemorrhagic cerebral arteriovenous malformations⁷⁸.

A history of migraine was reported in 15.9% of patients in our study, and may have been underestimated due to the lack of systematic reporting. In a recent large cohort⁹⁸, the prevalence of migraine was 16.4% in patients with HHT, and 21.2% in patients with HHT and PAVM; the occurrence of PAVM was significantly higher in patients with migraine (50% versus 36% in patients without migraine)⁹⁸. Similarly, a relationship between right-to-left shunt due to patent foramen ovale and migraine has been reported^{7,116}. It has been hypothesized that PAVM may increase the risk of migraine through a common genetic trait associated with both migraine and HHT, or more likely through the lack of trapping in the pulmonary circulation of vasoactive trigger substances. The significant reduction in the prevalence of migraine after percutaneous closure of a cardiac right-to-left shunt through a patent foramen ovale substantiates the latter hypothesis⁹⁹.

Imaging Features

When visible on chest radiograph, PAVM typically presents as a rounded or oblong opacity measuring 1–5 cm and with branching vessels⁴⁸. PAVMs were visible on chest radiograph in 54% of patients, compared with 73%–100% of the cases in previous series^{30,32,33,115}, and confirming that chest radiography should not be used as the sole investigation for screening purposes³⁰. A sensitivity of 84% has been reported for the detection of PAVM by chest radiograph; however some patients with a normal radiograph did not undergo chest CT or pulmonary angiography in that study, and small PAVMs may have been missed⁵².

Helical CT scan of the chest has become the reference for the morphologic evaluation of PAVM, showing a nodular opacity of variable size, with afferent and efferent vessels. The diagnosis of PAVM with CT is based on the presence of an opacity with anatomic configuration of a vascular lesion (mass or nodule fed by an enlarged artery). Intravenous injection of contrast medium is used only for evaluation of large PAVMs or for the differential diagnosis of nodules, and is followed by considerable enhancement of the PAVM¹⁰³. Chest CT has been compared to pulmonary angiography in a single study¹⁰³, and was shown to have a higher sensitivity than angiography, especially for the

detection of small or thrombosed PAVMs. However, other malformations such as pulmonary varices may occasionally mimic PAVMs^{56,79}. Nonspecific micronodular opacities potentially corresponding to small PAVMs and not treatable by embolization therapy may also be present on helical CT scan of the chest³⁰.

Pulmonary angiography has long been considered the gold standard for the diagnosis of PAVM. Due to the considerable improvement of helical chest CT, this invasive procedure is no longer used for diagnostic purposes, and its use is restricted to treatment⁴⁸. Angiographic magnetic resonance imaging is not as efficient as helical CT for the diagnosis of PAVM^{18,68}.

Pulmonary Function Tests and Evaluation of Right-to-Left Shunt

Pulmonary function tests available in a large majority of patients demonstrated overall normal values for FEV₁ and FVC. Fifteen percent of patients had a restrictive ventilatory defect (presumably due to obesity and/or lung surgery as reported²⁷). Forty-three percent of patients were hypoxemic at rest, demonstrating that normal arterial blood gases on room air do not exclude the possibility of PAVM. Orthodeoxia was rarely evaluated since we demonstrated the low diagnostic value of this measure as a screening test³⁰. A decrease in transfer coefficient for carbon monoxide (Kco) has been described in patients with HHT^{27,35,49}.

AaPO₂ was increased in 60% of tested patients in the supine position and 69% in the upright position, indicating that hypoxemia was related to right-to-left shunting in most tested patients, as classically reported in HHT⁴⁸. Presence of right-to-left shunting according to measurement of AaPO₂ has been suggested as a screening method for PAVM with a reported sensitivity of 87% and a specificity of 71% (although a reference test was not always available)⁵². We showed that increased AaPO₂ had excellent specificity (98%) but insufficient sensitivity (68%) for the diagnosis of PAVM³⁰. We suggest that this test with suboptimal reproducibility^{30,48} may be used for quantification of right-to-left shunting rather than for screening purposes.

Transthoracic contrast echocardiography uses microscopic gas bubbles to visualize right-to-left shunting^{10,113}. Intracardiac shunting (with presence of contrast in the left atrium within 1 cardiac cycle following its appearance in the right atrium) can be differentiated from intrapulmonary shunting (with a delay of 3–8 cardiac cycles, that is, 2–5 seconds). Contrast echocardiography usually does not locate the site of intrapulmonary shunting and PAVM, although contrast may be seen in a particular pulmonary vein⁹⁴. Quantification methods of the shunt by echocardiography have been suggested^{47,70,74,113}, which one hopes could predict the development of significant PAVM⁷⁴.

Contrast echocardiography is well tolerated in most cases. This test often remains positive after endovascular treatment of PAVM, even in patients with no residual PAVM seen on angiography⁷⁴. In addition, contrast echocardiography is positive in a proportion of patients with no visible PAVM on chest CT³⁰. Positive contrast echocardiography in

the absence of permeable PAVM presumably corresponds to microscopic and diffuse PAVMs causing right-to-left shunting^{70,71}. The clinical significance of such possible microscopic PAVMs and/or vascular dilatations is yet unknown. It is not known whether microscopic PAVMs evolve over time to hemodynamically significant PAVMs, then associated with a risk of severe complications. Such patients may be offered a closer clinical follow-up, and repeated diagnostic procedures for PAVM after several years.

It is noteworthy that intracardiac shunting due to patent foramen ovale and intrapulmonary shunting due to PAVM were both present in 10% of tested patients at contrast echocardiography. Patent foramen ovale is a risk factor for several serious clinical syndromes⁵⁸. The prevalence of patent foramen ovale in the healthy population may approximate up to 25% between 30 and 79 years of age^{3,58}. The presence of patent foramen ovale and/or atrial septal aneurysm in patients with HHT is therefore likely coincidental. During contrast echocardiography, attention must be paid by the operator to the delay of appearance of the contrast, in order to differentiate intrapulmonary and intracardiac right-to-left shunting.

Assessment of right-to-left shunting by radionuclide lung scanning consists of the detection of radioactivity in renal, cerebral, and thyroid areas following intravenous injection of 99m technetium-labeled albumin particles⁴⁸. This technique is expensive, not available in every center, poorly sensitive, and may no longer be recommended as a screening method for PAVM³⁰.

Treatment of PAVMs

Prevention of CNS complications of PAVM, especially brain abscesses, and relief of hypoxemia when present are the primary objectives of treatment. Treatment of PAVM by transcatheter occlusion of PAVMs using detachable steel coils (embolization therapy) obviates the need for thoracotomy, and decreases right-to-left shunting, thus improving arterial blood gases and dyspnea^{49,123} (see reference 110 for review). Treatment of PAVMs with feeding vessels of 3 mm diameter or more is justified¹²³, even if PAVMs are asymptomatic; smaller PAVMs (with a feeding vessel of 1.5–2.0 mm) may also be occluded when technically feasible and right-to-left shunting is present¹⁰⁵. Conversely, embolization of PAVMs with large feeding vessels (up to 14 mm) may be difficult and require specific devices such as balloons or Amplatzer occluders^{8,16,20}.

In this series, embolization procedures were performed by radiologists from 6 French centers experienced in the management and treatment of HHT-related PAVMs. As reported in the literature^{49,105,123}, several PAVMs were often occluded during a single procedure; however several procedures were often required to occlude all visible PAVMs. The feasibility of embolization was limited in 10 cases with small feeding arteries and/or diffuse disease. Although 16 patients who underwent embolization therapy had a previous history of surgical resection of another PAVM (before embolization was available), surgery was necessary after embolization therapy in only 1 case.

Careful positioning and adapted size of the steel coils to the PAVM vessels are considered the major determinants to reduce the risk of complications of the procedure, especially lung infarction and systemic migration of the device through the PAVM^{35,49,123}. Benign complications of embolization include pleural pain and pleural effusion that improve with symptomatic treatment. Air embolism, transient angina, cardiac arrhythmia, and deep venous thrombosis^{61,123} are more rarely encountered. Safety and efficacy of embolization improve with experience¹⁰⁵, and it is recommended that this treatment be performed by experienced operators^{35,73}. Residual right-to-left shunting may persist after embolization therapy, as demonstrated by persistent hypoxemia^{35,55,73} and/or positive cardiac contrast echocardiography, even if complete occlusion has been obtained as judged by pulmonary angiography⁷⁴. Reperfusion of a PAVM several months after embolization may result from the development of feeding vessels that were not visible or were very small when performing the first procedure¹²⁴, or more often from the permeabilization of the occluded vessel¹⁰¹.

The apparent clinical impression of the reduction of the risk of infection and cerebral ischemic events by transcatheter embolization has not yet been precisely assessed¹¹⁰. A long-term success rate of 75% of embolization has been reported¹⁰⁴. One case of cerebral abscess and 2 cases of neurologic ischemic events have been reported in patients who had undergone transcatheter embolization^{35,73}. In the present series, 5 patients had a cerebral abscess after the diagnosis of PAVM was made, including 2 patients who had been treated 18 and 18.5 years earlier by surgery without follow-up, respectively, and 3 patients in whom the PAVM had not been treated (in 1 of them the abscess occurred 3 months after the diagnosis of the PAVM, following unsuccessful percutaneous treatment and while surgery was being planned). In addition, vaso-occlusion of low resistance right-to-left shunts may unmask or facilitate the development of new PAVMs. Thus it is reasonable to maintain a long-term follow-up of patients with PAVMs, regardless of the type of treatment, since PAVMs treated by embolization may permeabilize over time, and PAVMs may recur in operated patients as in any HHT patients.

Surgical treatment of PAVMs consisting of conservative resection of lung lobes or segments with PAVMs was performed before catheter embolization was available or as an emergency procedure for hemothorax, as described^{73,115}. Recurrence of PAVMs may require iterative treatments resulting in significant loss of lung function, and surgery has been supplanted by catheter embolization in most cases. Surgery, however, remains necessary in patients with right-to-left shunting and PAVM not amenable to embolization therapy. Lung transplantation has been done in rare cases with severe and diffuse PAVMs^{38,107,114}.

Screening for PAVM

Given the high risk of cerebral abscesses and ischemic complications of PAVM that can be reduced by treatment, screening of patients with HHT for PAVMs has been

proposed, even in asymptomatic patients⁶⁴. Screening is particularly recommended in women of childbearing age before pregnancy⁶⁴, although our study shows that this remains a rare circumstance for the diagnosis of PAVM. Screening is also particularly recommended in patients with a familial history of PAVMs, or a known mutation of the ENG gene^{15,97}. However, PAVMs also occur in families with mutations of the ACVRL1 gene¹¹⁰. Patients should be adequately informed of the potential consequences of asymptomatic PAVMs when left untreated. Whether first-degree family relatives should also undergo screening⁵² regardless of the presence of symptoms of HHT is debated. The optimal screening interval in HHT patients with negative screening tests is not known.

Chest CT is at least as sensitive and specific as pulmonary angiography¹⁰³, and is now considered the gold standard for the diagnosis of PAVM, whereas pulmonary angiography is performed when confirmation of the diagnosis is warranted and simultaneous treatment by embolization therapy is considered. There has been continuing debate about which noninvasive screening methods should be used^{30,52,64,103,122}. We recently conducted a study to compare the diagnostic value of noninvasive tests for the screening of clinically relevant and treatable PAVMs (that is, PAVMs amenable to embolization therapy) in patients with HHT³⁰, using chest CT and/or pulmonary angiography as a reference. We demonstrated that contrast echocardiography was the most sensitive test (with a sensitivity and a negative predictive value of 93%) to detect right-to-left shunting, and was therefore well suited for screening for PAVM. A good sensitivity of contrast echocardiography had also been suggested by previous studies, although no definite conclusion could be drawn in the absence of a gold standard test in the group of patients with negative contrast echocardiography^{70,86,90}. In addition, a 100% sensitivity and negative predictive value could be obtained when combining anteroposterior chest radiograph and contrast echocardiography. The combination of contrast echocardiography and chest radiograph thus represents an excellent screening procedure, with the advantage of very large availability, noninvasiveness, lower cost, and much lower radiation exposure than chest CT³⁰. Assessments of self-reported dyspnea, chest radiograph alone, measurement of AaPO₂ by the 100% oxygen method, and radionuclide lung scanning were insufficient for screening and were abandoned by our group. We suggested a screening algorithm based on anteroposterior chest radiograph, and contrast echocardiography if the radiograph is normal, followed by chest CT if either test is positive^{30,84}. This algorithm may obviate the need of chest CT in the majority of patients without PAVM. Screening based only on chest CT is a quite acceptable alternative to this algorithm.

Pulmonary Hypertension and HHT

Pulmonary hypertension in HHT may result from increased cardiac output resulting from systemic arteriovenous malformations (mostly in the liver)^{17,19}, or may be isolated and similar to idiopathic pulmonary hypertension

(a disease in which mutations in the bone morphogenetic protein receptor type II (BMPR2) gene are common). "Primary" pulmonary hypertension in HHT mostly occurs in patients with mutations of the ACVRL1 gene (ALK1)^{1,60,118}; 1 case has been described in a patient who had taken dexfenfluramine and had a mutation in the ENG gene (endoglin)²⁶, as well as 2 other cases in patients with possible causes of secondary pulmonary hypertension⁶⁰. Of note, mutations of the ENG or ACVRL1 genes have also been described in patients with "primary" pulmonary hypertension in the absence of overt HHT clinical disease⁵⁹. How mutations within the ACVRL1 gene may give rise to HHT or to primary pulmonary hypertension is currently unknown, and may be better understood in the future with in-depth understanding of signaling through TGF- β .

The current series confirms that severe pulmonary hypertension is rare in HHT, although moderate pulmonary hypertension may be found more frequently⁸⁷. However, low-resistance PAVMs may decrease the pulmonary artery pressure and mask nonsevere pulmonary arterial hypertension. Therefore, particular attention must be paid to pulmonary hypertension following vaso-occlusion of PAVMs, which may unmask a genuine pulmonary vascular disease. Embolization of PAVMs in patients with known pulmonary hypertension is contra-indicated⁵³. We emphasize that cardiac echocardiography should be performed in every patient with HHT, for evaluation of both right-to-left shunting (using the contrast method) and pulmonary hypertension.

In conclusion, a high frequency of CNS complications and severe infections including brain abscesses was found in this large series of patients with HHT-related PAVM. This underscores the clinical relevance of systematic screening for PAVMs even in asymptomatic patients with HHT. PAVMs often remain undiagnosed even after a cerebral abscess has occurred, suggesting that physicians may not be sufficiently aware of this orphan disorder. Informing patients and physicians about HHT may be improved by internet-based (<http://www.orpha.net/>) and patient-oriented strategies. Accordingly, information booklets for HHT patients are made available by the GERM*O*P (<http://germop.univ-lyon1.fr/>)³⁴ and by patient associations such as the HHT Foundation (<http://www.hht.org/web/>) or the Association Maladie de Rendu-Osler in France (<http://www.amro-france.net/>). Patients diagnosed with HHT should be informed of the risk of PAVM-related complications, and systematic screening for PAVM should be proposed, regardless of symptoms, familial history, or genetic considerations.

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