A Pulmonary Right-to-Left Shunt in Patients With Hereditary Hemorrhagic Telangiectasia Is Associated With an Increased Prevalence of Migraine*

Martijn C. Post, MD; Tom G. W. Letteboer, MD; Johannes J. Mager, MD, PhD; Thijs H. Plokker, MD, PhD; Johannes C. Kelder, MD; and Cornelius J. J. Westermann, MD, PhD

Introduction: **Hereditary hemorrhagic telangiectasia (HHT) is a rare autosomal-dominant vascular dysplasia with a high prevalence of pulmonary arteriovenous malformation (PAVM). Recent studies report an increased prevalence of migraine in patients with a cardiac right-to-left shunt. The aim of our study was to evaluate whether there is also an increased prevalence of migraine in patients with a pulmonary right-to-left shunt (PAVM).**

Methods: **All patients with HHT referred to our hospital till April 2004 with or without PAVM and with or without migraine were included in the study.**

Results: **In total, 538 HHT patients (41.6% men; mean age ± SD, 39.3 ± 18.6 years) could be included. PAVM was present in 208 patients (38.7%; mean age, 39.3 ± 17.6 years). Significantly more women were present in the PAVM subgroup compared to the non-PAVM subgroup, 65.4% vs 53.9% (p = 0.009). Migraine occurred in 88 patients with HHT, a prevalence of 16.4%. The prevalence of migraine in women with HHT was significantly higher compared to men, 19.4% vs 12.1%, respectively (p = 0.03) The prevalence of migraine in patients with PAVM was 21.2%, which was significantly higher then in patients without PAVM, 13.3% (p = 0.02). The occurrence of PAVM in the patients with migraine is significantly higher than in those without migraine, 50.0% vs 36.4%, respectively (p = 0.02).**

Conclusion: **This study showed a higher prevalence of PAVM in patients with migraine and HHT. The right-to-left shunt due to the PAVM might play a causal role in the pathogenesis of migraine in patients with HHT. This needs to be determined in further studies.**

(CHEST 2005; 128:2485–2489)

Key words: hereditary hemorrhagic telangiectasia; migrane; pulmonary arteriovenous malformation; right-to-left shunt

Abbreviations: CAVM = cerebral arteriovenous malformation; HHT = hereditary hemorrhagic telangiectasia; PAVM = pulmonary arteriovenous malformation; PFO = patent foramen ovale; TIA = transient ischemic attack

Hereditary hemorrhagic telangiectasia (HHT), or Rendu-Osler-Weber syndrome, is a rare autosomal-dominant vascular disease and is caused by mutations of endoglin or activin receptor-like kinase 1.[1,2] Mutations of endoglin cause HHT-1 and mutations of activin receptor-like kinase 1, HHT-2. A third and rare subtype is associated with juvenile polyposis coli and is caused by mutation of SMAD-4.[3] The prevalence of HHT may exceed 1 in 10.000 in some regions.[4] One of the clinical manifestations of the disease is arteriovenous malformation. Most commonly, these malformations occur in the lung (pulmonary arteriovenous malformation [PAVM]).[5–7] A PAVM constitutes a right-to-left shunt and cause hypoxemia, and often serious complications such as stroke or cerebral abscess.[4,8] HHT-1 is associated with a higher prevalence of PAVM, compared to HHT-2.[9]

Recent studies[15,16] showed a higher prevalence of migraine in patients with a cardiac right-to-left shunt, due to a patent foramen ovale (PFO). Several authors[10,11] have suggested a causal relationship between a right-to-left shunt and migraine. We were

*From the Departments of Cardiology (Drs. Post, Plokker, and Kelder) and Pulmonology (Drs. Letteboer, Mager, and Westermann), St. Antonius Hospital, Nieuwegein, the Netherlands.

Manuscript received November 23, 2004; revision accepted March 4, 2005.

Correspondence to: Cornelius J. J. Westermann, MD, PhD, Department of Pulmonology, St. Antonius Hospital., 3435 CM Nieuwegein, The Netherlands; e-mail: e.blokland@antonius.net

interested to see whether HHT patients with a pulmonary right-to-left shunt (PAVM), a cerebral arteriovenous malformation (CAVM), or HHT alone have an increased prevalence of migraine.

Materials and Methods

Patient Selection and Inclusion Criteria

Patient selection was done by a search in our database in which all patients with HHT referred to our hospital from January 1956 until April 2004 were included. The following inclusion criteria were used.

First of all, a definite diagnosis of HHT had to be made based on the Curaçao criteria or evidence for specific gene mutations.[12]

Secondly, only those patients in whom the presence of PAVM could be demonstrated or those in whom PAVM could be excluded were included. PAVM was excluded when chest radiographic findings or arterial oxygen pressure ($Pao_2 \geq 104$ mm Hg minus $0.24 \times$ age in years) were normal, or normal oxygen saturation by oximetry (arterial oxygen saturation $\geq 96\%$) or absence of right-to-left shunt ($< 5\%$), measured with the 100% oxygen technique.[13] When PAVM was suspected, its presence was confirmed with CT scan or pulmonary angiography. All patients in whom the presence or absence of PAVM was uncertain were excluded from the study.

Thirdly, only those patients with or without a history of migraine were included. A routine questionnaire about the history of headache and migraine has been used systematically since 1990. No specific questions were asked about the type of migraine. All patients in whom the presence or absence of migraine was uncertain or those who did not complete a questionnaire were excluded from the study.

Neurologic Manifestation

Screening for CAVM was performed using IV digital subtraction angiography since 1984, CT of the brain since 1980, or MRI of the brain since 1992. If CAVM was suspected, its presence was confirmed with conventional cerebral angiography.

Statistical Analysis

Descriptive statistics were used to describe patient characteristics. Continuous variables with normal distribution are presented as mean ± SD. Between-groups comparison of continuous variables was done by the independent Student *t* test. Categorical variables were compared by the Fisher exact test; $p < 0.05$ was considered statistically significant. All analysis was performed using statistical software (Version 9.0 for Windows; SPSS; Chicago, IL).

Results

Patient Selection and Characteristics

Five hundred thirty-eight patients (41.6% men; mean age, 39.3 ± 18.6 years) could be selected from the database. Twenty-one patients were included before 1990. Seventeen of 555 patients (3.1%) were excluded because their history of migraine was uncertain. The basic characteristics, type of HHT, and neurologic and pulmonary characteristics are summarized in Table 1.

PAVM

A definite diagnosis of PAVM was made in 208 patients; the prevalence of PAVM in our study population was 38.7%. There was a significantly higher prevalence of PAVM in the patients with HHT type 1 compared to the other subtypes, HHT types 2 and 3 ($p < 0.001$). There were also significantly more women with PAVM than men, 65.4% vs 34.6%, respectively ($p = 0.009$). The patients in the PAVM subgroup had a higher prevalence of CAVM compared to those without PAVM, 13.0% vs 4.2%, respectively ($p < 0.001$). There was also a higher prevalence of neurologic complications, such as brain abscess, transient ischemic attacks (TIAs), or brain infarction in patients with PAVM compared to those without, 9.1% vs 0% for brain abscess, 8.7% vs 1.2% for TIA, and 16.8% vs 1.2% for brain infarction ($p < 0.001$ for all). The prevalence of migraine was higher in patients with PAVM compared to those without PAVM, 21.2% vs 13.3%, respectively ($p = 0.02$). There were significantly more women with migraine and PAVM compared to men in the same subgroup, 25.7% vs 12.5%, respectively ($p = 0.03$). There was not a significant difference between the prevalence of women with migraine without PAVM compared to men in the same subgroup, 14.6% vs 11.8%, respectively ($p = 0.52$). There were significantly more women with migraine

Table 1—*Basic Characteristics, Type of HHT, Neurologic and Pulmonary Manifestation of the Total Study Group

Characteristics	No.	%
Total	538	
Age (SD), yr	39.3 (18.6)	
Men	224	41.6
Women	314	58.4
HHT		
Type 1	348	64.7
Type 2	113	21.0
Type 3	2	0.4
Unknown	75	13.9
Neurologic		
CAVM	41	7.6
Brain abscess	19	3.5
TIA	22	4.1
Brain infarction	39	7.2
Migraine	88	16.4
Men	27	12.1
Women	61	19.4
Pulmonary		
PAVM	208	38.7