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

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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.**

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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

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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

in the PAVM subgroup compared to women with migraine without PAVM, 25.7% vs 14.6%, respectively ($p = 0.02$). These data are also summarized in Table 2. After exclusion of all patients with CAVM ($n = 41$), the prevalence of migraine was still significantly higher in the patients with PAVM compared to those without, 19.3% vs 12.7%, respectively ($p = 0.04$).

Migraine

Migraine was present in 88 patients with HHT, a prevalence of 16.4%. One of the patients included before 1990 had a history of migraine. The prevalences of migraine in women and men were 19.4% and 12.1%, respectively. There were significantly more women than men in the migraine subgroup, 69.3% vs 30.7%, respectively ($p = 0.02$). The prevalence of CAVM was significantly higher in the patients with migraine then in those without, 14.8% vs 6.2%, respectively ($p = 0.01$). The occurrence of PAVM was significantly higher in the patients with migraine, 50% vs 36.4%, respectively ($p = 0.02$). These data are summarized in Table 3.

Table 2—*Basic Characteristics, Type of HHT, and Neurologic Manifestation in Patients With and Without PAVM*

Characteristics	With PAVM		Without PAVM		p Value
	No.	%	No.	%	
Patients	208	38.7	330	61.3	
Age (SD), yr	39.3 (17.6)		39.3 (19.2)		0.79
Men	72	34.6	152	46.1	0.009
Women	136	65.4	178	53.9	
HHT					
Type 1	166	79.8	182	55.2	< 0.001
Type 2	6	2.9	107	32.4	
Type 3	2	1.0	0	0.0	
Unknown	34	16.3	41	12.4	
Neurologic					
CAVM	27	13.0	14	4.2	< 0.001
Brain abscess	19	9.1	0	0	< 0.001
TIA	18	8.7	4	1.2	< 0.001
Brain infarction	35	16.8	4	1.2	< 0.001
Migraine	44	21.2	44	13.3	0.02
Men	9	12.5	18	11.8	1.00
Women	35	25.7	26	14.6	0.02

Table 3—*Basic Characteristics, Type of HHT, and Neurologic and Pulmonary Manifestations in Patients With and Without Migraine*

Characteristics	With Migraine		Without Migraine		p Value
	No.	%	No.	%	
Patients	88	16.4	450	83.6	
Age (SD), yr	39.0 (14.7)		39.3 (19.3)		0.89
Men	27	30.7	197	43.8	0.02
Women	61	69.3	253	56.2	
HHT					
Type 1	61	69.3	287	63.8	0.40
Type 2	15	17.0	98	21.8	
Type 3	1	1.1	1	0.2	
Unknown	11	12.5	64	14.2	
Neurologic					
CAVM	13	14.8	28	6.2	0.013
Brain abscess	3	3.4	16	3.6	1.00
TIA	6	6.8	16	3.6	0.15
Brain infarction	5	5.7	34	7.6	0.66
Pulmonary					
PAVM	44	50.0	164	36.4	0.02

Discussion

In the general European population, migraine occurs in 10 to 12%, with 6% in men and approximately 12.9 to 17.6% in women.[14] A higher prevalence of migraine, 22.0 to 39.4%, has been described in men and women with a cardiac right-to-left shunt due to a PFO.[15,16] In addition, we found that the prevalence of migraine in patients with HHT is higher (16.4%) in comparison with the general population. There was a significantly higher prevalence of migraine in HHT patients with a pulmonary right-to-left shunt due to PAVM compared to those without, 21.2% vs 13.3%, respectively. The prevalence of PAVM in patients with HHT might be underestimated. This might be explained by the lack of sensitivity of our screening methods for PAVM; the use of contrast echocardiography may have detected more shunts than diagnosed with our technique.[17]

A high prevalence of migraine has been reported in patients with HHT and PAVM.[18,19] A causal relationship between the presence of a right-to-left shunt and migraine has been suggested but remains until now unproven. Several hypotheses have been formulated. Firstly, HHT and some subtypes of migraine are autosomal-dominant disorders. Possibly, a particular genetic substrate might determine both, a pulmonary right-to-left shunt in patients with HHT and migraine.[20] Secondly, and more likely, trigger substances might enter the systemic circulation through the right-to-left shunt instead of being trapped in the pulmonary capillaries. These trigger substances might induce cerebral vascular instability or increased excitability of the CNS and cause migraine. Trigger substances that are proposed are a vasoactive chemical such as serotonin or (micro) emboli.[21] The latter also explains why there is a significantly higher incidence of brain infarction or TIA in patients with PAVM compared to those without PAVM.[5,8] We found a prevalence of 16.8%

vs 1.2% for brain infarction and 8.7% vs 1.2% for TIA in patients with and without PAVM, respectively. Earlier, we showed a significant reduction in the prevalence of migraine after percutaneous closure of a cardiac right-to-left shunt through a PFO, from 38.4% before closure vs 15.8% after closure.[15] Kruit et al[22] showed an increased prevalence of subclinical brain infarction in some brain areas in patients with migraine compared to those without. These findings fit in the hypothesis that (micro) emboli play a causative role in the pathogenesis of migraine.

In patients without detectable PAVM, the prevalence of migraine is still 13.3%. This prevalence is slightly higher than described in the overall population. In these patients with HHT, there might be microscopic PAVM. The combination of a chest radiograph and arterial oxygen tension measurements after inhalation of 100% oxygen has a sensitivity of 86%, and thus small PAVMs may have been overlooked.[17] Individuals without a pulmonary right-to-left shunt may need a larger amount of trigger substances in the venous circulation, causing migraine by overwhelming the filter capacity of the lungs.

The occurrence of CAVM in patients with HHT is approximately 10 to 15%.[6] The prevalence of CAVM in this study is 7.6%, which is probably underestimated because screening for CAVM was not done routinely and several screening methods with different sensitivity have been used. Neurologic manifestations due to CAVM, which had been described,[17,23,24] are intracranial hemorrhage, seizures, epilepsy, and headaches. Roman et al[25] demonstrated that 6 to 8% of the patients with HHT and PAVM also have an intracranial arteriovenous malformation. Moussouttas et al[19] described a CAVM prevalence of 11 to 19% in 75 patients with single or multiple PAVMs. We found a prevalence of 13% of CAVM in our patients with PAVM. We also found an increased occurrence of CAVM in patients with migraine compared to those without migraine. It had been suggested by Steele et al[20] that CAVM might play a role in the pathogenesis of migraine in patients with HHT.

Our opinion is that the pulmonary right-to-left shunt due to PAVM plays a more important role in the pathogenesis of migraine. After exclusion of all patients with CAVM, there is still a significantly higher prevalence of migraine in those patients with PAVM. However, bias might be present because not all patients were screened for CAVM.

A higher prevalence of migraine in patients with HHT and PAVM is found compared to those without this shunt. Our data suggest that a pulmonary right-to-left shunt plays a role in the pathogenesis of migraine, as well as a cardiac right-to-left shunt, due to a PFO. How right-to-left shunts cause migraine needs to be determined in further studies.

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