Pulmonary arteriovenous malformations associated with migraine with aura

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ABSTRACT: Migraine with aura (MA) is associated with cardiac right-to-left shunt. We prospectively studied the association between pulmonary arteriovenous malformations (PAVMs) and MA in hereditary haemorrhagic telangiectasia (HHT).

All 220 consecutive HHT patients who underwent high-resolution chest computed tomography for PAVM screening were included prospectively. Prior to screening, a structured validated headache questionnaire was completed by 196 patients (57% female; mean$\pm$sd age 44.6$\pm$15.2 yrs). Two neurologists diagnosed migraine according to the International Headache Society Criteria.

A PAVM was present in 70 (36%) patients. The prevalence of MA was 24% in the presence of a PAVM compared with 6% in the absence of a PAVM (OR 4.6, 95% CI 1.84–11.2; p=0.001), and MA was an independent predictor for the presence of PAVM using multivariate analysis (OR 3.6, 95% CI 1.21–10.5; p=0.02). A PAVM was present in 68% of the patients with MA compared with 32% in the non-migraine controls (OR 4.6, 95% CI 1.84–11.2; p=0.001), and a PAVM was an independent predictor for MA using multivariate analysis (OR 3.0, 95% CI 1.00–9.20; p=0.05).

In conclusion, PAVMs are associated with MA in HHT patients.

KEYWORDS: Hereditary haemorrhagic telangiectasia, migraine, shunt

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Migraine is a disorder that occurs in 12% of the general population [1]. In one-third of patients, a migraine attack is accompanied by an aura [2]. Migraine is a complex disease and multiple factors seem to play a role in the pathogenesis. In the last decade, an association between a cardiac right-to-left shunt through the patent foramen ovale (PFO) and migraine has been described [3]. In particular, the prevalence of migraine with aura (MA) seems to be increased in the presence of a PFO [4].

Interestingly, an association between overall migraine and the presence of a pulmonary right-to-left shunt, a pulmonary arteriovenous malformation (PAVM), has been observed in a retrospective study [5]. A PAVM is an abnormality of the pulmonary vascular system characterised by direct communication between the pulmonary artery and vein. In patients with PAVM, >70% have hereditary haemorrhagic telangiectasia (HHT), an autosomal dominant disorder caused mainly by a mutation of endoglin (HHT type 1) or activin receptor-like kinase 1 (HHT type 2) [6]. A PAVM is present in ~40% of the patients with HHT, with a higher prevalence (≤50%) in HHT type 1 [7, 8].

The aim of the current prospective study was to evaluate the prevalence of migraine and especially MA in either the presence or absence of a PAVM.

METHODS

Patient selection

All 417 consecutive persons (>16 yrs of age) who were referred to our hospital (St. Antonius Hospital, Nieuwegein, The Netherlands) for screening for possible HHT, most of them family members of index cases, were studied prospectively between May 2004 and April 2008. Informed consent was obtained from all patients and the local ethical committee of St. Antonius Hospital (Nieuwegein, The Netherlands) approved the study.

HHT screening

A clinical diagnosis of HHT was based on the presence of at least three clinical characteristics in accordance with the Curaçao criteria [9]. These criteria consist of spontaneous and recurrent epistaxis, telangiectasia at characteristic sites, visceral arteriovenous malformations or telangiectasia, and a first-degree relative with HHT [9]. A genetic diagnosis was considered to be positive either when the family mutation was present or when the patient was an obligate carrier of the mutation. The affected patients were divided into three groups: 1) HHT type 1, 2) HHT type 2, and 3) HHT unknown on the basis

TABLE 1	Basic characteristics
Subjects n	196
Age yrs	44.6±15.2
Female	112 (57.1)
Male	84 (42.9)
Blood pressure mmHg	
Systolic	131±16
Diastolic	77±9
Neurological event	
TIA	3 (1.5)
CVA	4 (2.0)
TIA or CVA	7 (3.6)
CAVM[#]	11 (15.1)
Migraine	39 (19.9)
Migraine with aura	24 (12.8)
Migraine without aura	14 (7.1)
PAVM	
No	126 (64.3)
Yes	70 (35.7)
HHT	
Type 1	73 (37.2)
Type 2	105 (53.6)
Unknown	18 (9.2)

Data are presented as mean±SD or n (%), unless otherwise indicated. TIA: transient ischaemic attack; CVA: cerebral vascular accident; CAVM: cerebral arteriovenous malformation; PAVM: pulmonary arteriovenous malformation; HHT: hereditary haemorrhagic telangiectasia. [#]: data available in 73 patients.

of the mutations findings. The HHT unknown subgroup consisted of patients in whom the mutation was neither found nor investigated [8]. A definite diagnosis of HHT could be made in 236 patients out of 417 screened persons. HHT type 1 was present in 95 patients, HHT type 2 in 118 patients, and the HHT was unknown in 23 patients.

High-resolution computed tomography of the chest
In 228 (97%) patients, a high-resolution computed tomography (HRCT) scan of the chest was performed without contrast using the single breath-hold technique with a slice thickness of 1 mm (16-slice HRCT; Philips Medical Systems, Best, The Netherlands). Eight patients refused the HRCT or had a contraindication. HRCT is currently the gold standard in diagnosing a PAVM [10]. Identification of PAVM was based on the presence of a nodular or round opacity with both an afferent and efferent vessel. The eight patients in whom the diagnosis of PAVM was uncertain were excluded. A radiologist, blinded to the migraine diagnosis, diagnosed the presence of a PAVM.

Migraine diagnosis
A structured headache questionnaire was sent to all patients prior to the outpatient screening visit. The same questionnaire had been used in previous studies [11]. The patients were asked about the presence, time of onset, frequency, severity, duration, type and site of headache, accompanying symptoms, and the impact on activities. The questionnaire was focused on the 6-month time-period prior to the screening visit. Two
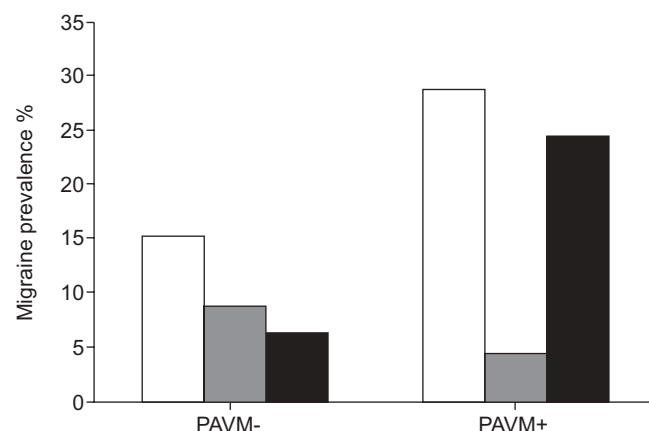

FIGURE 1. The prevalence of migraine with and without aura in the presence (+) or absence (-) of a pulmonary arteriovenous malformation (PAVM). □: any migraine (p=0.03); ▨: migraine without aura (p=0.42); ■: migraine with aura (p=0.001).

independent neurologists, blinded to the patients' data, diagnosed migraine or MA by reviewing the questionnaires according to the International Headache Society criteria [12]. Migraine was defined if at least one migraine attack occurred during the pre-defined period. The headache questionnaire was fully completed by 196 (89%) out of 220 patients in whom an adequate HRCT of the chest was performed.

Neurological event
The history of stroke or a transient ischaemic event was diagnosed by a neurologist and confirmed by the appropriate imaging techniques. Screening for cerebral arteriovenous malformations (CAVM) was recommended in patients who suffered HHT type 1 using magnetic resonance imaging of the brain, because the prevalence of CAVM in patients with HHT type 1 is much higher in comparison with the prevalence in HHT type 2 patients (15% versus 1%) [8].

Statistical analysis
Descriptive statistics were used to describe patients and migraine characteristics. Differences between groups were analysed by unpaired t-test for continuous variables and Chi-squared test for nominal variables. Data are given either as mean±SD or n (% of total), and the level of significance was set at p<0.05. Univariate and multivariate statistical analysis with logistic regression were used to identify and estimate risk factors for overall migraine and MA compared with non-migraine controls. Following univariate analysis, variables with p⩽0.1 were entered into a multivariate model. The odds ratios with their 95% confidence intervals were calculated. Interobserver variability was evaluated by measuring the kappa coefficient. Statistical analysis was performed with the SPSS software for Windows XP version 14.0.1 (SPSS, Chicago, IL, USA).

RESULTS
Patient characteristics
A total of 196 HHT patients (57% female; mean±SD age 44.6±15.2 yrs) could be included in the study. The baseline characteristics are given in table 1.

TABLE 2	Characteristics of patients with (+) and without (-) pulmonary arteriovenous malformation (PAVM), and the univariate and multivariate analysis for the prediction of PAVM					
	PAVM -	**PAVM +**	**Univariate OR (95% CI)**	**p-value**	**Multivariate OR (95% CI)**	**p-value**
Basic characteristics						
Total	126 (64.3)	70 (35.7)				
Age yrs	44.5±14.5	44.9±16.4	1.00 (0.98–1.02)	0.87		
Female	68 (54.0)	44 (62.9)	1.44 (0.79–2.63)	0.29		
Male	58 (46.0)	22 (37.1)				
Blood pressure mmHg						
Systolic	132±16	128±16	0.99 (0.97–1.00)	0.14		
Diastolic	78±8	76±10	0.97 (0.94–1.01)	0.16		
Neurological event						
TIA	1 (0.8)	2 (2.9)	3.68 (0.33–41.3)	0.29		
CVA	1 (0.8)	3 (4.3)	5.60 (0.57–54.9)	0.13		
TIA or CVA	2 (1.6)	5 (7.1)	4.77 (0.90–25.3)	0.10	1.41 (0.17–11.9)	0.75
CAVM[#]	4 (11.8)	7 (17.9)	1.64 (0.44–6.18)	0.52		
Migraine overall	19 (15.1)	20 (28.6)	2.25 (1.11–4.59)	0.03		
Migraine with aura	8 (6.3)	17 (24.3)	4.55 (1.84–11.2)	0.001	3.57 (1.21–10.5)	0.02
Migraine without aura	11 (8.7)	3 (4.3)	0.42 (0.16–2.19)	0.42	0.61 (0.14–2.63)	0.51
No migraine	107 (84.9)	55 (72.4)	Reference		Reference	
HHT[¶]						
Type 1	31 (42.5)	42 (57.5)	7.01 (3.50–14.1)	<0.001	6.33 (3.10–12.9)	<0.001
Type 2	88 (83.8)	17 (16.2)				
Unknown	7 (38.9)	11 (61.5)	NA			

Data are presented as n (%) or mean±SD, unless otherwise indicated. OR: odds ratio; CI: confidence interval; TIA: transient ischaemic attack; CVA: cerebral vascular accident; CAVM: cerebral arteriovenous malformation; HHT: hereditary haemorrhagic telangiectasia; NA: not available. [#]: data available in 73 patients (34 without PAVM and 39 with PAVM); [¶]: uni- and multivariate analysis without unknown subgroup.

PAVM

The prevalence of PAVM in our study population was 35.7%. The prevalence of migraine in patients with a PAVM was 28.6% compared with 15.1% in the patients without a PAVM (OR 2.25, 95% CI 1.11–4.59; p=0.03). The prevalence of MA was 24.3% in patients with a PAVM and 6.3% in patients without a PAVM (OR 4.55, 95% CI 1.84–11.2; p=0.001). These data are shown in figure 1. In the presence of a PAVM, the lifetime prevalence of a cerebral ischaemic event (both transient ischaemic attack and cerebrovascular accident) was 7.1% compared with 1.6% in the absence of a PAVM (OR 4.77, 95% CI 0.90–25.3; p=0.10). HHT type 1 was a predictor for the presence of a PAVM (OR 7.01, 95% CI 3.50–14.1; p<0.001). In a multivariate analysis model, MA (OR 3.57, 95% CI 1.21–10.5; p=0.02) and HHT type 1 (OR 6.33, 95% CI 3.10–12.9; p<0.001) were independent predictors for the presence of a PAVM after correction for the history of a cerebral ischaemic event. These data are summarised in table 2.

Migraine

The overall prevalence of any migraine was 19.9% (82% female, 41.3±15.5 yrs). MA was present in 12.8% of the HHT patients. The patients with any migraine were predominantly female (OR 4.40, 95% CI 1.83–10.6; p<0.001), had a higher lifetime prevalence of a cerebral ischaemic event (OR 5.87, 95% CI 1.26–27.4; p=0.03), had a higher prevalence of PAVM (OR 2.25, 95% CI 1.11–4.59; p=0.03) and suffered HHT type 2 (OR

1.96, 95% CI 0.93–4.13; p=0.09) compared with the non-migraine controls. In a multivariate analysis model, female sex was the only predictor for the presence of any migraine after correction for the history of a cerebral ischaemic event, the presence of a PAVM and type of HHT (OR 4.50, 95% CI 1.72–11.7; p=0.002).

Patients who suffered MA were predominantly female, had a higher lifetime prevalence of a cerebral ischaemic event, a higher prevalence of PAVM and a HHT type 1 genotype compared with non-migraine controls. The prevalence of a PAVM was 68% in the patients with MA compared with 32% in the non-migraine controls (OR 4.55, 95% CI 1.84–11.2; p=0.001). In a multivariate analysis model, the presence of a PAVM (OR 3.01, 95% CI 1.00–9.20; p=0.05) and female sex (OR 5.60, 95% CI 1.51–20.7; p=0.01) were both independent predictors for having MA, after correction for the history of a cerebral ischaemic event and HHT genotype. These data are summarised in table 3.

The saturation fraction in 17 HHT patients with a PAVM and MA was significantly lower compared with 49 non-migraine HHT patients with a PAVM, 95% versus 97%, respectively (OR 0.78, 95% CI 0.62–0.99; p=0.02). The arterial oxygen tension tended to be lower in the MA subgroup, at 10.2 kPa versus 11.0 kPa (OR 0.81, 95% CI 0.60–1.09; p=0.17). The kappa coefficient for interobserver variability for migraine was 0.93 (p<0.0001).

TABLE 3	Characteristics of patients with migraine with aura (MA) compared with non-migraine controls with the univariate and multivariate analysis for the prediction of MA					
	No migraine	**MA**	**Univariate OR (95% CI)**	**p-value**	**Multivariate OR (95% CI)**	**p-value**
Basic characteristics						
Total	157 (86.3)	25 (13.7)				
Age yrs	45.5±15.0	41.1±16.5	0.98 (0.95–1.00)	0.18		
Female	80 (51.0)	21 (84.0)	5.05 (1.66–15.4)	0.002	5.60 (1.51–20.7)	0.01
Male	77 (49.0)	4 (16.0)				
Blood pressure						
Systolic	131±15	126±17	0.98 (0.95–1.00)	0.15		
Diastolic	78±9	76±8	0.97 (0.92–1.03)	0.34		
Neurological event						
TIA	2 (1.3)	1 (4.0)	3.23 (0.28–37.0)	0.36		
CVA	1 (0.6)	2 (8.0)	13.6 (1.18–155)	0.05		
TIA or CVA	3 (1.9)	3 (12.0)	7.00 (1.33–36.9)	0.02	2.51 (0.28–22.5)	0.41
CAVM[#]	6 (12.2)	3 (18.8)	1.65 (0.36–7.55)	0.68		
PAVM						
No	107 (68.2)	8 (32.0)				
Yes	50 (31.8)	17 (68.0)	4.55 (1.84–11.2)	0.001	3.01 (1.00–9.20)	0.05
HHT[¶]						
Type 1	54 (79.4)	14 (20.6)	3.30 (1.25–8.68)	0.02	2.10 (0.68–6.47)	0.20
Type 2	89 (92.7)	7 (7.3)				
Unknown	14 (77.8)	4 (22.2)	NA			

Data are presented as n (%) or mean±SD, unless otherwise indicated. OR: odds ratio; CI: confidence interval; TIA: transient ischaemic attack; CVA: cerebral vascular accident; CAVM: cerebral arteriovenous malformation; PAVM: pulmonary arteriovenous malformation; HHT: hereditary haemorrhagic telangiectasia; NA: not availalble. [#]: data available in 77 patients (60 non-migraine controls and 17 MA); [¶]: uni- and multivariate analysis without unknown subgroup.

DISCUSSION

Migraine occurs in 10–12% of the general population, and the prevalence increases with age until a peak prevalence of 18% is reached in the fourth decade of life [1]. Migraine prevalence varies according to age, sex, ethnic origin and income. In one-third of patients with migraine, the attack is associated with transient focal neurological symptoms, *i.e.* the aura phenomenon [13]. The aura phonomenon is related to cortical activation followed by a temporary depression of neuronal activity, the so-called ''cortical spreading depression'' [14, 15]. Coupled with these cortical spreading depressions are cerebral blood flow changes that manifest themselves as initial hyperaemia followed by oligaemia. These changes in cortical blood flow are seen during the aura phenomenon in migraine [14]. Different migraine triggers can initiate an attack; however, the exact mechanism behind the initial start of the cortical cascade is still unknown.

Migraine, especially MA, is associated with the presence of a right-to-left shunt [16]. In the presence of a right-to-left shunt, the prevalence of MA is ~48% compared with 14% in those without a shunt [17], and seems to be independent of the localisation of the right-to-left shunt [3]. In the presence of a pulmonary or cardiac right-to-left shunt, the prevalence of MA is increased compared with those without a shunt [4, 18]. In our study, we have described the association between the presence of a pulmonary right-to-left shunt and the occurrence of MA, and found that the presence of a PAVM was an

independent predictor for having MA in HHT patients. Interestingly, we found that the presence of MA is an independent predictor for the presence of a PAVM in HHT patients.

Three small observational studies reported the efficacy of treatment of a large PAVM, and described the prevalence of self-reported migraine prior to the treatment. The prevalence of migraine in these patients with a large PAVM varies between 38 and 59% [19–21].

WILMSHURST and NIGHTINGALE [17] described the relationship between the presence of a right-to-left shunt and the prevalence of MA in 200 patients with a history of a decompression illness. The diagnosis of migraine was based on the International Headache Society criteria [12]. The MA prevalence was 29% in the presence of a pulmonary shunt (n=14) compared with 14% in patients without a shunt.

We previously reported the prevalence of self-reported migraine in 538 HHT patients. The overall prevalence of any migraine was 16%. In the presence of a PAVM, 21% of the patients suffered from any migraine, compared with 13% in the patients without a PAVM (p=0.02). In that study, the difference between migraine with or without aura could not be made [7]. Furthermore, embolisation of PAVM seems to reduce the prevalence of migraine, especially MA. In an observational retrospective study, the MA prevalence decreased from 33% before to 19% after embolisation of large PAVMs [22].

THENGANATT *et al.* [18] described the relationship between a PAVM and migraine in 124 HHT patients. The overall prevalence of migraine and MA in their study population was 38% and 31%, respectively. The prevalence of any migraine in patients with a PAVM was 46% compared with 33% in those without a PAVM (p=0.14). However, the presence of PAVM was associated with migraine after adjustment for age and sex (OR 2.4; p=0.04) [18]. In our study, we found an overall prevalence of any migraine of 29% in the presence of a PAVM compared with 15% in patients without a PAVM, without differences in age and sex between those two groups. The MA prevalence was 24% in patients with a PAVM and 6% in those without a PAVM. The prevalence of any migraine in the absence of a PAVM is the same as the peak prevalence in the general population found during the fourth decade of life. The presence of a PAVM was not associated with overall prevalence of any migraine. However, a PAVM was a strong independent predictor for MA after adjustment for sex, a history of a cerebral ischaemic event and type of HHT.

It is suggested that paradoxical embolism might play a role in the pathophysiology of migraine, especially in MA. The (micro)-emboli might trigger the migraine attack, thereby inducing the cascade of ''cortical spreading depression'' [23, 24]. Paradoxical thromboembolism through a right-to-left shunt has been postulated as a possible mechanism in the development of a (cryptogenic) cerebral ischaemic event [6, 25] An increased prevalence of cerebral ischaemic events is found in patients with a PAVM [26]. The prevalence of subclinical brain infarction, diagnosed by magnetic resonance imaging, is higher in patients with MA compared with non-migraine controls [27]. Furthermore, patients with MA have an increased lifetime risk for a cerebral ischaemic event [28]. In our study, we found a higher lifetime prevalence of a cerebral ischaemic event in the presence of a PAVM compared with those without. Interestingly, the lifetime prevalence of a cerebral ischaemic event was significantly higher in patients suffering MA compared with non-migraine controls. All these findings support the hypothesis that (micro)emboli might play a role in the pathogenesis of MA.

Several authors have described the association between migraine and the presence of a CAVM [29, 30]. In a study by STEELE *et al.* [31], it is suggested that CAVM might play a role in the pathogenesis of migraine in HHT patients. In the present study, we found no association between the presence of a CAVM and overall prevalence of no migraine or MA. The same observation was made by THENGANATT *et al.* [18], and was also reported in our large retrospective study [7]. However, the prevalence of CAVM might be underestimated because only a subgroup of patients has been screened for CAVM.

An autosomal dominant inherited pattern was found for the occurrence of a cardiac shunt and was linked to the inheritance of MA in some families [32]. As mentioned earlier, HHT is an autosomal dominant inherited disorder caused predominantly by two mutations, which lead to different types of HHT, each with their own phenotype [8, 33]. These two mutations, or a mutation that has not yet been specified, might determine both HHT and MA. However, we found no difference in the prevalence of any migraine or MA between both types of HHT in the presence of a PAVM. In support of this, the HHT genotype was not an independent predictor for MA.

An important limitation of our study might be the presence of a selection bias. First, our patient population was a selected cohort referred to our tertiary care centre (St Antonius Hospital, Nieuwegein, The Netherlands). Migraine prevalence in our HHT population might differ from the prevalence in the overall worldwide group of patients suffering HHT. It is possible that environmental and other unidentified factors interact to trigger a migraine attack [34], and these factors might differ between countries, and especially between ethnic origin and income. Secondly, 11% of the selected patients did not fill in the questionnaire accurately, which could either under- or overestimate the prevalence of migraine. Thirdly, we were unable to control for other risk factors for a cerebral ischaemic event, and this might influence the prevalence of migraine.

In conclusion, in this large prospective study, the presence of a PAVM is associated with MA in HHT patients. MA is a strong independent predictor for the presence of a PAVM, regardless of the HHT genotype.

STATEMENT OF INTEREST
None declared.

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