ERJ Express. Published on March 26, 2009 as doi: 10.1183/09031936.00179008

PULMONARY ARTERIOVENOUS MALFORMATIONS ASSOCIATED WITH MIGRAINE WITH AURA

Martijn C Post[1], Marco WF van Gent[1], Herbert WM Plokker[1], Cees JJ Westermann[2], Johannes C Kelder[1], Johannes J Mager[2], Tim T Overtoom[3], Wouter J Schonewille[4], Vincent Thijs[5, 6], Repke J Snijder[2]

Department of Cardiology[1], Pulmonology[2], Radiology[3], and Neurology[4], St Antonius Hospital, Nieuwegein, The Netherlands, and Department of Neurology[5], University Hospital Gasthuisberg, and Vesalius Research Center[6], Leuven, Belgium

Word count Abstract and Text: 184 and 2179 words

E-mail addresses of the authors:

m.van.gent@antonius.net; t.plokker@antonius.net; c.westermann@antonius.net; keld01@antonius.net; jjmager@mesos.nl; t.overtoom@antonius.net; w.schonewille@antonius.net; vincent.thijs@uz.kuleuven.ac.be; r.snijder@antonius

Short title: PAVM and migraine with aura

Disclosure: The authors have no conflicts of interest.

Address for correspondence:

Martijn C. Post, M.D, PhD

Department of Cardiology, St Antonius Hospital

Koekoekslaan 1, 3435 CM Nieuwegein, The Netherlands

Phone: 0031-30-6099111 and Fax : 0031-30-6092274

E-mail: m.post@antonius.net

Abstract

Background: 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 hemorrhagic teleangiectasia (HHT).

Methods: All 220 consecutive HHT patients who underwent a 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 age 45±15 years). Two neurologists diagnosed migraine according to the International Headache Society Criteria.

Results: A PAVM was present in 70 (36%) patients. The prevalence of MA was 24% in the presence of a PAVM compared to 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 to 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).

Conclusion: PAVMs are associated with MA in HHT patients.

Key words: hereditary hemorrhagic teleangiectasia – migraine - shunt

Introduction

Migraine is a disorder and 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 a the patent foramen ovale (PFO), and migraine has been described.[3] Especially, 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, characterized by direct communication between the pulmonary artery and vein. At least 70% of patients with PAVM have hereditary hemorrhagic teleangiectasia (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 about 40% of the patients with HHT, with a higher prevalence in HHT type 1 up to 50%.[7;8]

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

Methods:

Patient selection

All 417 consecutive persons (>16 years of age) who were referred to our hospital 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 approved the study.

HHT screening

A clinical diagnosis of HHT was based on the presence of at least 3 clinical characteristics in accordance to the Curaçao criteria. These criteria consist of spontaneous and recurrent epistaxis, teleangiectasia at characteristic sites, visceral arteriovenous malformations or teleangiectasia, and a first degree relative with HHT.[9] A genetic diagnosis was considered to be positive 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, HHT type 1, HHT type 2, and HHT unknown on the basis of the mutations findings. The HHT unknown subgroup consisted of patients in whom the mutation was not found or 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.

HRCT of the chest

In 228 patients (97%), a high-resolution computer tomography (HRCT) scanning of the chest was performed without contrast using the single breath-hold technique with a slice thickness of 1 mm (Philips, 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. Those patients (n=8) 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 was 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 six months time period prior to the screening visit. Two independent neurologists, blinded to the patients' data, diagnosed migraine or migraine with aura by reviewing the questionnaires according to the International Headache Society (IHS) criteria.[12] Migraine was defined if at least one migraine attack occurred during the predefined period. The headache questionnaire was fully completed by 196 out of 220 patients (89%) in whom an adequate HRCT of the chest was performed.

Neurological event

The history of stroke or a transient ischemic event was diagnosed by a neurologist, and confirmed by the appropriate imaging techniques. Screening for cerebral arteriovenous malformations (cerebral AVM) was recommended in patients who suffered HHT type 1 using magnetic resonance imaging of the brain, because the prevalence of cerebral AVM in patients with HHT type 1 is much higher in comparison to 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 analyzed by unpaired Student's *t* test for continuous variables and Chi-square test for nominal variables. Data are given as mean ± standard deviation or number with the percentage 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 to non-migraine controls. Following univariate

analysis, variables with a p-value of less or equal to 0.1 were entered into a multivariate model. The Odds ratios (OR) with their 95% confidence intervals (CI) 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 (Chicago, IL).

Results:

Patient characteristics

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

Pulmonary arteriovenous malformation

The prevalence of PAVM in our study population was 35.7%. The prevalence of migraine in patients with a PAVM was 28.6% compared to 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 ischemic event (both transient ischaemic attack and cerebrovascular accident) was 7.1% compared to 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 ischemic event. These data are summarized in table 2.

Migraine

The overall prevalence of any migraine was 19.9% (82% female, 41.3±15.5 years). 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), have a higher lifetime prevalence of a cerebral ischemic event (OR 5.87: 95% CI 1.26 – 27.4; p=0.03), have 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 to the non-migraine controls. In a multivariate analysis model female gender was the only predictor for the presence of any migraine, after correction for the history of a cerebral ischemic event, the presence of a PAVM, and type of HHT (OR 4.50: 95% CI 1.72 – 11.7; p=0.002).

Patients who suffer MA were predominantly female, had a higher lifetime prevalence of a cerebral ischemic event, a higher prevalence of PAVM, and a HHT type 1 genotype, compared to non-migraine controls. The prevalence of a PAVM was 68% in the patients with MA compared to 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 gender (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 ischemic event and HHT genotype. These data are summarized in table 3.

The saturation fraction in HHT patients with a PAVM and MA (n=17) was significantly lower compared to non-migraine HHT patients with a PAVM (n=49), 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, 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).

Discussion

Migraine occurs in 10 to 12% of the general population, the prevalence increases with age till a peak prevalence of 18% is reached in the fourth decade of life.[1] The migraine prevalence varies by age, sex, ethnic origin, and income. In one third of the patients with migraine the attack is associated with transient focal neurological symptoms, the aura phenomenon.[13] The aura 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 as initial hyperaemia followed by oligemia. 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 about 48% compared to 14% in those without a shunt.[17] This 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 to those without a shunt.[4;18] In this study, we 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 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 IHS criteria. The MA prevalence was 29% in the presence of a pulmonary shunt (n=14) compared to 14% in the patients without a shunt.[17]

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 to 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, embolization 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 embolization of large PAVM.[22] Thenganatt et al. described the relationship between a PAVM and migraine in 124 HHT patients.[18] 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 to 33% in those without a PAVM (p=0.14). However, the presence of PAVM was associated with migraine, after adjustment for age and gender (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 to 15% in patients without a PAVM, without difference 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 at 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 gender, a history of a cerebral ischemic 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, and induce 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 ischemic event.[6;25] An increased prevalence of cerebral ischemic events is found in patients with a PAVM.[26] The prevalence of sub-clinical brain infarction, diagnosed by MRI, is higher in patients with MA compared to non-migraine controls.[27] Furthermore, patients with MA have an increased life-time risk for a cerebral ischemic event.[28] In our

study, we found a higher lifetime prevalence of a cerebral ischemic event in the presence of a PAVM compared those without. Interestingly, the lifetime prevalence of a cerebral ischemic event was significantly higher in patients suffering MA compared to non-migraine controls. All these findings support the hypothesis that (micro) emboli might play a role in the pathogenesis of MA.

Several authors described the association between migraine and the presence of a cerebral AVM.[29;30] In a study by Steele et al. it is suggested that cerebral AVM might play a role in the pathogenesis of migraine in HHT patients.[31] In the present study, we found no association between the presence of a cerebral AVM and overall prevalence of neither any migraine nor MA. The same observation was made by Thenganatt et al. and was also reported in our large retrospective study.[7;18] However, the prevalence of cerebral AVM might be underestimated because only a subgroup of patients has been screened for cerebral AVM.

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 by mainly two mutations, leading to different types of HHT with both their own phenotype.[8;33] These two mutations or a mutation that has not been specified yet 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, the HHT genotype was not an independent predictor for MA.

An important limitation of our study might be the presence of a selection bias. Firstly, our patient population was a selected cohort referred to our tertiary care centre. Migraine prevalence in our HHT population might differ from the prevalence in the overall worldwide group of patients suffering HHT. Whereas, environmental and other unidentified factors interact to trigger a migraine attack.[34] These factors might differ between countries, especially ethnic origin and income. Secondly, 11% of the selected patients did not fill in the questionnaire appropriately, this might under – or overestimated the prevalence of migraine.

Thirdly, we were not able to control for other risk factors for a cerebral ischemic event, and this might influence the prevalence of migraine.

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

Reference List

1. Stewart WF, Shechter A, Rasmussen BK. Migraine prevalence. A review of population-based studies. Neurology 1994;44:S17-S23.

2. Launer LJ, Terwindt GM, Ferrari MD. The prevalence and characteristics of migraine in a population-based cohort: the GEM study. Neurology 1999;53:537-542.

3. Post MC, Budts W. The relationship between migraine and right-to-left shunt: Fact or fiction? Chest 2006;130:896-901.

4. Schwerzmann M, Nedeltchev K, Lagger F et al. Prevalence and size of directly detected patent foramen ovale in migraine with aura. Neurology 2005;65:1415-1418.

5. Post MC, van Gent MW, Snijder RJ et al. Pulmonary arteriovenous malformations and migraine: a new vision. Respiration 2008;76:228-233.

6. Shovlin CL, Letarte M. Hereditary haemorrhagic telangiectasia and pulmonary arteriovenous malformations: issues in clinical management and review of pathogenic mechanisms. Thorax 1999;54:714-729.

7. Post MC, Letteboer TG, Mager JJ et al. A pulmonary right-to-left shunt in patients with hereditary hemorrhagic telangiectasia is associated with an increased prevalence of migraine. Chest 2005;128:2485-2489.

8. Letteboer TG, Mager JJ, Snijder RJ et al. Genotype-phenotype relationship in hereditary haemorrhagic telangiectasia. J.Med.Genet. 2006;43:371-377.

9. Shovlin CL, Guttmacher AE, Buscarini E et al. Diagnostic criteria for hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber syndrome). Am.J.Med.Genet. 2000;91:66-67.

10. Remy J, Remy-Jardin M, Wattinne L, Deffontaines C. Pulmonary arteriovenous malformations: evaluation with CT of the chest before and after treatment. Radiology 1992;182:809-816.

11. Mortelmans K, Post M, Thijs V, Herroelen L, Budts W. The influence of percutaneous atrial septal defect closure on the occurrence of migraine. Eur.Heart J. 2005;26:1533-1537.

12. The International Classification of Headache Disorders: 2nd edition. Cephalalgia 2004;24 Suppl 1:9-160.

13. Launer LJ, Terwindt GM, Ferrari MD. The prevalence and characteristics of migraine in a population-based cohort: the GEM study. Neurology 1999;53:537-542.

14. Olesen J, Larsen B, Lauritzen M. Focal hyperemia followed by spreading oligemia and impaired activation of rCBF in classic migraine. Ann.Neurol. 1981;9:344-352.

15. Olesen J, Friberg L, Olsen TS et al. Timing and topography of cerebral blood flow, aura, and headache during migraine attacks. Ann.Neurol. 1990;28:791-798.

16. Wammes-van der Heijden EA, Tijssen CC, Egberts AC. Right-to-left shunt and migraine: the strength of the relationship. Cephalalgia 2006;26:208-213.

17. Wilmshurst P, Nightingale S. Relationship between migraine and cardiac and pulmonary right-to-left shunts. Clin.Sci.(Lond) 2001;100:215-220.

18. Thenganatt J, Schneiderman J, Hyland RH et al. Migraines linked to intrapulmonary right-to-left shunt. Headache 2006;46:439-443.

19. Puskas JD, Allen MS, Moncure AC et al. Pulmonary arteriovenous malformations: therapeutic options. Ann.Thorac.Surg. 1993;56:253-257.

20. White RI, Jr., Lynch-Nyhan A, Terry P et al. Pulmonary arteriovenous malformations: techniques and long-term outcome of embolotherapy. Radiology 1988;169:663-669.

21. Moussouttas M, Fayad P, Rosenblatt M et al. Pulmonary arteriovenous malformations: cerebral ischemia and neurologic manifestations. Neurology 2000;55:959-964.

22. Post MC, Thijs V, Schonewille WJ et al. Embolization of pulmonary arteriovenous malformations and decrease in prevalence of migraine. Neurology 2006;66:202-205.

23. Post MC, Luermans JG, Plokker HW, Budts W. Patent foramen ovale and migraine. Catheter.Cardiovasc.Interv. 2007;69:9-14.

24. Wilmshurst PT, Nightingale S, Walsh KP, Morrison WL. Effect on migraine of closure of cardiac right-to-left shunts to prevent recurrence of decompression illness or stroke or for haemodynamic reasons. Lancet 2000;356:1648-1651.

25. Webster MW, Chancellor AM, Smith HJ et al. Patent foramen ovale in young stroke patients. Lancet 1988;2:11-12.

26. Maher CO, Piepgras DG, Brown RD, Jr., Friedman JA, Pollock BE. Cerebrovascular manifestations in 321 cases of hereditary hemorrhagic telangiectasia. Stroke 2001;32:877-882.

27. Kruit MC, van Buchem MA, Hofman PA et al. Migraine as a risk factor for subclinical brain lesions. JAMA 2004;291:427-434.

28. Etminan M, Takkouche B, Isorna FC, Samii A. Risk of ischaemic stroke in people with migraine: systematic review and meta-analysis of observational studies. BMJ 2005;330:63.

29. Goadsby PJ. Neurovascular headache and a midbrain vascular malformation: evidence for a role of the brainstem in chronic migraine. Cephalalgia 2002;22:107-111.

30. Haas DC. Arteriovenous malformations and migraine: case reports and an analysis of the relationship. Headache 1991;31:509-513.

31. Steele JG, Nath PU, Burn J, Porteous ME. An association between migrainous aura and hereditary haemorrhagic telangiectasia. Headache 1993;33:145-148.

32. Wilmshurst PT, Pearson MJ, Nightingale S, Walsh KP, Morrison WL. Inheritance of persistent foramen ovale and atrial septal defects and the relation to familial migraine with aura. Heart 2004;90:1315-1320.

33. Bayrak-Toydemir P, McDonald J, Markewitz B et al. Genotype-phenotype correlation in hereditary hemorrhagic telangiectasia: mutations and manifestations. Am.J.Med.Genet.A 2006;140:463-470.

34. Rapoport A, Edmeads J. Migraine: the evolution of our knowledge. Arch.Neurol. 2000;57:1221-1223.

Table 1. Basic characteristics

	Number	Percentage
Total	196	-
Age ± SD (years)	44.6±15.2	-
Female	112	57.1
Male	84	42.9
Blood pressure (mmHg)		
Systolic ± SD	131±16	-
Diastolic ± SD	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

SD, standard deviation; mmHg, millimetres of mercury; TIA, transient ischemic attack; CVA, cerebral vascular accident; CAVM, cerebral arteriovenous malformation; PAVM, pulmonary arteriovenous malformation; HHT, hereditary hemorrhagic teleangiectasia; *, data available in 73 patients

Table 2. Characteristics of patients with and without PAVM, the univariate and multivariate analysis for the prediction of PAVM.

	PAVM -	PAVM +	Univariate OR (95% CI)	p	Multivariate OR (95% CI)	p
Basic characteristics, n (%)						
Total	126 (64.3)	70 (35.7)	-	-		
Age ± SD (years)	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)	-			
Bloodpressure (mmHg)						
Systolic ± SD	132±16	128±16	0.99 (0.97 – 1.00)	0.14	-	
Diastolic ± SD	78±8	76±10	0.97 (0.94 – 1.01)	0.16	-	
Neurological event, n (%)						
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, n (%)**						
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)	n.a.		-	-

SD, standard deviation; n, number; CI, confidence interval; OR, odds ratio; mmHg, millimetres of mercury; TIA, transient ischemic attack; CVA, cerebral vascular accident; CAVM, cerebral arteriovenous malformation; PAVM, pulmonary arteriovenous malformation; HHT, hereditary hemorrhagic teleangiectasia; *, data available in 73 patients (34 without PAVM and 39 with PAVM); ** uni- and multivariate analysis without unknown subgroup

Table 3. Characteristics of patients with MA compared to non-migraine controls with the univariate and multivariate analysis for the prediction of MA.

	No migraine	Migraine with aura	Univariate OR (95% CI)	p	Multivariate OR (95% CI)	p
Basic characteristics, n (%)						
Total	157(86.3)	25 (13.7)	-	-	-	-
Age ± SD (years)	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)	-	-	-	-
Bloodpressure (mmHg)						
Systolic ± SD	131±15	126±17	0.98 (0.95 – 1.00)	0.15	-	-
Diastolic ± SD	78±9	76±8	0.97 (0.92 – 1.03)	0.34	-	-
Neurological event, n (%)						
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, n (%)						
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, n (%)**						
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)	n.a.		-	-

SD, standard deviation; n, number; CI, confidence interval; OR, odds ratio; mmHg, millimetres of mercury; TIA, transient ischemic attack; CVA, cerebral vascular accident; CAVM, cerebral arteriovenous malformation; PAVM, pulmonary arteriovenous malformation; HHT, hereditary hemorrhagic teleangiectasia; *, data available in 77 patients (60 non-migraine controls and 17 MA). ** uni- and multivariate analysis without unknown subgroup

Legends:

Figure 1. The prevalence of migraine with and without aura in the presence or absence of a PAVM.

Figure 1