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Pulmonary Arteriovenous Malformations and Migraine: A New Vision

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Key Words
Hereditary hemorrhagic telangiectasia · Migraine · Pulmonary arteriovenous malformations · Right-to-left shunt

Abstract
Migraine is a common neurological disorder with a great impact on the quality of life and social activities. Pulmonary arteriovenous malformations (PAVMs) are mostly congenital, with a prevalence of 5–50% in patients with hereditary hemorrhagic telangiectasia (HHT). A high prevalence of PAVMs is found in patients with HHT and migraine. Embolization of PAVMs seems to decrease the prevalence of migraine. Different pathophysiological hypotheses have been proposed to explain the association between migraine and the different right-to-left shunts. This review article describes the association between a pulmonary right-to-left shunt and the occurrence of migraine.

Introduction

Migraine is a common neurological disorder, and because of absence from work due to illness it is indirectly responsible for a loss of work productivity. The etiology of migraine is multifactorial. One of the factors possibly associated is a right-left shunt (RLS). Recently, an association between cardiac RLS, the so-called patent foramen ovale (PFO), and migraine has been described [1, 2]. This association is considered controversial, particularly in the field of neurology, because it is mainly based on small retrospective non-controlled studies. However, the association between RLS and migraine does not seem to be confined to an intracardiac RLS, but also occurs in pulmonary RLS, the pulmonary arteriovenous malformation (PAVM). This review article discusses this observation.

Migraine

Definition

Migraine is characterized by severe headache and autonomic nervous system changes. The diagnosis is based on headache characteristics and associated symptoms which have been specified by the International Headache Society (IHS) [3]. The typical headache is unilateral, throbbing, and may be severe. If untreated, the migraine attacks typically last 4–72 h. The attacks are usually associated with nausea, vomiting, and sensitivity to sound, light, or movement. In addition, migraine with aura is characterized by transient focal neurological symptoms, which are usually visual, and precede, accompany, or follow the headache attack [4].

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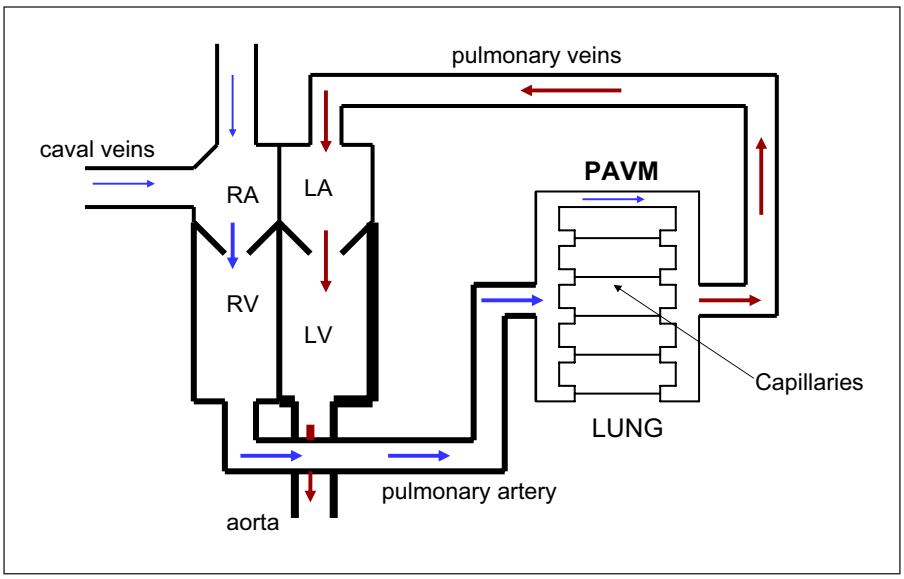

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Fig. 1. Schematic picture of a PAVM. RA = Right atrium; LA = left atrium; RV = right ventricle; LV = left ventricle.

Prevalence

Migraine occurs in 10–12% of the population; 6% of all men and 18% of all women. The prevalence increases with age and reaches a maximum of 27% in women and 8% in men at the age of 40 years [5]. In one third of the patients, migraine is accompanied by aura (MA) [6].

Pathophysiology

Migraine is a complex disease in which genetic, environmental, behavioral, and other as yet unidentified factors probably play a role. Putative migraine triggers include a variety of endogenous (menses) and exogenous factors (diet and weather changes) [7]. Genetic factors might play an important role by lowering the trigger threshold for migraine attacks [8]. Despite the fact that migraine has been the subject of much research, little is known about the pathophysiology of the initiation of a migraine attack. The fifth cranial nerve (n. trigeminus) and the trigeminovascular system play, by means of vasodilatation and neurogenic inflammation, a crucial role in the origin of the headache [9]. The aura is caused by the so-called 'cortical spreading depression', a phenomenon characterized by neuronal activation followed by suppression [10]. In this process, different mediators are released causing a change in cerebral blood flow. Initially, the aura is associated with a hyperemic phase followed by a reduced cortical blood flow [11]. The mechanism behind the start of this cascade is still unknown.

Pulmonary Arteriovenous Malformation

Anatomy and Prevalence

PAVMs are rare (usually congenital) abnormalities of the pulmonary vascular system characterized by a shunt between the pulmonary artery and vein (fig. 1).

At least 70% of the patients with PAVMs have hereditary hemorrhagic telangiectasia (HHT) [12, 13]. HHT, an autosomal dominant disease, is characterized by multiple mucocutaneous telangiectasia and arteriovenous malformations in the visceral organs. There are four known types of HHT; by far the most common are HHT I and HHT II. HHT I is caused by a mutation in the gene encoding for endoglin on chromosome 9 and is associated with a high prevalence of PAVM, up to 50% [13, 14]. In HHT II the genetic substrate is a mutation in the gene encoding for activin receptor-like kinase-1 on chromosome 12; the prevalence of PAVM in this particular subtype is approximately 5% [13, 15]. In The Netherlands, the prevalence of HHT is estimated at 1 in 3,000 inhabitants. The highest prevalence to date of 1 in 1,300 has been described in The Netherlands Antilles [16].

Symptoms, Diagnosis and Treatment of PAVM

PAVMs cause an RLS and therefore hypoxemia and in some cases dyspnea, but can also be responsible for more serious complications such as hemoptysis or hemothorax. However, neurological complications as a result of paradoxical (septic) embolism are the most common complications; cerebral ischemia occurs in 27% and cere-

bral abscess in 9% of the patients with untreated PAVMs [17].

Screening for PAVM usually consists of a chest X-ray, arterial blood gas analysis (while breathing 100% oxygen) and contrast transthoracic echocardiography. The 'gold standard' for the diagnosis of PAVM is a high-resolution CT scan of the thorax and/or angiography of the pulmonary vessels [18, 19].

Treatment nowadays consists of embolization with 'coils' and 'vascular plugs'. This technique has proven effective during long-term follow-up in 83–96% of the patients treated [20].

Pulmonary Arteriovenous Malformations and Migraine

Relationship between PAVM and Migraine

Three small observational studies about the embolization of symptomatic PAVMs described a prevalence of migraine between 38 and 59% [21–23]. Firstly, a study by White et al. [22] described the long-term outcome of embolization of PAVMs in 76 patients (45 females; mean age 36 years), and 67 (88%) of their patients suffered from HHT. The authors mentioned a migraine prevalence of 43%, but further details were not given. Secondly, Puskas et al. [21] described different strategies for the treatment of PAVM in 21 patients (13 females; mean age 37.5 years); HHT occurred in 57%. The neurological findings as a symptom of PAVM in these patients were described based on the review of their medical records. In 24% of the patients, migraine was the initial symptom of PAVM. The life-time prevalence of migraine was 38%. Thirdly, Moussouttas et al. [23] described the occurrence of neurological manifestations in 75 patients (53 females; mean age 43 years) with single or multiple PAVMs, retrospectively. In the presence of multiple PAVMs (n = 49), the prevalence of migraine was 63%, compared to 50% in case of a single PAVM (n = 26; p = 0.27).

The diagnostic criteria for migraine and the presence or absence of aura were not described in these studies. Also, the effect of PAVM treatment on migraine was not studied.

In a study by Wilmshurst and Nightingale [24], the prevalence of MA has been described in 200 patients with a history of decompression illness. The diagnosis of MA was based on the IHS criteria. An RLS, diagnosed by transthoracic echocardiography with contrast, was present in 60% of the patients. A pulmonary RLS was thought to be present in 14 patients (7%). The prevalence of migraine with aura was 29% in those with a pulmonary RLS and 14% in those without a shunt.

Relationship between HHT and Migraine

The relationship between HHT and headache was for the first time suggested by Hodgson et al. [25] in 1959. They described 231 persons out of 331 members of a large HHT family. Almost 40% of them probably had HHT. Four of these patients (4.4%) had unexplained symptoms related to the central nervous system, such as headache and transitory episodes of paresthesia, speech defects, weakness of a hand or leg, faintness, vertigo and visual disturbances [25]. The prevalence of migraine in HHT patients (with or without PAVMs) varies between 16 and 57% [26–29]. In 1993, Steele et al. [29] were the first to study the association between HHT and migraine. They send a headache questionnaire to 58 HHT patients and 40 controls and diagnosed migraine according to the IHS criteria. Fifty-three HHT patients (58% females; mean age 48 years) and 35 controls (54% females; mean age 39 years) completed the questionnaire. They found a prevalence of MA of 55% in the 53 HHT patients compared to 14% in the control group (n = 35, $p < 0.001$). The prevalence of migraine without aura was 8% in the HHT patients and 26% in the controls [29]. Bayrak et al. [28] described a genotype-phenotype correlation in 111 patients (52% females; mean age 40 years) with HHT. The overall prevalence of self-reported migraine in this study was 26%. In the 61 patients (52% females; mean age 35 years) with HHT I the prevalence of migraine was 35% compared to a prevalence of 16% in the 50 patients (52% females; mean age 46 years) suffering from HHT II (p = 0.04). The relationship between PAVMs and migraine was not a subject of these studies [28, 29]. Recently, we described this association in 538 patients (58% females; mean age 39 years) diagnosed with HHT. The prevalence of self-reported migraine in this group as a whole was 16%. Of interest, in patients with PAVMs (n = 208), 21% experienced migraine compared to 13% of the patients without PAVMs (p = 0.02) [26]. Fifty percent of HHT patients with migraine had a detectable PAVM versus 36% of the patients without migraine (p = 0.02). In this study no differentiation was made between migraine with or without aura [26]. Thenganatt et al. [27] also described the relation between PAVMs and migraine in 124 HHT patients (65% females; mean age 43 years). The diagnosis of migraine was based on a telephone interview and the IHS criteria. They found an overall prevalence of migraine of 38%, and 81% of these patients reported symptoms of migraine with aura. The overall migraine preva-

Table 1. Prevalence of migraine or MA in the presence or absence of a PAVM in patients with hereditary HTT

Authors	Patients n	Females %	Age years	M %	MA %	PAVM %	M, %		p
							PAVM+	PAVM–	
Steele et al. [29]	58	58	48	57	50	–	–	–	–
Bayrak et al. [28]	111	52	40 (1–82)	26	–	46	–	–	–
Cottin et al. [30]	126	63	43 ± 17	16	–	100	16	–	–
Post et al. [26]	538	58	39 ± 19	16	–	39	21	13	0.02
Thenganatt et al. [27]	124	65	43 (15–87)	38	31	41	46	33	0.14

Means ± SD and ranges are shown for age. M = Overall migraine; PAVM+/PAVM– = prevalence of migraine in the presence (PAVM+) or absence of PAVM (PAVM–).

lence was non-significantly higher in HHT patients with PAVMs (46%) compared to those without PAVMs (33%). However, after correction for age and sex there appeared to be an association between PAVMs and migraine (odds ratio 2.4, 95% confidence interval 1.1–5.5; p = 0.04) [27]. Recently, Cottin et al. [30] described a prevalence of self-reported migraine of 16% in 126 patients (63% females; mean age 43 years) with HHT and PAVM. The number of PAVM was not significantly different in patients with migraine compared to the patients without migraine. The authors did not differentiate between migraine with or without aura [30]. Data of the above-mentioned studies are summarized in table 1.

Embolization of PAVM and Migraine

In two observational retrospective studies of HHT patients, embolization of PAVMs appeared to influence the prevalence of migraine [27, 31]. Recently, we described the effect of embolization in 84 HHT patients (61% females; 48 ± 15 years). The prevalence of migraine was reduced from 45% before embolization to 35% 6 months afterwards (p = 0.01). In line with these results, a reduction in the prevalence of MA was seen from 33% before the intervention to 19% 6 months after embolization (p = 0.002). In patients, in whom the migraine (n = 28) or MA (n = 15) persisted after embolization, a non-significant reduction in the severity of headache was experienced (p = 0.15 for migraine; p = 0.11 for MA) [31]. In the study by Thenganatt et al. [27], the effect of embolization of PAVMs on migraine was briefly described in 14 HHT patients. They found a decrease in the frequency of migraine attacks in 8 patients (57%). In both studies, the migraine diagnosis was based on a validated questionnaire or telephone interview using the IHS criteria.

Limitations

The above-mentioned interventional studies are retrospective and observational in design, deal with a relatively small number of patients, and have a limited follow-up time. No control group was included in the closure studies. The diagnosis is based on self-reported migraine, a validated questionnaire, or a telephone interview. In addition, the diagnostic criteria for migraine might differ between the studies. However, most studies used the IHS criteria. Therefore, these results should be interpreted with caution and are difficult to translate to the general population.

Pathophysiological Hypotheses

Several hypotheses are proposed to explain these findings.

Firstly, it was hypothesized that microthrombi reach the systemic and cerebral circulation via PAVMs and cause migraine attacks. In support of this hypothesis is the finding that patients with migraine, especially those with MA, have an increased risk for cerebral ischemia [32–34]. Furthermore, using MRI, it was recently shown that the prevalence of subclinical brain infarction is significantly higher in migraine patients compared to a control group [35]. These findings are in line with the fact that cerebral ischemia is one of the most important complications of untreated PAVMs [17]. Finally, the use of high-dose acetylsalicylic acid and coumarins in migraine patients seems to have a therapeutic effect on the disease [36, 37]. However, anti-platelet and coumarin therapy is relatively contraindicated and rarely used in patients with HHT because of the increased bleeding risk and severe nosebleeds [38].

Secondly, the hypothesis that vasoactive substances (e.g. serotonin) can induce migraine attacks by reaching

the cerebrum via the systemic circulation through PAVMs parallels the first hypothesis. Serotonin might be liberated by activated platelets. These platelets become activated by adherence to the microbubbles that bypass the lung filter [39]. Detoxification of such substances is supposed to take place in the lungs, but in some conditions the quantity may exceed the pulmonary capacity. The latter could be the explanation for the presence of migraine in patients without RLS or after its closure [39–41].

Thirdly, in HHT patients with PAVM a prevalence of cerebral arteriovenous malformations (CAVM) of about 10% has been described [23, 26, 42]. It has been suggested by Steele et al. [29] that CAVM might play a role in the pathogenesis of migraine in patients with HHT. However, in our study describing more than 500 HHT patients, the prevalence of migraine was significantly higher in the patients with a PAVM compared to those without, even after exclusion of all patients with a CAVM [26].

Fourthly, a pulmonary RLS is usually accompanied by hypoxemia [43, 44]. This may lead, by a compensatory mechanism, to an increased hemoglobin level. Aamodt et al. [45] found a positive correlation between the hemoglobin level and the prevalence of migraine. However, the role of hemoglobin in the pathogenesis of migraine is not well understood, and most HHT patients suffer from iron deficiency anemia due to severe nosebleeds or gastrointestinal bleeding [28].

Fifthly, hypoxemia due to an RLS will cause theoretically an increase in the cardiac output [46]. A high cardiac output will probably lead to an increase in the carotid blood flow and this might be related to the pathophysiology of migraine. Interestingly, calcitonin-gene-related peptide (CGRP), a neuropeptide which induces headache in migraine patients, leads to an increase in carotid blood flow and cardiac output [47, 48]. Anti-migraine drugs, dihydroergotamine and sumatriptan, were able to reverse the carotid blood flow changes induced by CGRP [48]. However, the presence of a high cardiac output in patients with PAVM has not been studied, except for a small study in 7 patients [46]. Also, in patients with an intermittent RLS due to PFO, the prevalence of MA is increased [49]. PFO does not cause an increase in cardiac output.

Sixthly, a particular genetic substrate might determine both, MA and a pulmonary RLS in HHT. Wilmshurst et al. [50] found an autosomal dominant inherited pattern for the occurrence of an atrial shunt, linked to the inheritance of MA in some families.

Conclusion

There appears to be an association between RLS, both cardiac and pulmonary, and migraine. The finding that not only a cardiac (PFO) but also a pulmonary RLS (PAVM) is associated to migraine suggests a causal relationship. These shunts offer an opportunity for vasoactive substances or microthrombi in the venous vascular system to reach the brain via the systemic circulation and induce a migraine attack. In support of this is the finding that closure of a pulmonary or cardiac shunt leads to a decrease in migraine attacks. Studies concerning the causality of the relationship are mainly retrospective in design and therefore have important limitations. A large prospective trial is needed to further elucidate the role of closure of an RLS in reducing migraine.

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