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Chapter 4

Right-to-left shunts and micro-embolization in migraine

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Abstract

Purpose of review

The present review covers the latest studies on right-to-left shunts (RLSs) in migraine patients and different types of emboli capable of triggering migraine.

Recent findings

Although three recent studies found no increased RLS prevalence in migraine with aura patients, there remains ample evidence that the prevalence of RLS is increased in migraine with aura. Introduced emboli in the carotid artery of mice have been shown to cause cortical spreading depression, which has been considered the pathophysiological mechanism of migraine aura. In humans, iatrogenic introduced (micro)emboli can provoke migraine attacks; available evidence, however, is limited.

Summary

RLS and migraine with aura (but not without) are comorbid conditions, but the biological mechanism remains speculative. Specific emboli are probably able (although infrequently) to induce migraine symptoms. There is no convincing evidence that closure of a RLS alters migraine frequency; therefore, diagnosis or treatment of RLS in migraine has no place in daily clinical practice and should only take place in controlled studies.

Introduction

Since 1998, several studies have reported on the increased prevalence of right-to-left shunt (RLS) in patients with migraine with aura, but not in migraine without aura [1 – 4]. The biological mechanism linking RLS and migraine with aura remains speculative. There have been several retrospective and uncontrolled studies, also recently, indicating promising effects of closure [5 – 9], but a robust effect of shunt closure on migraine severity has not been shown in the single randomized controlled trial published back in 2008 [10].

Several questions remain. First, migraine with aura and a RLS are associated but is this a causal relation, and if so by what biological mechanism? Second, does closure of the RLS benefit the migraine patient? The aim of the current article is to answer these questions and comment on whether diagnosing RLS in migraine patients should be advised in clinical practice or not.

Background

A RLS is an abnormal communication between the right (venous) circulation and the left (arterial) circulation. Several structural abnormalities can cause right-to-left shunting; the most frequent cause is a patent foramen ovale (PFO) [11,12], a remnant from the fetal period that is located in the atrial septum of the heart. Other causes of RLS are atrial and ventricular septal defects and arteriovenous malformations or fistulae (PAVMs) at the pulmonary level [13]. When comparing publications on this subject, one should distinguish between the various types of RLS investigated. We will review the relationship between migraine and RLS, and more specifically PFO and PAVM.

Right-to-left shunt is more frequent in migraine with aura

Since 1998, several clinic-based case – control studies have been published, indicating a two to three times increased prevalence of RLS in migraine with aura patients compared with controls and migraine without aura patients using transcranial Doppler with aircontrast (TCD-c) [1 – 4,14]. This increased prevalence was also found specifically for PFO using cardiac echography [4]. A systematic review reported that PFO was more prevalent in migraine with aura patients than in the general population (pooled odds ratio 2.54, 95% confidence interval 2.01 – 3.08) [15]. Recently, two new case – control studies evaluating PFO prevalence were published. In the first, a population-based sample of mostly non-white participants from the North-

Manhattan study (NOMAS) was questioned about migraine and – as part of extensive cardiovascular evaluation – transthoracic echocardiography (TTE) was performed [16]. In this study evaluating 288 persons, the reported prevalence of PFO was similar in migraine with aura patients (16%), without aura (11%) and controls (15%). It was striking that as many as 79% of migraineurs were diagnosed with migraine with aura, whereas generally migraine with aura only makes up maximally 30% of migraineurs [17]. A great number of the migraine with aura patients perhaps were misdiagnosed and probably were migraine without aura patients in which the prevalence of RLS is known to be comparable with controls. Garg et al. [18] also found no differences in PFO prevalence among migraine with aura patients (27%), migraine without aura (26%) and age-matched and sex-matched controls (26%). The study used both TTE and TCD-c in 288 persons recruited from a headache center. Due to a very short evaluation time, pulmonary RLSs and small PFOs could have been missed. Finally, preliminary data from a large population-based Dutch study using TCD-c presented recently at a conference seems to confirm the increased prevalence of RLS among migraine with aura patients, and its publication is eagerly awaited.

A PAVM allows right-to-left shunting at the pulmonary level. Post et al. [19] studied 196 consecutive persons referred for screening of hereditary hemorrhagic telangiectasia (HHT) and showed that migraine with aura was present in 24% of these patients with a PAVM and only in 6% in patients without PAVM ($P = 0.001$). The prevalence of migraine without aura was not increased in individuals with a PAVM. A limitation of this study was that the migraine diagnosis was made only by reviewing returned questionnaires. Marziniak et al. [20] investigated 106 HHT patients and also showed that prevalence of migraine with aura in patients with PAVM (39%) was higher than that in patients without PAVM (10%); numbers of HHT patients with migraine with aura, however, were small ($n = 18$).

Only recently it was shown that, similar to PFO, the occurrence of PAVM is also relatively common in the general population. Woods et al. [12] described 104 healthy individuals (63% women) who were recruited to undergo TTE for RLS screening: 71% were found to have a RLS (38% had a PFO, 28% had a PAVM, 5% had evidence of both). In this study, any appearance of left-sided heart microcavitations was considered positive for a RLS, which is the lowest threshold possible and explains this very high prevalence of RLS. Before TTE, a 15-question migraine questionnaire was completed by participants, which was graded by a neurologist blinded for TTE results. Migraine with aura was diagnosed in 12% and migraine without aura in 29%. The prevalence of RLS in migraine with aura was 67%, which was not higher than that in migraine

without aura patients (77%) and controls (72%). Small or moderate PAVMs were also not associated with migraine, which was not broken down to migraine with and without aura. Results have to be evaluated with caution, as in this study only few large PFOs and no large PAVMs were found. Apart from the resulting power problem, one important limitation of this study is the limited questionnaire, which could have caused diagnostic bias.

In conclusion, a RLS is associated with migraine with aura. This is true for PFO, and probably also for PAVM. However, the prevalence of RLS in migraine with aura patients is increased probably less than two-fold to three-fold compared with controls, which was initially reported [1,2], as both PFO and PAVM are also common in the general population [12]. A causal relation between RLS and migraine with aura, as hypothesized by some, can only be shown by well designed randomized shamcontrolled RLS closure trials evaluating migraine frequency. While awaiting these studies, some recent publications have shown that there may be a reasonable linking biological mechanism, at least in animal studies.

Emboli triggering migraine attacks

For years, a mechanism linking RLS to migraine with aura was only speculative. One proposed mechanism was the transport through the RLS of unknown venous blood constituents that are normally not (or at decreased levels) present in the arterial circulation. Such postulated constituents were venous (paradoxical) emboli and serotonin [21]. The latest publications supporting the postulated embolic mechanism will be reviewed here. Nozari et al. [22] showed in mice that small particulate or air emboli injected into the carotid artery were able to evoke a cortical spreading depression (CSD) without causing ischemia, hereby linking emboli to migraine aura. It is unknown whether venous originated emboli (having passed through a RLS), as opposed to arterial originated emboli, also could cause CSD. If in humans it could also be demonstrated that small emboli are able to evoke a CSD, blood (vessel) abnormalities would then be acknowledged as a migraine trigger [23]. There are some clinical situations in humans that approximate these animal models. Four different types of emboli in humans will be discussed.

Air emboli causing migraine attacks

Migraine aura occurring during a TCD-c procedure has been reported as case reports [24,25] and recently the occurrence of migraine after a TCD-c procedure was studied prospectively. Caputi et al. [26] showed that among migraineurs with aura

immediately after TCD-c, migraine attacks were present in 8% of 159 participants; all of them had a permanent RLS. Sorensen et al. [27] prospectively questioned 445 individuals for the occurrence of different symptoms, including visual aura, after TCD-c in different patient groups (transient ischemic attack, cryptogenic stroke, migraine). TCD-associated symptoms such as migraine headache or ischemic symptoms were noted in 21% of participants. Occurrence of visual fortification aura occurred in 8% of migraine patients (n = 214) and in 0.4% of 231 nonmigraineurs (nonsignificant difference). Note that it was not reported whether the individuals experiencing specific symptoms had a RLS; generally it was concluded that any neurological symptom after TCD was more frequent in the RLS group (27%), compared with the non-RLS group (11%) ($P < 0.001$). Contrary to these studies [26,27], provoked migraine aura after aircontrast study seldom seems to occur in daily neurological practice. The relatively frequent occurrence of symptoms in these studies can also be explained by chance or other precipitating factors such as stress or the tight head frames used for TCD investigation. The nocebo effect, in which participants are (probably as a result of specific questioning) more likely to report side-effects, is also likely to play a role, especially when individuals can hear noise when emboli are detected by TCD.

Emboli after sclerotherapy

A second type of exogenous venous emboli occurs in sclerotherapy with the use of foam or liquids to treat varicose veins. Emboli in the middle cerebral artery (presumably after crossing a RLS) have been observed with TCD in the absence of neurological complications in up to 42% of patients undergoing foam sclerotherapy [28]. The composition of the emboli (e.g. gas, platelets or other compounds) is not known. A study using polidocanol (thought to cause smaller emboli) reported emboli during the sclerotherapy in as many as 89% of 61 participants with a RLS, but no neurological signs or symptoms [29]. A systematic review of cohort studies and randomized trials including 10 801 persons who underwent sclerotherapy reported the occurrence of visual disturbances (not considered to be a transient ischemic attack or stroke) in 84 persons (0.8%) [30]. Migraine (not further specified) occurred in 29 persons (0.3%) [30]. In these studies, percentages of individuals with a history of migraine were not reported and only in few of the included studies the RLS status in those experiencing migraine symptoms was known.

An alternative explanation for the occurrence of migraine attacks after sclerotherapy could be an increase of endothelin-1 following sclerotherapy, which has been shown in rats [31*]. Endothelin-1 is able to induce CSD in rats, linking endothelial

irritation following sclerotherapy to CSD [32]. In conclusion, individuals with RLS are at increased risk of micro-emboli after sclerotherapy, although clinical symptoms such as migraine aura attacks are infrequent. Future studies should report on RLS status and the history of migraine in participants.

Nitric oxide emboli

Third, in scuba diving, nitric oxide is released in the venous system and this gas is thought to cause neurologic decompression sickness [33]. Individuals with the largest RLS were at highest risk of neurological decompression illness (broadly defined as seizure, syncope, sensory, motor or visual unilateral symptoms) [34]. This suggests that nitric oxide from the venous system acts as a possible migraine aura trigger after passing through a RLS. The ability of nitric oxide (donors) to provoke migraine attacks has been clearly established before [35]; however, these are mainly migraine without aura attacks. In 83 scuba divers, a prospective (not randomized) study showed that closure of PFO significantly decreased major decompression illness during 5-year follow-up [36].

Fat emboli

The fourth type of venous originated emboli is fat emboli. After long bone fractures, the presence of semi-solid fat emboli in the venous system has been reported. Those emboli easily reach the cerebral circulation if a RLS is present and can give rise to (reversible) neurological symptoms [37]. In a study on 42 individuals with a femur shaft fracture who underwent daily detection of emboli, the presence of high micro-embolic signals in individuals with RLS was strongly predictive of the occurrence of neurological symptoms. Seventeen per cent of individuals developed neurological symptoms (cognitive or stroke symptoms), and all of those 17% had a RLS [38]. Aura symptoms were not reported and past migraine history was unknown. It seems that the fat globules inflict encephalopathy or focal defects but not aura phenomena, although based on the results of this study a link between fat emboli and migraine aura cannot be excluded.

Taken together, it seems that exogenous venous emboli (air, emboli following sclerotherapy and nitric oxide) in susceptible individuals can trigger migraine (aura) attacks. Theoretically, a RLS can be seen as a risk factor as it enables venous emboli to reach the arterial circulation. However, in most individuals with a RLS, these thousands of emboli entering the arterial circulation did not result in symptoms. The potential of micro-emboli to trigger a migraine attack is probably very limited, if present at all.

Emboli that are larger or more solid (and probably less present), such as fat emboli, have not been recognized as a trigger, although studies are scarce.

Other explanations for a causal relation between right-to-left shunt and migraine with aura

A causal mechanism linking RLS with a migraine attack could also be hemodynamic. Generally, RLS are of no hemodynamic significance, but some PFOs have been associated with the platypnea – orthodeoxia syndrome. In this syndrome, the patient complains of dyspnea only while sitting or standing, accompanied by arterial desaturation [39]. Furthermore, resting hypoxemia related to (left-to-right) shunting across a PFO has been reported [40]. Mild arterial desaturation due to a RLS, therefore, should be considered as a possible mechanism linking RLS with migraine, as hypoxia is a known trigger of migraine [41].

Migraine treatment as a cause of right-to-left shunt?

Increased pulmonary vascular resistance is associated with PFO [42]. It was shown that sildenafil decreased the RLS size, probably by decreasing pulmonary artery pressure [43]. The opposite occurs with 5HT1B agonists (e.g. triptans), which can cause pulmonary artery constriction [44]. The use of triptans, therefore, theoretically could enlarge or open a PFO by a transient increase of right-sided heart pressure. However, this does not explain that RLS prevalence is only increased in migraine with aura.

Are there proven beneficial effects of right-to-left shunt closure as prophylactic treatment of migraine?

Migraine patients have been referred to cardiologists for PFO closure, as migraine treatment [45]. Evidence for this therapy, however, is lacking, as the only randomized controlled study published so far is the Migraine Intervention with Starflex Technology (MIST) trial, which did not show an effect on the primary endpoint, cessation of migraine [10].

On the basis of (preliminary) findings of the MIST study, Diener et al. [46] in this journal concluded that there was insufficient evidence that PFO closure has a beneficial effect on migraine. Since then several observational (but no randomized) studies have been published [5 – 7,9]. Therefore, results from ongoing randomized PFO closure trials for migraine are eagerly awaited. Both the Stop pain, septal closure of PFO and the Escape trial (St. Jude, St. Paul, Minnesota, USA) have been terminated due to insufficient enrollment or ethical concerns. The Premium (sham controlled,

USA) and Prima (openlabel, Canada and Europe) trials, both by AGA Medical Corporation (St. Paul, Minnesota, USA) started in 2006, are still recruiting (http://www.con trolled-trials.com). A single-arm study on migraine prophylaxis is planned by Coherex, Salt Lake city, Utah, USA (http://clinicaltrials.gov).

Conclusion

There is reasonable evidence that migraine with aura is associated with RLS [15], and this is not altered by recent negative studies [12,16,18]; however, the difference might not be as marked as reported initially [1–4]. Significant gaps in our understanding of this association remain. In mice, it was demonstrated that arterial emboli were able to trigger CSD, which supports the hypothesized embolic mechanism linking RLS with migraine aura [22]. In humans, several kinds of emboli have been associated with migraine attacks. Reported frequencies vary widely, probably a nocebo effect of the aircontrast procedure plays an important role. There is insufficient evidence that RLS closure has a beneficial effect on migraine. Therefore, diagnosis or treatment of RLS in migraineurs has no place in current clinical practice and should as such only take place in controlled studies.

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