Migraine and brain changes

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Chapter 6

Systemic right-to-left shunts, ischemic brain lesions, and persistent migraine activity

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ABSTRACT

Objective: To assess whether migraine in the general population is associated with increased risk of systemic right-to-left shunts (RLS) and whether RLS are associated with increased prevalence of brain infarcts and persistent recurrence of migraine attacks at older age.

Methods: Brain MRI and transcranial Doppler with air contrast in 166 unselected migraineurs (mean age 6 SD 56 6 7.7 years; 70% women; n = 96 migraine with aura) and 69 controls (mean age 6 SD 55 6 7.6 years; 65% women) from the general population.

Results: Participants with migraine with aura more frequently had Valsalva-induced RLS (60%), in particular large-sized, compared to controls (42%; odds ratio [OR] 2.1; 95% confidence interval [CI] 1.1–3.9; *p*=0.02) and participants with migraine without aura (40%; OR 2.3; 95% CI 1.2– 4.3; *p*=0.01). They also more frequently had spontaneous RLS (35%) than participants with migraine without aura (17%; OR 2.6; 95% CI 1.3–5.6; *p*=0.01) but not compared to controls (26%; OR 1.6; 95% CI 0.8–3.1; *p*=0.2). Participants with migraine with aura and spontaneous RLS more frequently had persistent migraine activity (85%) than participants with migraine without spontaneous RLS (63%; OR 3.4; 95% CI 1.2–10.1; *p*=0.03). Nine percent of participants with RLS had silent posterior circulation infarcts compared to 3% of participants without RLS (OR 2.8; 95% CI 0.9–9.3; *p*=0.08), independent of migraine status. RLS were not associated with white matter lesions.

Conclusions: RLS are more prevalent in migraineurs with aura but do not explain the increased prevalence of silent posterior circulation infarcts or white matter lesions in migraineurs. Spontaneous RLS are associated with persistent migraine.

GLOSSARY

CAMERA=Cerebral Abnormalities in Migraine: An Epidemiological Risk Analysis Study; **CI**=confidence interval; **CSD**=cortical spreading depression; **MB**=microbubble; **OR**=odds ratio; **PFO**=patent foramen ovale; **RLS**=right-to-left shunts; **TCD-c**=transcranial Doppler with air contrast

INTRODUCTION

Epidemiologic and animal studies have suggested a complex relation between migraine, ischemic brain lesions, and systemic right-to-left shunts (RLS).[1–6] Participants with migraine had higher prevalence of subclinical deep white matter hyperintensities and brain infarcts,[2,3,5] migraine with aura was associated with increased prevalence of ischemic stroke [1,7] and RLS,[4,6] and RLS were more prevalent in patients with cryptogenic stroke.[8,9] In uncontrolled and open-label studies,[10–12] but not in a sham-controlled study,[13] closing patent foramen ovale reduced migraine attack frequency and risk of stroke recurrence.[14,15]

In mice, carotid injection of small experimental emboli induced cortical spreading depression (CSD),[16,17] the electrophysiologic correlate of migraine aura and a putative trigger for migraine attacks.[18] Altogether, microemboli through RLS might cause cerebral ischemia and might trigger attacks of migraine with aura. Thus while in most migraineurs attacks cease, recurring spontaneously at older age,[19] in migraineurs with RLS, attacks might continue recurring. Most of these data, however, were obtained in patients from headache clinics who likely were more severely affected than the average migraineur. It thus is uncertain whether and to what extent these conclusions can be extrapolated to the migraineur at large.

In the present study, we assessed whether RLS are (1) more prevalent in migraineurs from the general population, (2) associated with a higher prevalence of ischemic brain lesions on MRI, and (3) associated with ongoing migraine activity. To this end, we assessed and correlated (1) presence, type, and size of RLS; (2) presence and type of ischemic brain lesions; and (3) migraine activity, defined as number of attacks in the preceding year in a cohort of unselected but well-defined migraineurs (n = 203) and controls (n = 83) from the general population-based Cerebral Abnormalities in Migraine: An Epidemiological Risk Analysis Study Part 2 (CAMERA-2).[3] As CAMERA-2 is a 9-year follow-up of the CAMERA-1 study,[2] in which all migraineurs were initially diagnosed and characterized, we could reliably analyze both still active migraineurs in whom attacks were still recurring and inactive migraineurs in whom attacks had meanwhile ceased recurring.

METHODS

Study population and procedures

Study participants were invited from the CAMERA-2 study,[3] which was primarily designed to assess the prevalence, incidence, and progression of MRI-detectable ischemic brain lesions in migraineurs over a 9-year follow-period from the CAMERA-1 study.[2]

In CAMERA-1, 295 well-characterized individuals with migraine[20] and 140 controls who were randomly selected from a community-based study of the general population

were included and assessed with brain MRI in 2000.[2,21] For CAMERA-2, all original CAMERA-1 participants were invited in 2009 for a follow-up study, which included a structured computer-guided telephone interview, brain MRI, physical examination, and cognitive testing, all similar to the CAMERA-1 protocols.[3] Although MRI scanners had significantly improved over the follow-up period, we decided to use the same MRI scanners in CAMERA-2 as in CAMERA-1 to preclude finding changes solely due to improved technology and sensitivity. Transcranial Doppler with air contrast (TCD-c) was performed on the same day as the MRI. MRI and TCD-c were performed and read without knowledge of migraine status.

Standard protocol approvals, registrations, and patient consents

The study was approved by the ethics committees and participants gave written informed consent.

Outcome measures

The primary outcome measure was the prevalence of RLS in migraineurs with and without aura compared to controls. Secondary outcome measures were the prevalence of ongoing recurrence of migraine attacks (defined as having had at least one migraine attack in the previous 12 months)[22] in migraineurs with RLS compared to migraineurs with migraine but no RLS, and ischemic brain lesions in participants with RLS compared to those without.

RLS

Presence of RLS was determined by TCD-c in accordance with international guidelines and recent recommendations.[23] Briefly, the right cubital vein was cannulated with a 20-G indwelling catheter. A microbubble (MB) medium was prepared by mixing 9 mL saline, 1 mL air, and 0.5 mL of participants' own blood at least 10 times vigorously between 2 syringes connected by a 3-way tap and injected with the participant in supine position while insonating the middle cerebral artery through the temporal bone window. We used a hand-held 2-MHz probe connected to a Doppler system (Multi Dop T2 [DWL, Sipplingen, Germany], Pioneer TC 8080 [Nicolet, Kleinostheim, Germany], or PMD 100 or ST3 [Spencer Technologies, Seattle, WA]). Signal recording was commenced 10 seconds before application of the contrast medium and halted after 60 seconds recording time. The procedure was carried out 3 times in a standardized and fixed order: in the first measurement, to detect spontaneous RLS, contrast medium was injected during normal breathing. In the second and third measurement, to detect RLS after provocation, contrast medium was injected and followed after 5 seconds by a 5-second Valsalva maneuver. Participants were instructed and coached in a standardized way to press

firmly with their mouth closed to produce a Valsalva maneuver. The procedure was performed by 2 experienced investigators (H.K. and I.H.P.-M.) blinded for MRI findings and migraine diagnosis; participants were instructed not to talk about their medical history. TCD-c investigation was performed immediately after MRI on the same day.

Offline reading started after completion of the study. Two experienced observers (R.W.K. and W.H.M.) rated presence and size category of RLS, blinded to participant characteristics. Passing MBs were unequivocally characterized acoustically by the typical chirping sound and visually by the spike-like appearance in the frequency spectrum. RLS were rated according to number of MBs detected during 60 seconds of each TCD-c investigation: no RLS (0 MB), small (1–9 MB), or large (> 9 MB). The interrater agreement for presence of RLS was excellent ($K = 0.95$; $p < 0.001$).

MRI

As suggested recently,[24] we replaced the previously used term infarct-like lesions[2,3] with silent infarcts. Silent infarcts were defined as non-mass parenchymal defects with a vascular distribution, isointense to CSF signal on all sequences, and when supratentorial, surrounded by a hyperintense rim on fluidattenuated inversion recovery images.[2] Virchow-Robin spaces were excluded based on typical location, shape, and absence of a hyperintense rim.[2] In the basal ganglia, in order to exclude nonspecific lesions, only parenchymal defects larger than 3 mm in diameter were considered.[2] Location and vascular territory of new and preexisting infarcts were read by 2 experienced neuroradiologists (M.C.K. and Junya Konishi), who were blinded to diagnosis. The interrater agreement was excellent ($k = 0.87$; $p<0.001$).[2]

White matter lesions were segmented automatically. Deep white matter hyperintensities were located supratentorial and not attached to the lateral ventricle.[2] High volume of deep white matter lesions (upper 20th percentile) was used as variable. For infratentorial hyperintensities, presence vs absence was used.

Migraine and ongoing recurrence of migraine attacks

Participants were asked during a telephone interview whether they ever had had migraine attacks and, if so, what the average attack frequency had been prior to CAMERA-1 and since then. One participant who was classified as control at CAMERA-1 had become migraineur without aura during the follow-up period. Participants who fulfilled the criteria of migraine at CAMERA-1 but had stopped experiencing migraine attacks during last year of follow-up were considered currently inactive lifetime migraineurs[22] The interview was structured by using personal benchmarks (e.g., pregnancy) for when a different migraine pattern had started or stopped.[3] These benchmarks were used to define periods and to compute the average migraine attack frequency (expressed as mean number of attacks per month).Information was collected on migraine prophylaxis

and treatment. Active recurrence of migraine attacks was defined as having had at least one migraine attack in the 12 months[22] prior to the CAMERA-2 MRI investigation.

Table 1 characteristics of study participants

			Migraine		
Characteristic	Total (n=235)	Controls (n=69)	Migraine (n=166)	Aura (n=96)	No aura (n=70)
Age, mean (SD),y	56 (7.7)	55 (7.6)	56 (7.7)	56 (8.0)	57 (7.6)
Women	161 (69)	45 (65)	116 (70)	69 (72)	47 (67)
BMI, mean (SD)	25.5 (3.9)	25.9 (4.1)	25.3 (3.9)	25.3 (3.3)	25.3 (4.6)
Hypertension[a]	73 (31)	22 (32)	51 (31)	31 (32)	20 (29)
Diabetes[a]	15 (6)	0 (0)	15 (9)[c]	7 (7)	8 (11)
Myocardial infarction[a]	5 (2)	3 (4)	2 (1)	1 (1)	1 (1)
Cardiac arrhythmia[a]	25 (11)	5 (7)	20 (12)	15 (16)	5 (7)
Pulmonary embolism[a]	3 (1)	0 (0)	3 (2)	1 (1)	2 (3)
Deep venous thrombosis[a]	7 (3)	2 (3)	5 (3)	3 (3)	2 (3)
History of transient ischemic attack[a]	10 (4)	1 (1)	9 (5)	4 (4)	5 (7)
History of stroke[b]	7 (3)	0 (0)	7 (4)	3 (3)	1 (1)
Smoking					
Ever	159 (67)	46 (67)	113 (68)	66 (69)	47 (67)
Pack years, mean (SD)	17 (16)	17 (16)	17 (15)	15 (14)	20 (18)
Postmenopausal state or ovariectomy	86 (66)	23 (58)	63 (70)	35 (66)	28 (76)
Current medication use					
Platelet inhibitors	20 (9)	7 (10)	13 (8)	9 (9)	4 (6)
Oral contraceptives	2 (1)	0	2 (2)	2 (3)	0
Hormonal substitution	3 (2)	1 (2)	2 (2)	2 (3)	0
Beta blockers	37 (16)	11 (16)	26 (16)	17 (18)	9 (13)
ACE inhibitor	9 (4)	4 (6)	5 (3)	4 (4)	1 (1)
Antiepileptic	1 (0)	0	1 (1)	1 (1)	0
Migraine years, mean (SD)	NA	NA	30 (12)	32 (12)	27 (12)[d]
Age at migraine onset, mean (SD)	NA	NA	22 (12)	21 (11)	22 (11)
Mean attack frequency per year	NA	NA	12 (22)	15 (24)	19 (21)
Ongoing recurrence of attacks	NA	NA	101 (106)	68 (71)	33 (47)

Abbreviations: ACE=angiotensin-converting enzyme; BMI=body mass index (calculated as weight in kilograms divided by height in meters squared); NA =not applicable.

Active migraine= migraine attacks during the last 12 months. Postmenopausal state= at least 3 months no menstruation or history of ovariectomy (unknown postmenopausal state due to hysterectomy in 31). Data are presented as n (%) unless otherwise specified. Oral contraceptives and hormonal substitution data presented as n (%) among women. Unless indicated otherwise, differences were not significant ($p > 0.05$).

[a] Cardiovascular history self-reported, doctor diagnosed.

[b] Ischemic or hemorrhage, self-reported, doctor diagnosed.

[c] Compared with controls; $p = 0.007$.

[d] Compared with migraine with aura; $p = 0.01$.

Study population

Of the 435 original participants of CAMERA-1, 286 (66%) underwent a follow-up MRI scan (migraine with aura: n = 114; migraine without aura: n = 89; nonmigraine controls: n = 83).[3] Mean follow-up was 8.5 years (range 7.9–9.2; SD 0.24 years).[3] Of these, 272/286 (95%) agreed to undergo TCD-c. Usable TCD-c data could be obtained from 235/272 (86%) participants: in 23/272 (8%), no adequate bone window was found, 9/272 (3%) had no adequate cubital venous access, and in 5/272 (2%) offline analysis was not possible due to technical failures. The 37 participants for whom no usable TCDc was available were otherwise comparable to the participants with usable TCD-c data with respect to age, sex, cardiovascular history, and migraine status.

As explained before,[3] there were no obvious reasons to assume that there was a serious selection bias from CAMERA-1 to CAMERA-2, which could have materially affected the results.[3]

Reasons for nonparticipation were no interest (n = 51), inability to visit research center (n = 30), claustrophobia (n = 8), and non-neurologic illness (n = 6).[3] There was no association between participation rate and diagnosis of migraine. Compared to nonparticipants, participants were slightly younger, more frequently reported high educational level, and smoked fewer packyears.[3]

Covariates and definitions

Sociodemographic and medical history characteristics were assessed by telephone interview.[3] Cardiovascular risk diagnoses were based on patient report of a physician's diagnosis.[3] In women, postmenopausal state was defined as last menstruation at least 3 months previously or a history of ovariectomy.

Statistical analysis

Differences in the distributions and means of characteristics among the study groups were tested with x^2, 2-tailed Fisher exact, unpaired t, and MannWhitney U test when appropriate. The presence of ongoing migraine attack recurrence was examined by RLS diagnosis (yes/no) using a model adjusting for age, sex, and postmenopausal state. Likewise, using logistic regression, the risk of MRI outcomes was examined by RLS diagnosis (yes/ no) and migraine and age as covariates.

Based on findings in previous studies, we decided beforehand to conduct 3 specific analyses. First, because an increased prevalence of RLS had only been found for migraine with aura,[4,6] we analyzed the prevalence of RLS separately for migraine with and without aura. To detect a difference of 20% in RLS frequency with a power of 0.8 and a set at 0.05, we would need 162 participants (total number in 2 arms). Second, because silent infarcts were found increased only in the posterior cerebral circulation,[2] we ana-

lyzed their presence separately for this part of the circulation. Finally, because higher prevalence of deep white matter lesions was only found in women with migraine,[3] we conducted this analysis stratified for sex. All performed statistical tests are shown in text or tables; reported p values are not corrected for multiple testing as this study was an exploratory hypothesis-generating study rather than confirmatory research. Data were analyzed using Statistical Software Package for Social Sciences (SPSS version 20.0; IBM, Armonk, NY).

RESULTS

Clinical and demographic data of the participants are summarized in table 1. Except for diabetes, there were no differences between migraineurs and controls in age, sex, or cardiovascular history.

Table 2 summarizes the prevalence of RLS among the various study groups. Of the migraineurs with aura, 60% had RLS vs 42% of controls (unadjusted odds ratio [OR] 2.1; 95% confidence interval [CI] 1.1–3.9; p=0.02) and 40% of migraineurs without aura (OR 2.3; 95% CI 1.2–4.3; p=0.01). Large RLS were found in 45% of migraineurs with aura vs 28% of controls (OR 2.1; 95% CI 1.1–4.2; p=0.03) and 20% of migraineurs without aura (OR 3.3; 95% CI 1.6–6.6; p=0.01). The prevalence of spontaneous large RLS was low in migraineurs without aura (1%) compared to controls (16%) and migraineurs with aura (19%). Otherwise, there were no differences in the prevalence of spontaneous RLS among the various groups.

We correlated the presence of total and spontaneous RLS with ongoing recurrence of migraine attacks in the last year as shown in table 3. Migraineurs with spontaneous RLS more frequently had ongoing recurrence of migraine attacks (76%), vs migraineurs without spontaneous RLS (55%) (unadjusted OR 2.6; 95% CI 1.2–5.6; p=0.01). When analyzed separately for migraine with and without aura, overrepresentation of participants with migraine with ongoing recurrence of migraine attacks was only found in migraineurs with aura and spontaneous RLS (85%) vs without spontaneous RLS (63%) (unadjusted OR 3.4; 95% CI 1.2– 10.1; p=0.02). These results did not change after adjusting for age, sex, and postmenopausal state. Furthermore, migraine inactivity was not due to higher use of migraine prophylactic agents (data not shown). Mean attack frequency was not correlated with the presence or absence of spontaneous RLS (data not shown).

Table 2. Prevalence of right-to-left shunt types

Right-to-left shunt	Controls (n=69)	Migraine with aura (n=96)	*P* Value [a]	Migraine without aura (n=70)	*P* Value [b]	*P* Value [c]
Spontaneous	18 (26)	34 (35)	0.2	12 (17)	0.2	0.01
Small no.(%)	7 (10)	16 (17)	0.2	11 (16)	0.3	0.9
Large no.(%)	11 (16)	18 (19)	0.6	1 (1)	0.02	0.001
Total after provocation	29 (42)	58 (60)	0.02	28 (40)	0.8	0.01
Small no.(%)	10 (15)	15 (16)	0.8	14 (20)	0.4	0.5
Large no.(%)	19 (28)	43 (45)	0.03	14 (20)	0.3	0.01

Data are expressed as number (%)

Small shunt defined as passage of 1-9 microbubbles. Large shunt defined as passage of at least 10 microbubbles.

[a] *P* value Controls vs Migraine with aura

[b] *P* value Migraine without aura vs controls

[c] *P* value Migraine with aura vs migraine without aura

Table 3. Prevalence of ongoing recurrence of migraine attacks by presence and subtype of right-to-left shunt

	Migraine (all)		Migraine with aura		Migraine without aura	
	With RLS	Without RLS	With RLS	Without RLS	With RLS	Without RLS
Spontaneous RLS	n = 46	n = 120	n = 34	n = 62	n = 12	n = 58
Ongoing recurrence	35 (76)	66 (55)[a]	29 (85)	39 (63)[a]	6 (50)	27 (47)
Total RLS	N = 86	N = 80	N = 58	N = 38	N = 28	N = 42
Ongoing recurrence	57 (66)	44 (55)	44 (76)	24 (63)	13 (46)	20 (48)

Abbreviation: RLS = right-to-left shunts.

Data are expressed as n (%). [a] $p < 0.05$ Unless indicated otherwise, differences were not significant ($p > 0$ .05).

Table 4 and table e-1 on the Neurology® Web site at Neurology.org summarize the prevalence of MRI detectable brain lesions by RLS type in the 229/235 (97%) participants who underwent TCD-c and for whom MRI data were available. Prevalence of silent infarcts in the posterior cerebral circulation in participants with RLS (9%) was not different from those without RLS (3%; OR 2.8; 95% CI 0.9–9.3; p=0.08). This was irrespective of migraine status (data not shown).

The risk of posterior circulation silent infarcts was further assessed using a multivariate regression model (with migraine presence, RLS presence, and age as covariates). Higher age (p=0.004) and possibly RLS (p=0.08), but not migraine (p=0.7), were associated with an increased infarct risk. No significant associations were found between RLS (subtypes) and deep white matter lesions, also not when stratified for sex.

Table 4. Prevalence of MRI findings by RLS type

	Spontaneous RLS			Total RLS		
	No RLS N=167	RLS N=62	*P* Value[a]	No RLS N=118	RLS N=111	*P* Value[b]
Any brain infarct-like lesion	23 (14)	7 (11)	0.6	13 (11)	17 (15)	0.3
Multiple infarct-like lesions	9 (5)	2 (3)	0.5	3 (3)	8 (7)	0.1
Silent brain infarct posterior circulation	10 (6)	4 (7)	0.9	4 (3)	10 (9)	0.08
Infratentorial hyperintensities	23 (14)	13 (21)	0.2	20 (17)	16 (14)	0.6
High volume deep white matter hyperintensities	31 (19)	13 (21)	0.7	20 (17)	24 (22)	0.4

Data are expressed as number (%).

Abbreviations: RLS, Right-to-left shunt; Any brain infarct indicates a brain infarct in any vascular territory. Multiple brain infarct-like lesions indicates more than one infarct-like lesion in any vascular territory. High volume deep white matter hyperintensities defined as upper 20th percentile.

Progression DWML : progression yes or no within follow up.

[a] *P* Value: No spontaneous RLS vs Spontaneous RLS [b] *P* value : No RLS vs RLS.

DISCUSSION

We assessed and correlated (1) presence, type, and size of RLS, (2) presence and type of ischemic brain lesions on MRI, and (3) persistent migraine activity in a large and unbiased general population-based cohort of phenotypically well characterized migraineurs and controls. We found, first, that in particular large-sized RLS are more prevalent among migraineurs with aura but not in migraineurs without aura. Second, migraineurs with aura and spontaneous RLS more often had ongoing migraine activity compared to migraineurs with aura without RLS or migraineurs without aura with or without RLS. Third, participants with RLS did not have more silent infarcts in the posterior cerebral circulation, irrespective of whether or not they also had migraine. There was no association of RLS with white matter lesions.

Our finding that RLS are more prevalent in migraineurs with aura from the general population is well in line with observations from clinic-based studies[4,6] and extends the RLS-migraine association from selected severe cases who are attending headache clinics to the average patient with migraine with aura. Two previous population-based studies, however, failed to find an association between RLS and migraine,[25,26] most likely due to limited statistical power, use of detection methods with only limited sensitivity to identify RLS, and, possibly, selection bias. In the first study,[25] 79% of participants had migraine with aura, whereas in the general population only one third of migraineurs have migraine with aura.[21] Moreover, in that study, transthoracic echo was used, which is known to have a lower sensitivity to detect RLS compared to TCD-c.[27] The second study[26] most likely was underpowered, with only 42 participants with migraine with

aura and 44 with migraine without aura. Moreover, RLS might have been missed in many participants as the TCD signal was assessed within 10 seconds after injection of contrast, which generally is considered too soon.[28] Use of TCD-c, which is more sensitive to detect RLS than the other methods generally used,[27] and the longer time window (60 seconds), which increases the chances of detecting very small cardiac shunts, may explain why we found somewhat higher RLS prevalences than were found in other studies.[4,6,25,26] Two clinic-based studies[29,30] assessed RLS with TCD-c in chronic (high frequent) migraine but with inconsistent findings: 66%[30] vs 37%.[29] Control groups such as participants with episodic migraine or participants without migraine were lacking in both studies.

The relationship between RLS and migraine with aura is intriguing and might be explained at least in part by shared genetic factors.[31] Alternatively, there might be a direct causal relationship.[32] In mice, it was shown that carotid injection of small particles or air emboli injected could evoke CSD,[16] the electrophysiologic correlate of migraine aura and a putative trigger for migraine attacks.[18] Migraineurs who were injected with agitated saline developed EEG alterations and headache attacks, particularly those with large RLS.[17] Finally, in a small open-label study, 87% of migraine patients with RLS had a 50% or greater reduction in migraine frequency when using the emboli-preventing drug clopidogrel.[33] It has also been hypothesized that substances like amines and other chemicals might bypass the pulmonary filter in participants with RLS, precipitating migraine attacks in susceptible individuals.[11] A direct relationship between RLS and migraine in at least some people is further suggested by our finding that participants with migraine with aura (but not those without aura) more often had ongoing migraine activity if they also had spontaneous RLS. As TCD cannot distinguish between cardiac and pulmonary RLS, we cannot determine which type is most relevant in migraine. Trials testing the migraine attack-reducing effect of closing patent foramen ovale (PFO), the most frequent cause of RLS,[11] traditionally included participants with both migraine with and without aura, and participants with Valsalva-induced rather than spontaneous PFO.[10–13] Whereas retrospective studies[10–12] showed promising results, a prospective, randomized, sham-controlled trial[13] failed to show any effect. Interestingly, preliminary results of the open-label but randomized Percutaneous Closure of PFO in Migraine with Aura (PRIMA) trial comparing PFO closure with antimigraine medication suggested selective elimination of attacks of migraine with aura in participants in whom large spontaneous PFOs had been closed (presented at the Transcatheter Cardiovascular Therapeutics Meeting, Washington, DC, September 2014).

Presence of RLS was not associated with higher prevalence of silent infarcts in the posterior circulation; this is in line with studies reporting that RLS is not associated with specific ischemic patterns.[34]

Furthermore, there was no association of RLS with deep white matter hyperintensities or infratentorial hyperintensities, which is in line with other studies.[35,36]

The design and study population of the present study allow for a broad extrapolation of the results to the average migraine patient. Although still too small for additional subgroup analyses, the study sample should be considered large in view of the fact that all participants had brain MRI. Moreover, the study participants were drawn from a phenotypically well-defined, general population-based, long-term follow-up study,[20,37] and their clinical characteristics covered a wide range of disease severities and attack frequencies. The fact that even patients were included in whom attacks had ceased recurring enabled reliable analysis of the relationship between RLS and persistent migraine activity at older age. Compared to methods used in most other studies, TCD-c, although less specific for subtype, is more sensitive for detecting RLS. Finally, both TCD-c and MRI were performed and interpreted by investigators who were strictly blinded to the clinical diagnoses and characteristics of the participants.

Migraine with aura, but not without aura, is associated with increased prevalence of in particular large RLS. Spontaneous, but not Valsalva-induced, RLS are associated with persistent recurrence of migraine attacks beyond the age most patients normally cease having attacks. Finally, RLS were not associated with increased risk of ischemic brain lesions, irrespective of comorbid migraine status.

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Table e-1. MRI findings by RLS type, odds ratio unadjusted [OR] and adjusted [OR]

Spontaneous RLS	OR unadjusted	Model 1 OR adjusted[a]
Any silent brain infarct	OR 0.8 (0.3-1.9)	OR 0.9 (0.4-2.3)
Multiple silent brain infarcts	OR 0.6 (0.1-2.8)	OR 0.8 (0.2-4.3)
Silent infarct posterior circulation	OR 1.1 (0.3-3.6)	OR 1.5 (0.4-5.2)
Infratentorial hyperintense lesions	OR 1.6 (0.8-3.5)	OR 1.9 (0.9-4.3)
High volume deep white matter lesions	OR 1.2 (0.6-2.4)	OR 1.4 (0.7-3.0)
Total RLS		
Any silent brain infarct	OR 1.5 (0.7-3.2)	OR 1.5 (0.7-3.3)
Multiple silent brain infarcts	OR 3.0 (0.8-11.5)	OR 3.2 (0.8-12.9)
Silent infarct posterior circulation	OR 2.8 (0.9-9.3)	OR 3.0 (0.9-10.0)
Infratentorial hyperintense lesions	OR 0.8 (0.4-1.7)	OR 0.8 (0.4-1.6)
High volume deep white matter lesions	OR 1.4 (0.7-2.6)	OR 1.4 (0.7-2.7)

Abbreviations: RLS, Right-to-left shunts; Any silent brain infarct indicates infarct in any vascular territory. Multiple silent brain infarcts indicate more than one infarct in any vascular territory.
High volume deep white matter lesions defined as upper 20th percentile
[a] Model 1: adjustments for diagnosis of migraine and age.

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