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ORIGINAL ARTICLE

Cold extremities in migraine: a marker for vascular dysfunction in women

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Background and purpose: Migraine is recognized as a vascular risk factor, especially in women. Presumably, migraine, stroke and cardiovascular events share pathophysiological mechanisms. Self-reported cold extremities were investigated as a marker for vascular dysfunction in migraine. Secondly, it was hypothesized that suffering from cold extremities affects sleep quality, possibly exacerbating migraine attack frequency.

Methods: In this case–control study, a random sample of 1084 migraine patients and 348 controls (aged 22–65 years) from the LUMINA migraine cohort were asked to complete questionnaires concerning cold extremities, sleep quality and migraine.

Results: A total of 594 migraine patients and 199 controls completed the questionnaires. In women, thermal discomfort and cold extremities (TDCE) were more often reported by migraineurs versus controls (odds ratio 2.3, 95% confidence interval 1.4–3.7; $P < 0.001$), but not significantly so in men (odds ratio 2.5, 95% confidence interval 0.9–6.9; $P = 0.09$). There was no difference in TDCE comparing migraine with or without aura. Female migraineurs who reported TDCE had higher attack frequencies compared to female migraineurs without TDCE (4 vs. 3 attacks per month; $P = 0.003$). The association between TDCE and attack frequency was mediated by the presence of difficulty initiating sleep ($P = 0.02$).

Conclusion: Women with migraine more often reported cold extremities compared with controls, possibly indicating a sex-specific vascular vulnerability. Female migraineurs with cold extremities had higher attack frequencies, partly resulting from sleep disturbances. Future studies need to demonstrate whether cold extremities in female migraineurs are a predictor for cardiovascular and cerebrovascular events.

Introduction

Migraine is three times more prevalent in women than in men [1]. Patients with migraine have an increased risk for cerebrovascular and cardiovascular disease, which is even more pronounced in young women, especially those with migraine with aura [2]. A systemic vascular vulnerability, possibly influenced by female sex hormones, is hypothesized to underlie this association [3]. Comorbidities of migraine include small vessel disease such as coronary artery vasospasm and Raynaud's phenomenon [2,3]. These syndromes are more often reported in women, similar to increased thermal discomfort and cold extremities (TDCE) [4]. Difficulties in regulating body temperature are associated with a delay in sleep onset, termed

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difficulty initiating sleep (DIS). Normally, peripheral vasodilation causes redistribution of heat, enabling the reduction of core body temperature that is essential for rapid sleep induction [5]. Experiencing cold extremities may indicate an autonomic or peripheral microvascular dysfunction and may interfere with falling asleep. For patients with migraine, insufficient sleep may be a trigger factor for attacks [6]. Based on these observations, the present study aimed to investigate self-reported cold extremities as a marker for vascular dysfunction in migraine. Additionally, it was hypothesized that suffering from cold extremities may be associated with DIS, and therefore with an increased migraine attack frequency.

Methods

Subjects

This study was conducted as part of the Leiden University Migraine Neuro-Analysis (LUMINA) programme [7]. Participants of the LUMINA project are Dutch adults aged 18–80 years who fulfil the criteria for migraine with or without aura according to the International Classification of Headache Disorders (previous ICHD-2, now ICHD-3) [8]. Healthy controls were free of any known neurological or psychiatric disorders and did not have any primary or secondary headaches apart from an occasional episodic tension type headache. Further description of the LUMINA cohort is found in Appendix S1. The study was approved by the medical ethics committee of Leiden University Medical Centre. All subjects provided written informed consent prior to participation. A random selection of 1084 migraine patients and 348 controls (aged 22–65 years) was made from the LUMINA cohort for the present study.

Questionnaires

Participants were invited to fill out questionnaires concerning TDCE and DIS, between December 2016 and January 2017. For TDCE, questions included whether and to what extent participants suffered from cold hands and/or feet over the past month. For DIS, questions concerned to what extent participants experienced problems with falling asleep and/or a sleep onset latency of more than 30 min in the last month. The questionnaires and ratings are presented in detail in Appendix S2. The questionnaires were developed and externally validated with objective finger skin temperature measurements in a large population-based study [4]. Recent information on migraine characteristics and medication use was obtained through extended questionnaires. Vasoactive medication use was defined as chronic daily use of triptans, ergotamines, beta-blockers, amphetamines and/or selective serotonin re-uptake inhibitors.

Data analysis

In general, non-parametric statistical tests were used. Chi-squared statistics were used to calculate prevalence rates of TDCE and DIS in migraineurs and controls. Odds ratios (ORs) were calculated for the association between TDCE and DIS and migraine for each sex separately. The association of migraine subtype and attack frequency with TDCE and DIS was calculated for each sex. Multiple linear regression was performed to investigate the association of TDCE and migraine in women, correcting for age, body mass index (BMI), smoking and vasoactive medication use, followed by correction for multiple comparisons. The Sobel test for mediation was applied to investigate whether DIS was a mediator in the association between TDCE and increased migraine attack frequency. All analyses were performed using SPSS 24.0 (SPSS Inc., IBM, Armonk, NY, USA).

Data availability

Anonymized data will be shared by request from any qualified investigator for the sole purpose of replicating procedures and results presented in the paper and as long as data transfer is in agreement with European Union legislation on the general data protection regulation.

Results

Questionnaires were completed by 594 (55%) migraine patients and 199 (57%) controls. Women were overrepresented in this study and amongst migraineurs compared to controls (88% vs. 61%). Vasoactive medication use was higher amongst migraineurs compared to controls (15% vs. 5%). There were no significant differences in the distribution of age, BMI or smoking (Table 1).

Thermal discomfort and cold extremities (TDCE)

In women, TDCE was more often reported by migraine patients versus controls [OR 2.1, 95% confidence intervals (CI) 1.3–3.3] (34% vs. 20%; $P < 0.01$) (Fig. 1). The difference remained statistically significant after adjustment for age, BMI, smoking and vasoactive medication (OR 2.3, 95% CI 1.4–3.7; $P < 0.001$). In men, TDCE was reported more often

Table 1 Clinical and headache characteristics[a]

Variable	Migraine patients (n = 594)	Controls (n = 199)
Age, years	45 (13)	46 (10)
Sex		
Female	520 (87.5)	123 (61.8)
Male	74 (12.5)	76 (38.2)
BMI[b]	25.0 (6.8)	24.1 (3.6)
Current smoker	77 (13.0)	22 (11.0)
Vasoactive medication[c]	90 (15.2)	9 (4.5)
Age at onset, years	19 (10)	n.a.
Migraine with aura	212 (35.7)	n.a.
Attack frequency[d]	3.0 (3.4)	n.a.

BMI, body mass index; n.a., not applicable. [a]Data are represented as mean ± SD or number of subjects (%). [b]calculated as weight in kilograms divided by height in metres squared. [c]daily use of triptans, ergotamines, beta-blockers, amphetamines and/or selective serotonin re-uptake inhibitors. [d]number of attacks per month.

by migraineurs versus controls (OR 2.5, 95% CI 0.9–6.9) (18% vs. 8%); however, this difference was not statistically significant (P = 0.09). No difference in TDCE was found comparing migraine subtypes (migraine with aura versus migraine without aura) (OR 1.2, 95% CI 0.8–1.7; P = 0.43).

Difficulties initiating sleep (DIS)

In general, a positive outcome of TDCE was associated with DIS (OR 2.4, 95% CI 1.7–3.5; P < 0.001). DIS was reported more often in both women (OR 5.2, 95% CI 2.4–11.4; P < 0.0001) and men (OR 3.8; 95% CI 1.2–12.4; P = 0.02) suffering from migraine compared to healthy controls (Fig. 1).

Both female and male migraineurs who reported TDCE had significantly higher migraine attack frequencies compared to migraineurs who did not report TDCE, increasing from an average of three to four attacks per month (P = 0.02) for women and six attacks per month for men (P = 0.002). The Sobel test for mediation indicated that this association between TDCE and migraine attack frequency was mediated by the presence of DIS (P = 0.02) (Fig. 2).

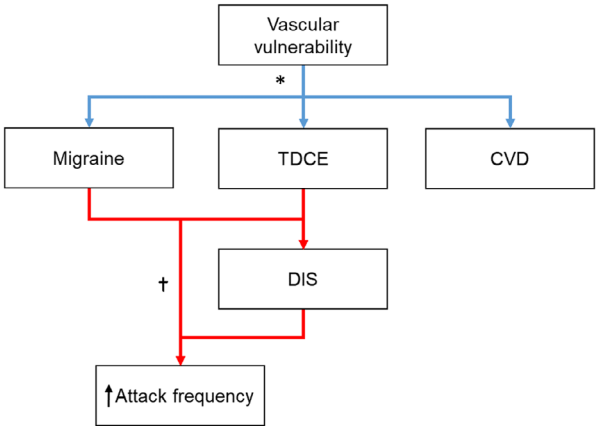

Figure 2 Schematic representation of the proposed mechanism and Sobel analysis. Proposed mechanism of sex-specific vascular vulnerability underlying the association between cerebrovascular and cardiovascular disease (CVD), thermal discomfort and cold extremities (TDCE) and migraine (*) and direction of Sobel analysis for mediation of the association between migraine attack frequency as dependent variable and relevant TDCE (yes/no) as independent variable and relevant difficulties initiating sleep (DIS) (yes/no) as mediator (†). [Colour figure can be viewed at wileyonlinelibrary.com]

Discussion

It was possible to substantiate an association between migraine and cold extremities in our large, well-defined cohort of migraine patients. It was found that this observation was significant only in women. Previous studies showed decreased peripheral skin temperature in migraineurs. However, these studies had severe limitations with small sample sizes, poor migraine diagnosis and illogical findings (showing an association with right-sided headache only), and all lacked appraisal of sex differences [9,10]. Our findings coincide with the current views concerning the sex-specificity of the vascular risk for migraine patients, and with suggestions that the underlying vascular vulnerability may be a systemic female type pathophysiology, possibly involving sex hormones [3]. It has been debated whether the increased vascular risk for migraineurs is in fact exclusive to women or is less

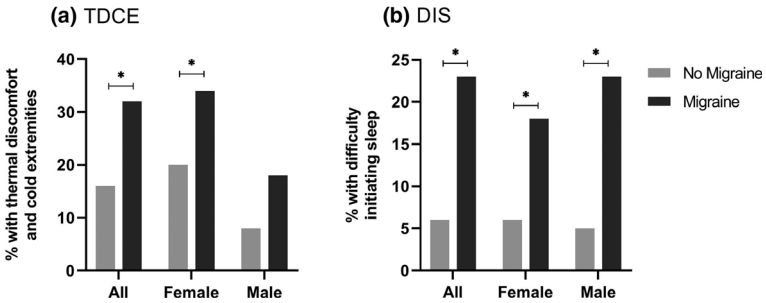

Figure 1 (a) Thermal discomfort and cold extremities (TDCE) and (b) difficulties initiating sleep (DIS). Showing patients with migraine (light grey) and controls (dark grey) separately in percentages, within all participants (n = 793), female participants (n = 520) and male participants (n = 273), *P < 0.05.

apparent in men due to underpowered analyses for male migraineurs [2]. This limitation might also have influenced our findings as the majority of our participants were women and therefore the confidence intervals around the OR in men were relatively wide. Larger studies are needed to further clarify the role of TDCE in men with migraine. Based on the higher increased risk of vascular disease for migraine with aura [2] it was expected that a difference in TDCE between migraine types would be found, but no evidence was found although the percentage of migraine with aura patients (36%) is what is generally expected in population-based studies [1]. It is noteworthy that our findings are still significant after adjustment for age, since the association of migraine with cardiovascular disease is especially prominent in young women (>45 years) [2]. Although age was present as a covariate in our regression analysis, pre- or post-menopausal state was not taken into account. However, when our groups were divided into ≤45 years (presumably premenopausal) and >45 years (presumably peri- or postmenopausal) it was found that the younger female migraineurs in particular contributed to our findings on TDCE as the OR in this group was 2.3 (95% CI 1.2–4.5; $P = 0.012$) comparing migraineurs with controls, whereas for the >45 year groups the OR was 1.9 (95% CI 0.9–3.7; $P = 0.067$). Further studies investigating the mechanisms of hormonal contribution could provide interesting insights. Another finding worth mentioning is the increased attack frequency for migraineurs who reported TDCE. This association was mediated by DIS. This is comprehensible since the disability to decrease core temperature through peripheral vasodilation may lead to delayed sleep onset and this in turn may be detrimental for migraine sensitivity [4-6]. It can be hypothesized that cold extremities are associated with more severe migraine because the underlying vascular vulnerability is likely to be more prominent in these patients. This would concur with suggestions that a higher attack frequency is associated with an even further increased cerebrovascular and cardiovascular risk in migraine patients [2]. Using clinical markers such as TDCE might thus provide useful clinical tools to assess vascular vulnerability but also migraine treatment response in the future.

Conclusion

Women with migraine report cold extremities more often than women without migraine, which may indicate the presence of a systemic vascular vulnerability in migraine. Migraineurs with cold extremities experience higher migraine attack frequencies, which is partly due to DIS. If cold extremities in female migraineurs are proven to be associated with the development of vascular complications later in life, this may present an easily assessed marker for vascular vulnerability.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. LUMINA background information

Appendix S2. Questionnaires and rating on thermal discomfort and cold extremities (TDCE) and difficulties initiating sleep (DIS)

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