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Ultrasonic assessment of carotid intima-media thickness in migraine: a meta-analysis

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Abstract

Objective: Migraine is believed to be a risk factor for cerebrovascular diseases, and previous studies have indicated an association between migraine and cerebral atherosclerosis. Carotid artery intima-media thickness (IMT) is considered to be a biomarker of atherosclerosis pathology. This study aimed to investigate the relationship between carotid IMT and migraine by conducting a meta-analysis.

Methods: We searched Web of Science, PubMed, and the Cochrane Library for eligible studies assessing carotid IMT in patients with migraine and controls. Data were extracted independently by two reviewers and analyzed using Review Manager 5.3 software.

Results: The meta-analysis included seven articles with 555 subjects (279 migraine patients, 276 controls). Carotid IMT was significantly greater in patients with migraine compared with controls. However, there were no significant differences in IMT between patients with migraine with aura (MA) and controls, migraine without aura (MO) and controls, and patients with MA and MO.

Conclusion: Patients with migraine have greater carotid IMT than individuals without migraine, suggesting an association between atherosclerosis and migraine. However, further studies with more samples are needed to confirm this finding.

Keywords

Migraine, carotid intima-media thickness, ultrasound, meta-analysis, carotid artery, atherosclerosis

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Introduction

Migraine is a common neurovascular disorder in both children and adults,[1,2] affecting about 12% of the population worldwide.[3] It is characterized by recurrent headache attacks with symptoms such as nausea, vomiting, phonophobia, and photophobia.[4] Although not life threatening, migraine can severely impair the patient's quality of life.[5,6] Drugs currently used to treat migraine include nonsteroidal anti-inflammatory drugs, anti-epileptic drugs, and beta-adrenoceptor blockers;[7,8] however, all these all aim to alleviate the intensity and duration of attacks, and no cure has yet been found. It is therefore necessary to demonstrate the mechanism and risk factors of migraine.

Previous studies have indicated that ischemic stroke and migraine may share the same causes,[9] and accumulating evidence suggests that migraine is associated with increased incidences of stroke and white matter lesions.[10,11] The disorder has also been associated with vascular atherosclerosis,[12] which is one of the most important mechanisms of ischemic stroke, and which increases the risk of migraine. Carotid artery stenosis is an important change in patients with ischemic stroke,[13,14] and carotid intima-media thickness (IMT) is often assessed to monitor the pathological condition of atherosclerosis in clinical practice.[15] Some studies have also assessed this index in patients with migraine[16,17] and showed that migraine patients had greater carotid IMT than controls.[17–20] IMT may thus be a possible marker for assessing the risk of migraine. The current meta-analysis aimed to compare carotid IMT between patients with migraine and healthy individuals.

Materials and methods

This meta-analysis was carried out according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[21,22] Because it was a meta-analysis, no patient consent or institutional board approval was needed.

Search strategy

We searched Web of Science, PubMed, and the Cochrane Library up to November 2018 for eligible studies comparing carotid IMT in patients with migraine and controls, using various combinations of the following terms: (carotid artery OR carotid) AND (migraine OR migraineur) AND (intima-media thickness OR intima-media OR IMT). There were no pre-defined restrictions on publication type or language. The inclusion criteria were: case-control studies; studies investigating carotid IMT in migraineurs and controls; and IMT detected using ultrasound. The diagnosis of migraine was based on the criteria of the International Headache Society.[23]

Data extraction

Two reviewers independently examined the titles, abstracts, and whole texts of the identified papers and extracted information on the following items: publication year, authors, region, study period, age, sex, numbers of patients with migraine and controls, and numbers of patients with migraine with aura (MA) and migraine without aura (MO). The carotid artery IMT for the participants in each study was recorded in an Excel file.

Quality analysis

The qualities of the included studies were assessed by two independent researchers using the Newcastle–Ottawa Scale (NOS).[24] NOS is a nine-star scale used to validate the quality of non-randomized trials in meta-analyses. The scale included eight measured items: selection of the study populations (cohort study 4 stars,

cross-sectional study 5 stars), comparability of the groups (maximum 2 stars), and ascertainment of outcome of interest for case-control or cohort trials (maximum 3 stars).

Statistical analysis

Data were analyzed using Review Manager 5.3 software using a random- or fixed-effects model according to the results of heterogeneity analysis: if I^2 was $\geq 50\%$, a random-effects model was selected for the comparison, otherwise a fixed-effects model was used. The significance level was set at $P < 0.05$. Publication bias analysis would be assessed if the number of studies included in each comparison was >10. Sensitivity analysis was performed using the leave-one-out method, by analyzing the data when each individual study was omitted.

Results

Study characteristics

An initial search of Web of Science, PubMed, and the Cochrane Library identified 455 papers (Figure 1). A total of 435 papers were left after duplicate records were removed, and 398 of these were excluded after careful review of their titles and abstracts. Thirty-seven records were enrolled in the next step and underwent examination of their complete texts by two reviewers. Seven studies were finally included in the meta-analysis (Table 1).[17–19,25–28] All seven papers were published between 2010 and 2016 and were carried out in five countries: Egypt, Turkey, Germany, Croatia, and Italy. All studies enrolled patients with both MA and MO, except for the trial by Liman et al.[27] Two studies[17,27] only enrolled female subjects. A total of 555 participants were included in the meta-analysis, of whom 279 had migraine and 276 were controls. All studies were relatively high quality, with an average score of 6.71.

Analysis of IMT

Carotid IMT was significantly greater in patients with migraine compared with controls (P=0.008, degrees of freedom = 6, I^2=90%) (Figure 2). However, subgroup comparisons revealed no significant difference in IMT between patients with MA and controls (Figure 3) or between patients with MO and controls (Figure 4). There was also no significant difference in IMT between patients with MA and those with MO (Figure 4).

We performed sensitivity analysis to detect the potential sources of heterogeneity, but no individual study was shown to significantly affect the results. However, the association between IMT and migraine became non-significant when only female subjects were included from the studies by Liman et al.[27] and Gunes et al.[17] Publication bias was not analyzed because fewer than 10 studies were included.

Discussion

This study provides the first meta-analysis to summarize the current evidence for a relationship between carotid IMT and migraine. The analysis demonstrated that carotid IMT was significantly greater in migraineurs compared with controls, but no significant relationship was found between IMT and either MA or MO.

Carotid IMT is a common marker used to assess atherosclerotic changes in clinical practice.[29,30] It represents vascular wall lesions, and is usually used as a predictor for ischemic stroke.[31,32] Previous studies have indicated that patients with ischemic stroke tend to have a higher incidence of migraine,[10,33,34] suggesting that migraine and ischemic stroke, as well as cardiovascular diseases, have a shared vascular

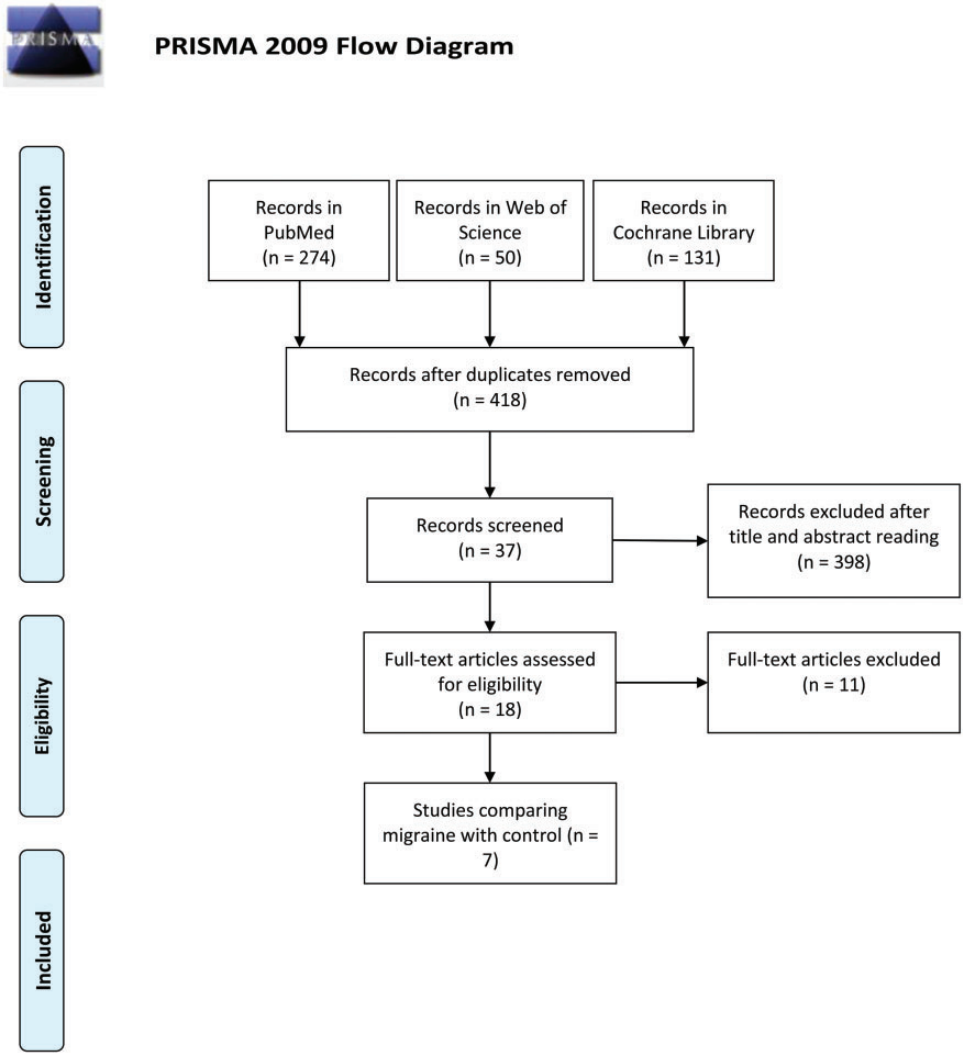

Figure 1. Flow diagram of the meta-analysis.

pathology.[35,36] Furthermore, ischemic stroke and cardiovascular diseases have been associated with the occurrence of migraine.[20,25] The results of the current meta-analysis were consistent with previous studies, indicating that carotid IMT was elevated in patients with migraine. One study[17] showed a mean (±standard deviation) carotid IMT of $701 \pm 114\,\mu m$ in patients with migraine compared with $400 \pm 64\,\mu m$ in controls. Poyrazoglu et al.[19] and Parmeggiani et al.[18] also reported higher carotid IMT values in children with migraine. This implies that atherosclerosis may be a causative factor for migraine, and that carotid atherosclerotic changes may begin during childhood. It should thus be vital to monitor the index in potential migraine sufferers while they are young. One study also found a higher frequency of procoagulant gene mutations in migraineurs,[25] thus supporting a genetic

Table 1. Baseline characteristics of included studies.

Study	Hamed et al.[28]	Besir et al.[26]	Liman et al.[27]	Kes et al.[25]	Gunes et al.[17]	Parmeggiani et al.[18]	Poyrazoglu et al.[19]
Period	NA	2010.06 –2010.08	2010.10 –2011.09	2009.10 –2009.12	2014.05 –2015.02	NA	2013.10 –2014.06
Region	Egypt	Turkey	Germany	Croatia	Turkey	Italy	Turkey
Migraine type	MA and MO	MA and MO	MA	MA and MO	MA and MO	MA and MO	MA and MO
Age							
Migraine	MA: 25.57 ± 66.96 MO: 28.92 ± 68.21	29.43 ± 6.37	34.1 ± 10.4	39.35 ± 9.95	32 ± 9	11.4 ± 2.4	12.31 ± 2.97
Control	29.22 ± 69.08	28.85 ± 5.29	33.5 ± 10.7	37.80 ± 4.72	33 ± 9	11.1 ± 2.2	12.2 ± 2.57
Sex (M)							
Migraine	5	5	0	15	0	16	19
Control	8	13	0	15	0	17	25
No.							
Migraine	38	30	39	60	25	30	57
Control	35	60	30	45	27	32	47
IMT							
Migraine	0.73 ± 59.22[a]	0.493 ± 0.074[a]	484 ± 119[b]	0.50 ± 0.13[a]	701 ± 114[b]	0.48 ± 0.07[a]	0.48 ± 0.04[a]
Control	0.54 ± 60.06[a]	0.409 ± 0.05[a]	508 ± 60[b]	0.44 ± 0.08[a]	400 ± 64[b]	0.45 ± 0.04[a]	0.45 ± 0.04[a]
IMT							
MA	0.68 ± 60.05[a]	NA	484 ± 119[b]	NA	NA	NA	NA
MO	0.76 ± 60.03[a]	NA	508 ± 60[b]	NA	NA	NA	NA
Quality	6	7	7	6	8	6	7

M, male; NA, not applicable; MA, migraine with aura; MO, migraine without aura; IMT, intima-media thickness; [a]millimeter; [b]μm. Values given as mean ± standard deviation.

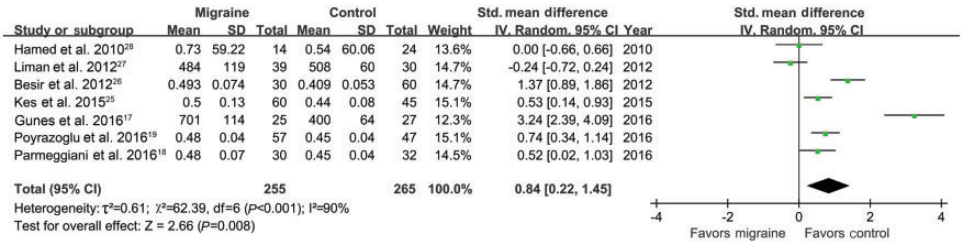

Figure 2. Meta-analysis of carotid IMT in migraineurs and controls. IMT, intima-media thickness, SD: standard deviation, CI: confidence interval, IV: inverse variance, Std.: standard, df: degrees of freedom.

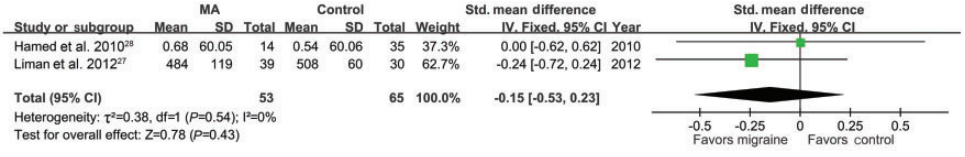

Figure 3. Meta-analysis of carotid IMT in patients with migraine with aura (MA) and controls. SD: standard deviation, CI: confidence interval, IV: inverse variance, Std.: standard, df: degrees of freedom.

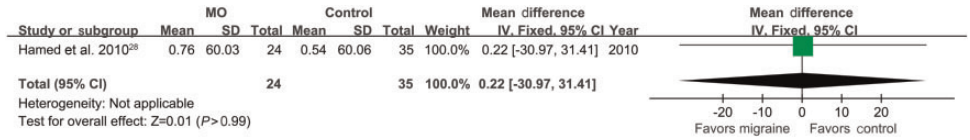

Figure 4. Meta-analysis of carotid IMT in patients with migraine without aura (MO) and controls, and in patients with migraine with aura (MA) and MO. SD: standard deviation, CI: confidence interval, IV: inverse variance.

connection between the two pathologies. Nevertheless, the precise mechanism linking migraine and carotid atherosclerosis remains unclear, and further studies are needed to clarify this.

The current meta-analysis demonstrated high heterogeneity among the included studies (I^2=90%). However, an initial sensitivity analysis did not find the variation significant. Furthermore, analysis of studies[17,27] that only enrolled female participants found no difference in IMT between patients with migraine and controls. This suggested that differences between men and women could be a possible source of the high heterogeneity. However, no sex-specific details of the relationship between migraine and IMT were available from other studies, and no further exploration was possible. In addition, the studies were carried out in different countries, and the sensitivity of accuracy of ultrasound assessment may have been affected by the experience of the practitioners, both of which could also have been sources of heterogeneity.

We also analyzed IMT in relation to the presence of aura in migraineurs, but found no differences in any of the comparisons (MA vs. control; MO vs. control; MA vs. MO). This could be attributed to the pathogenesis of MA and MO. Around 51.2% of patients with migraine experience MA and 43% present without aura.[37] It has been suggested that cortical spreading depression, as a slow depolarization wave traveling anteriorly in brain, may be responsible for the occurrence of aura.[37,38] However, the number of included studies for each was limited, and further large trials are needed to clarify this relationship.

This study had some limitations. First, there were fewer than 10 studies, making it difficult to detect publication bias and heterogeneity, and no further analysis of this was carried out. Second, inconsistencies in the age ranges and populations among the studies may have led to high heterogeneity. Finally, the sample size was relatively small, and more subjects should be included in this study in the future.

In conclusion, patients with migraine tend to have a greater carotid IMT than individuals without migraine, indicating the role of atherosclerosis in the pathogenesis of migraine. However, further studies with more samples are required to clarify this relationship.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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