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Migraine and cardiovascular risk factors: A clinic-based study

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ABSTRACT

Objective: The relation between migraine and vascular risk factors is an unclear issue. Furthermore, the reasons for chronification are still unknown. Probably, the age-related risk and other factors leading to migraine progression will also change in the future. Under these questions, we aimed to investigate whether or not there is a specific association with vascular risk factors between several age groups and subtypes of migraine and also in their families.

Methods: A dataset (the Turkish Headache Database) from four tertiary headache centres in Turkey was used. This database included headache-defining features according to ICHD criteria based on face-to-face interviews and examinations by a Neurologist. Vascular risk factors of migraine without aura (MwoA), migraine with aura (MwA) and chronic migraine (CM) were compared between three age groups (under 30 years, 30–50 years and over 50 years) and in first-degree relatives of the patients. Our study included 2712 patients comprising 1868 (68.9 %), 246 (9.1 %) and 598 (22.1 %) subjects with MwoA, MwA and CH, respectively.

Results: This study showed that both the patients and the first-degree relatives were more frequently associated with vascular risk factors in CM than episodic MwA and MwoA. MwoA showed a weaker association with vascular risk factors than MwA and CM.

Conclusion: Chronic migraine was associated with vascular risk factors at all ages and first-degree relatives as well. Vascular risk factors should be investigated with greater focus on chronic migraine.

1. Introduction

Migraine is the most common neurovascular disorder and one of the leading causes of disability and economic loss [1,2]. The high disability arising from a migraine is directly related to disease chronicity and frequency of attacks [3]. It should also be considered that other painful conditions play an important role in the chronicity of migraine. These are mainly fibromyalgia, myofascial pains, visceral pains and other painful conditions [4,5]. The coexistence of many painful conditions probably causes them to affect each other. As a result, they cause an increase in pain frequency and chronicity of pain. Although the mechanisms are not exactly clear, central sensitization can be considered as one of these [6].

Moreover, migraine is accompanied with other several comorbid diseases or disorders such as depression, anxiety, epilepsy, Raynaud's phenomenon, hypertension, ischemic stroke, patent foramen ovale, mitral valve prolapse, coronary heart disease, sleep apnoea, and asthma and allergy [7]. Although migraine usually seems a relatively benign condition, it is related with an increased risk of cerebrovascular disease, especially cerebral ischemia [8]. The relationship between migraine and stroke is multifactorial, bidirectional and still unclear.

Despite recent data suggesting the concept of migraine as a neurovascular disease [9], there is accumulative evidence linking a genetic susceptibility amongst migraine and vascular disorders [10]. In migraine, changes in cerebral vascular reactivity due to endothelial involvement as, well as changes in the peripheral arterial system are observed [11,12]. Studies have demonstrated the close relationship between age and gender, strokes and the subgroups of migraine,

Abbreviations: ICHD, International Classification of Headache Disorders; MwoA, Migraine without Aura; MwA, Migraine with Aura; CM, Chronic migraine.

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[13–17]. The risk for an ischemic stroke increases in MwA patients aged below 45 years who smoke and use oral contraceptives. Furthermore, the risk of ischemic stroke (IS) is two-fold higher in women than men [13]. Some studies suggest that migraine is associated with an unfavourable cardiovascular risk profile and heart disease. Moreover, migraine may be a potentially modifiable vascular risk factor for cardiovascular disease requiring further investigation in high-risk populations.

Genetic predisposition is another highlighted issue. Inheritance is between 40–60 % and there is a strong familial aggregation in migraine [13]. Furthermore, there are a few studies regarding first-degree relatives of the migraine patients who were evaluated according to the risk factors. [14–16]

The studies have been focusing on the fact that the clinical features of migraine and comorbidity vary by age. Ozge et al., suggested that elderly female patients with chronic migraine had different characteristics; [17]. Depending on the age, the characteristics of headache may change and perhaps age-related risk and other factors leading to migraine progression will also change. We have yet to answer these questions.

Progression from episodic migraine to chronic migraine still raises many questions. Currently, it has been found that chronicity is most often associated with hypertension, obesity and depression [18]. We do not yet have sufficient knowledge regarding chronification mechanisms.

The objective of this study was to investigate whether or not there is a specific association between conventional vascular risk factors amongst the age groups and subtypes of migraine. The other goal of this study was to evaluate the presence of similar vascular risk factors between patients with migraine and their first-degree relatives.

2. Materials and methods

In this study, a dataset (the Turkish Headache Dataset) from four tertiary headache centres in Turkey was used. A neurologist diagnosed patients after a face-to-face interview and proper neurological examination, and all the records were saved in a headache database. The diagnosis of headache was classified according to the International Classification of Headache Disorders and revised according to the third edition (ICHD-III) [19]. The CM definition was updated from the ICHD-III.

The Turkish Headache study is a prospective study. The patients were included in the order of arrival. Our study was a subgroup analysis of these data. The number of patients in the file given to us from the main file was 3342. Patients with more than one diagnosis of headache (combined headache) and patients with a possible diagnosis of migraine were excluded from the analysis. Since the study was conducted in tertiary headache centres, almost every patient who had presented to the outpatient clinic was using triptan and an additional NSAI for acute migraine treatment, both of which have a significant impact on the cardiovascular system [20]. The number of patients with drug overuse was very low and unreliable (61 patients). Due to its intense association with chronic migraine, it was not included in the analysis because it would affect the study results. Analyses were performed on the remaining 2712 patients.

The patients with MwoA, MwA, and CM were allocated into three groups. All patients aged 30 years, 30–50 years old and over 50 years were assigned also to three age groups. The patients with MwA had visual and sensory aura.

Vascular risk factors have been questioned in both patients and their close relatives to indicate the presence and importance of vascular risk factors in episodic and chronic migraine groups. All subjects were also scanned with respect to vascular risk factors for an ischemic stroke or transient ischemic attack (TIA), including history of hypertension, diabetes mellitus, coronary artery disease and hyperlipidaemia. For this type of study formal consent is not required.

3. Statistical analysis

The Kruskal-Wallis test was used to test the headache characteristics regarding the age group and the subgroups. The relationship between the headache types and the categorical variables was evaluated with the Chi-square test. The statistical analysis using the SPSS Version 24 statistical analysis was conducted and the level of statistical significance was accepted as 0.05.

4. Results

This study included a total of 2712 adult patients with a mean age of 38.4 ± 11.3 years. Of those patients, 1868 (68.9 %) were diagnosed with MwoA, 246 (9.1 %) with MwoA and 598 (22.1 %) were CH. Patients with MwA had the longest duration of headache while the CM group had a shorter duration ($p < 0.030$). In all ages, the headache frequency was significantly higher ($p = 0.001$) in the CM than those with episodic MwA and MwoA.

Vascular risk factors: No significant difference was found with regard to hyperlipidaemia and the cardiovascular event. Furthermore, no significant difference was determined regarding the oral contraceptive use in women.

We found that hypertension, diabetes mellitus and coronary artery disease were statistically significantly more frequent in the chronic migraine group than the MwA and MwoA in all age groups. On the contrary, diabetes mellitus was statistically more frequent in MwoA in the 30 and 50-age group.

Under 30- age group (Tables 1a and 1b): We found that hypertension, diabetes mellitus and coronary artery disease were statistically more frequent in the chronic migraine group than the Mwa and MwoA groups. With regard to their family history, coronary artery disease and migraine histories were more common in first-degree relatives of chronic and MwA patients. Hypertension and diabetes mellitus were more frequent in chronic migraine and MwA groups than in MwoA.

Between the 30 and 50- age group (Tables 2a and 2b): Hypertension and coronary artery disease were frequent in CM, and diabetes mellitus was statistically more frequent in MwoA. According to the family history, a migraine history, hypertension and coronary artery disease were more frequent in CM and MwA than in MwoA. On the other hand, diabetes mellitus was more frequent in MwoA.

The over 50- age group (Tables 3a and 3b): Hypertension, diabetes and coronary artery disease were more frequent in chronic migraine patients than in MwoA. Additionally, a migraine history, diabetes and coronary artery disease were more frequent in the first-degree relatives of chronic migraine patients than the relatives of the MwoA patients

Table 1a
The risk factors of the subjects who are under 30 years old.

Risk factors	MwoA	MwA	CM	P value
Oral contraceptive usage	12/148 (8.1 %)	2/19 (10.5 %)	2/31 (6.5 %)	0.876
Cerebrovascular event	0/475 (0.0 %)	1/69 (1.4 %)	0/167 (0.0 %)	0.096
Hyperlipidemia	3/481 (0.6 %)	0/70 (0.0 %)	1/167 (0.6 %)	0.804
Hypertension[1]	57/241 (23.7 %)	5/30 (16.7 %)	34/72 (47.2 %)	0.000173
Diabetes Mellitus[1]	55/238 (23.1 %)	4/30 (47.9 %)	34/71 (47.9 %)	0.000043
Coronary artery disease[1]	54/237 (22.8 %)	4/30 (13.3 %)	34/72 (47.2 %)	0.000050
Smoking (packed/year) [1]	137/497 (27.6 %)	12/73 (16.4 %)	64/169 (37.9)	0.001868
Alcohol (frequent from 2 days a week)[1]	63/493 (12.8 %)	5/73 (6.8 %)	35/168 (20.8 %)	0.006122

Kruskal-Wallis test.
[1] CM vs migraine WOA and migraine WA.

Table 1b
The risk factors for first degree relatives under 30 years old.

Risk factors	MwoA	MwA	CM	P value
Migraine[1]	193/293 (65.9 %)	44/51 (86.3 %)	70/80 (87.5 %)	0.000040
Hypertension[2]	85/223 (38.1 %)	17/35 (48.6 %)	36/53 (67.9 %)	0.000400
Diabetes Mellitus[2]	59/208 (28.4 %)	9/29 (31.0 %)	23/48 (47.9 %)	0.032601
Coronary artery disease[1]	40/196 (20.4 %)	14/29 (48.3 %)	25/47 (53.2 %)	0.000003

Kruskal-Wallis test.
[1] Migraine WAO vs migraine WA and CM.
[2] Migraine WAO vs CM.

Table 2a
The risk factors of the subjects who are between 30 and 50 years old.

Risk factors	MwoA (n = 1122)	MwA (n = 149)	CM (n = 336)	P value
Cerebral ischemic event	4/1036 (0.4 %)	1/141 (0.7 %)	0/294 (0.0 %)	0.441
Hyperlipidaemia	55/1053 (5.2 %)	4/143 (2.8 %)	16/300 (5.3 %)	0.441
Oral contraceptive usage	21/287 (7.3 %)	3/33 (9.1 %)	9/65 (13.8 %)	0.235
Hypertension[1,2]	179/482 (52.2 %)	22/55 (40.0 %)	88/156 (56.4 %)	0.000120
Diabetes mellitus[1,2]	135/446 (45.1 %)	14/50 (5.1 %)	63/137 (13.8 %)	0.002094
Coronary artery disease[1,2]	120/435 (27.6 %)	14/50 (28.0 %)	54/131 (41.2 %)	0.011246
Smoking (packed/year)	314/1060 (29.6 %)	42/145 (29.0 %)	127/316 (40.2 %	0.001423
Alcohol (frequent from 2 days a week)[1]	131/1053 (12.4 %)	13/145 (9.0 %)	57/313 (18.2 %)	0.008332

Kruskal-Wallis test.
[1]Migraine WOA vs CM.
[2]All different.

Table 2b
The risk factors for first degree relatives in 30-50 ages groups.

Risk factors	MwoA (n = 1122)	MwA (n = 149)	CM (n = 336)	P value
Migraine[1]	349/554 (63.0 %)	69/84 (82.1 %)	113/140 (80.7 %)	0.000005
Hypertension[1]	204/443 (46.0 %)	33/51 (64.7 %)	81/118 (68.6 %)	0.000012
Diabetes mellitus[2]	136/398 (34.2)	17/41 (41.5 %)	55/96 (57.3 %)	0.000159
Coronary artery disease[1]	112/379 (29.6 %)	26/48 (54.2 %)	51/100 (51.0 %)	0.000008

[1] Migraine WOA vs migraine WA and CM.
[2] Migraine WOA vs CM.

were.

5. Discussion

In this study, the experienced headache centres-based dataset had the purpose of investigating a relationship between migraine and vascular risk factors associated with different age groups and families. However, conventional vascular risk factors showed a limited relationship between migraine and stroke. [6,21]. That is why we wanted to re-examine these risk factors in a large number of databases. The results of our study show that both patients and first-degree relatives are more frequently associated with conventional vascular risk factors in CM than episodic MwA and MwoA.

The relationship between stroke in migraine patients using oral

Table 3a
The risk factors of the subjects who are over 50 years old.

Risk factors	MwoA (n=	MwA	CM	P value
Oral contraceptives	1/67 (1.5 %)	1/7 (14.3 %)	2/7 (28.6 %)	0.003
Cerebrovascular event	0/203 (0.0 %)	0/17 (0.0 %)	1/75 (1.3 %)	0.230
Hyperlipidaemia	16/204 (7.8 %)	3/19 (15.8 %)	4/78 (5.1 %)	0.287
Hypertension[1]	73/130 (56.2 %)	7/12 (58.3 %)	40/48 (83.3 %)	0.003701
Diabetes mellitus[1]	35/107 (32.7 %)	5/9 (55.6 %)	19/29 (65.5 %)	0.004132
Coronary artery disease[1]	27/100 (27.0 %)	2/9 (22.2 %)	17/27 (63.0 %)	0.001687
Smoking	46/210 (21.9 %)	6/20 (30.0 %)	27/83 (32.5 %)	0.148
Alcohol	27/209 (12.9 %)	2/19 (10.5 %)	44/311 (14.1 %)	0.468

Kruskal-Wallis test.
[1] Migraine WOA vs CM.

Table 3b
Risk factors for first degree relatives in over 50 ages groups.

Risk factors	Mwoa	Mwa	Cm	P value
Migraine[1]	60/103 (58.3 %)	8/11 (72.7 %)	25/27 (92.6 %)	0.003351
Hypertension	29/82 (35.4 %)	3/6 (50.0 %)	13/20 (65.0 %)	0.051423
Diabetes mellitus[1]	13/73 (17.8 %)	2/5 (40.0 %)	8/15 (53.3 %)	0.011109
Coronary artery disease[1]	16/73 (21.9 %)	1/5 (20.0 %)	13/21 (61.9 %)	0.001946

[1] Migraine WOA vs CM.

contraceptives has been widely discussed [22–24], but in our database, the number of oral contraceptive use was low, and no difference was found between the groups. No significant difference was found with regard to the hyperlipidaemia and cardiovascular event. The low number of the above-mentioned risk factors in our patients prevents reaching a realistic conclusion.

Although migraine was most strongly related to ischemic stroke [25], we have very little knowledge about MwoA, MwA and CM as risk factors for cardiovascular disease. The pathophysiology of migraine has close links to the vascular system. Since migraine with aura is characterized by cortically spreading depression, oligemia and changes in vascular perfusion, changes in vascular perfusion may be associated with vasospasm, which could lead to cerebral hypoperfusion and ischemic stroke [26,27]. With regard to possible mechanisms such as migraine pathophysiology or changes in vascular reactivity, endothelial dysfunction, changes in platelet function, cardiovascular risk factors and congenital heart defects, migraine patients have shown direct vascular damage due to an association with migraine-specific therapy [28,29]. However, the mechanisms by which migraine increases the risk of stroke remain uncertain. The increased risk of stroke and TIA mainly occurs in migraine patients with aura. In fact, this risk is approximately 2 times higher compared to migraine patients without aura. Smoking and using oral contraceptives further increase the risk of stroke in young patients. [5]. In particular, the relationship between aura and vascular disease and migraine has been supported by epidemiological, neuroimaging and genetic studies. Aura with migraine is independently associated with both cardiovascular disease and ischemic stroke [25,30–33]. MwoA appears to have a more modest association. It seems that there is a stronger correlation between classical risk factors and MwA than MwoA. Our study suggests that the weakest relationship with vascular risk factors was in MwoA and the strongest association was in CM.

In addition, although the incidence of haemorrhagic stroke is low in

patients with migraine, it has been reported that migraine sufferers have an increased risk of haemorrhagic stroke [34]. Its mechanism is not fully knowns. In another meta-analysis, no relationship was found between haemorrhagic stroke and migraine [35]. Haemorrhagic stroke was not found in our patients.

The prevalence of CM is 1.4–2.2 %. Approximately 2.5 % of patients become an episodic migraine and CM each year [36]. Fava et al. found that insulin resistance, depression and hypertension were independent risk factors in CM patients [18]. However, insulin resistance is still controversial [37].

Strokes and heart disease affected both CM and EM groups equally. Therefore, CM differed from EM sociodemographic- and comorbidity-wise in population-based studies [18]. Some conditions known to be comorbid with episodic migraine have been shown to be more abundant in the CM population after adjustments for age, sex and income, including psychiatric, respiratory, cardiovascular and related risk factors (angina, hypertension, high cholesterol, obesity and cerebrovascular event) and chronic pain. Today, the mechanisms that lead to chronicity are not fully understood.

There is another hypothesis regarding the understanding of the mechanisms of progression. Migraine chronification is characterized by an anatomical progression (cortically spreading depression and periaqueductal grey matter lesion) and disorders outside of the brain (increased risk of myocardial infarction, stroke and atherosclerosis, etc.) [38,39]. Several studies have suggested that comorbid medical conditions such as hypertension, diabetes mellitus, cardiovascular diseases, and obesity may induce migraine chronification [40,41]. Furthermore, migraine can be seen more frequently in overweight and thin people and this is closely related to the frequency of migraine. [42,43]. In our study, hypertension and coronary syndrome in CM patients were more frequent in all the age groups than in MwoA and MwA. Diabetes mellitus was also high in MwoA patients between the ages of 30–50, and it was more frequent in the chronic migraine group in other age groups. The conclusions about diabetes are different in the variety of studies that have been conducted [44,45]. Studies report that insulin resistance and obesity are more common in chronic migraine than in diabetes [32,46,47].

The strength of our work is that we compared not only the episodic or chronic migraine, but also the MwoA, MwA and CM, and all the age groups in a comprehensive dataset. We had the opportunity to compare migraine subtypes separately. Moreover, we assessed the familial predisposition. As in many diseases, genetic and environmental factors can play a role in migraine. Relatives have a shared environment and life as well as a genetic one. When assessed in this respect, vascular risk factors may be an important clinical implication of research in relatives of migraineurs. We believe that this comparison is relevant in recognizing the exact aetiology of cardiovascular disease after defining migraine and to formulate preventive strategies for cardiovascular disease after diagnosing migraine.

The present study had some limitations due to the subgroup analysis of the predefined structure of the database. We could not assess the effect of some important and well-known risk factors for cardiovascular diseases, such as obesity or body mass index. Furthermore, the study design did not permit consideration of the effects of previous preventative medications for migraine. Likewise, the most recent migraine preventatives acting on the calcitonin gene-related peptide (CGRP, which is a potent vasodilator, and there are concerns about its possible role in increasing the vascular risk in migraineurs [48].

6. Conclusion

Migraine may increase the risk of comorbid condition, or the comorbid condition may increase the risk of migraine. Chronic migraine is not chronic from the beginning; migraine becomes chronic. Therefore, it is crucial to prevent chronicity by recognizing the factors that cause chronic migraine. Our findings emphasized that vascular risk factors should be investigated with greater emphasis on migraine, especially on chronic migraine. The differences in the profiles between the three groups suggest that CM and EM diverge, not just in the degree of headache frequency, but in these other important areas, too. These differences may reflect the differences in the biological risk factors and provide valuable clues to explore the differences between EM, especially MwA and CM. Moreover, these differences may also reflect the association with progression from EM to CM, which may provide critical clinical markers and therapeutic target areas. Another essential point that suggests that the pathophysiology of migraine without aura may be different to MwA and CM is because MwoA has a less significant relationship to vascular risk factors.

Compliance with ethical standards

There is no Funding for this study.

Authorship

The manuscript has been read and approved by all the authors, that the requirements for authorship have been met, and that each author believes that the manuscript represents honest work.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Since we used the Turkish Headache Dataset, for this type of study (retrospective analysis) formal consent is not required.

Prior presentation of the study

12th European Headache Federation Congress, Florence, Italy, 28–30 September 2018

CRediT authorship contribution statement

Gulnur Tekgol Uzuner: Conceptualization, Investigation, Writing - original draft. **Osman Ozgur Yalın:** Conceptualization, Investigation. **Derya Uluduz:** Conceptualization, Investigation. **Aynur Ozge:** Conceptualization, Methodology, Investigation, Validation. **Nevzat Uzuner:** Conceptualization, Methodology, Formal analysis.

Declaration of Competing Interest

None.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.clineuro.2020.106375.

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