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# Migraine and its relation to other risk factors in patients with acute ischemic stroke and acute coronary syndrome

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## Abstract

**Background:** Migraine has been recently studied as a risk factor for ischemic stroke (IS) and a possible link to a broader range of ischemic vascular disorders including angina and myocardial infarction is suggested.

**Objectives:** to study migraine and its relation to other risk factors in patients with acute IS and acute coronary syndrome (ACS).

**Patients and methods:** We studied 200 patients, 114 patients had acute IS and 86 patients with ACS, in addition to 850 control participants. All patients were subjected to detailed clinical and laboratory evaluation; including evaluation of traditional risk factors. All stroke patients were subjected to CT scan. Diagnosis of acute coronary syndrome was established clinically by ECG and cardiac specific enzymes. Migraine was diagnosed according to the international headache society and assessment of migraine severity was measured by the Migraine Disability Assessment (MIDAS) questionnaire.

**Results:** In patients with ischemic stroke, Risk Ratios (RR) of migraine was 3.3 for all migrainous patients, higher for migraine with aura (MA). In the cardiovascular group, it was 2.75 and again higher in MA. A positive correlation between migraine severity and both stroke severity and cardiac affection severity was found though non-significant in the cardiovascular group. There was no significant difference in hospital outcome in migrainous patients in both groups.

**Conclusions:** Patients with migraine have higher risk than non-migrainous patients for both cerebrovascular and coronary vascular diseases. Risk is stronger in MA in both conditions. Considering migraine in risk stratification of cerebrovascular and cardiovascular diseases is recommended.

**Keywords:** Migraine, Risk factors, Ischemic stroke, Coronary artery disease

## Introduction

Cerebral ischemia and ischemic heart diseases, common entities nowadays, are the main manifestation of circulatory diseases [1, 2]. Ischemic stroke (IS) shows a variety of pathogenic mechanisms not present in ischemic heart disease. An ischemic stroke increases the risk of suffering a coronary heart disease (CHD), and vice versa [3].

Identifiable risk factors may explain up to 90% of CHD but only 60% of IS [3]. In patients with a history of CHD, the risk of repeating a new acute coronary syndrome (ACS) is much higher than the risk of IS; and in individuals with a history of IS, the risk of recurrent stroke is higher than the risk of ACS. However, stroke is a major complication associated with high mortality in patients with CHD, especially when hypertension is also associated [4].

The association between migraine and ischemic vascular events has been recently studied. Migraine with

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aura (MA) has been investigated as a possible risk factor for subclinical ischemic lesions of the brain [5]. On the other hand, many studies link migraine to a broader range of ischemic vascular disorders including angina and myocardial infarction [1, 6–9], though this link may be disputed by other studies, since the evidence is not consistent [10].

It remains unclear which mechanisms link migraine with vascular events and whether the biological mechanisms leading to ischemic stroke differ from the mechanisms leading to myocardial infarction [11].

*Aim of work* to study migraine as a risk factor and its relation to other risk factors in patients with acute ischemic stroke and acute coronary syndrome.

## Methods

This study population consisted of 200 patients collected from the stroke unit of the Neurology Department of Minia University Hospital, Critical Care Department of Fayoum University Hospital and Intensive Care Department of Minia Insurance Hospital. Randomly selected 850 age and sex matched outpatient attendants to internal medicine clinic and their relatives were studied as control. This is approved by the department ethical committee as the faculty ethical committee was not established at that time.

Patients were divided into 2 groups; group I that included 114 patients with acute non-hemorrhagic ischemic stroke (IS), and group II that included 86 patients with acute cardiovascular ischemia: acute coronary syndrome (ACS) including unstable angina, ST elevation myocardial infarction (STEMI) and non-ST elevation myocardial infarction (NSTEMI).

Exclusion criteria: patients with IS who had clinical or radiological evidence of a source of emboli, Intracranial hemorrhage, other lesions that may contribute to the insult as in cases of brain tumor, complete resolution of symptoms within 24 h, aphasic or unconscious patients who had improved during hospital stay and unstable patients (e.g., patients on mechanical ventilation) were excluded.

Patients were subjected to detailed clinical evaluation (especially diabetes, hypertension, chest pain, ICU admission, smoking) and assessment of stroke severity by National Institute of Health Stroke Scale (NIHSS) [12]. Resting ECG, continuous ECG monitoring were done for all patients with ACS and selected cases of IS as well as cardiac enzymes (CK–MB, troponin I) for patients with ACS and routine laboratory investigation. The diagnostic criteria of migraine with aura (MA) and migraine without aura (MO) were applied to patients not receiving anti-migrainous medications according to the International Headache Society (IHS) [13]. Assessment of migraine severity was done for all patients and control by the Migraine Disability Assessment (MIDAS) questionnaire [14], which measured the effect of migraine on daily activity in the past 3 months. Finally, CT brain was done for group I and selected cases of group II.

### Statistical analysis

SPSS version 20 was used for data analysis. Quantitative data were presented by mean and standard deviation, while qualitative data were presented by frequency distribution. Chi Square, Fisher exact test, Student *t* test, and one-way ANOVA test were used. In addition, multiple regression analysis was used to evaluate the combined effect of different independent variables on the target (dependent variable). The probability of less than 0.05 was used as a cut off point for all significant tests.

## Results

The study included 200 patients; their demographic data are shown in Table 1. Age and sex were matched between the two studied groups as well as the control group (statistically insignificant).

In patients with ischemic stroke (group I; *n*: 114), migraine was found in 20 patients (17.5%); 11 (9.6%) had MA and 9 (7.9%) had MO. In the cardiovascular group (group II; *n*: 86) migraine was detected in 13 patients (15.1%); 7 (8.1%) had MA and 6 (7%) had MO. In the control group (*n*: 850), migraine was found in 52 participants (6.1%); 18 (2.2%) had MA and 34 (3.9%) had MO; Table 2.

Risk ratios of migraine were adjusted for gender, age, BMI, smoking, physical inactivity, hypertension (controlled and uncontrolled), diabetes mellitus and abnormal lipid profile in both cerebrovascular and cardiovascular groups. Adjusted odds ratios associated with a personal

**Table 1** Comparison between the demographic data between the three groups

| Demographic data | Cerebrovascular group (*n* = 114) | Cardiovascular group (*n* = 86) | Control group 3 (*n* = 850) | *p* | $X^2$ |
|---|---|---|---|---|---|
| Age (in years) Mean ± SD | 52.3 ± 10.3 | 50.6 ± 9.9 | 51.8 ± 9.4 | 0.1 | 1.2 |
| Male | 84 (73.7%) | 65 (75.6%) | 645 (75.4%) | 0.1 | 3.8 |
| Female | 30 (26.3%) | 21(24.4%) | 211 (24.6%) | | |

Tests were done are ANOVA test for age and Chi square for sex

**Table 2** Risk of migraine in cerebrovascular, cardiovascular and control groups

| Parameter | Cerebrovascular group (*n*: 114) Number (%) | Cardiovascular group (*n*: 86) Number (%) | Control group (*n*: 850) Number (%) |
|---|---|---|---|
| Migraine (with and without aura) | 20 (17.5%) | 13 (15.1%) | 52 (6.1%) |
| Migraine with aura | 11 (9.6%) | 7 (8.1%) | 18 (2.2%) |
| Migraine without aura | 9 (7.9%) | 6 (7%) | 34 (3.9%) |

**Table 3** Multivariate analysis and adjusted odds ratios of migraine in stroke patients (cerebrovascular group) and acute coronary patients (cardiovascular group) compared to control group

| Parameter | Cerebrovascular group | | Cardiovascular group | |
|---|---|---|---|---|
| | Odds ratio (95% confidence interval) | *p* value | Odds ratio (95% confidence interval) | *p* value |
| Migraine (with and without aura) | 3.3 (2.17–5.32) | < 0.001 | 2.75 (1.14–3.77) | < 0.001 |
| Migraine with aura | 4.97 (3.12–6.45) | < 0.0001 | 4.12 (3.3–5.6) | < 0.0001 |
| Migraine without aura | 2.14 (1.5–3.32) | < 0.01 | 1.88 (1.34–2.12) | < 0.01 |

**Table 4** Multivariate analysis and odds ratios of other risk factors of ischemic stroke and acute coronary syndrome compared to control

| Parameter studied | Cerebrovascular group | | Cardiovascular group | |
|---|---|---|---|---|
| | Odds | *p* value | Odds | *p* value |
| Smoking | 3.2 | 0.001 | 4.3 | 0.001 |
| Physical inactivity | 2.1 | 0.01 | 2.5 | 0.01 |
| Hypertension | 5.6 | 0.001 | 5 | 0.001 |
| Uncontrolled hypertension | 3.8 | 0.001 | 3.3 | 0.001 |
| Controlled hypertension | 1.8 | 0.01 | 1.7 | 0.01 |
| Diabetes Mellitus | 2.6 | 0.001 | 3.4 | 0.001 |
| TIAs | 13.3 | 0.0001 | 2.23 | 0.01 |

*TIAs* transient ischemic attacks

history of migraine in both cerebrovascular and cardiovascular groups are shown in Table 3.

Clinical risk factors for stroke and acute coronary syndromes were studied compared with control participants. Adjusted odds ratios (with 95% confidence interval) for smoking, physical inactivity, hypertension (controlled and uncontrolled), diabetes mellitus and transient ischemic attacks are illustrated in Table 4. Lipid profile was assessed only in patients not controls. Total cholesterol and LDL levels were elevated in both groups compared to the normal values and both were significantly elevated in the cardiovascular group compared to the cerebrovascular group. Triglyceride level was elevated in the cardiovascular group compared to the normal values and was significantly elevated in relation to the cerebrovascular group; Table 5.

We compared risk factors in both migrainous and non-migrainous patients in the cerebrovascular and cardiovascular groups. We found that migraine sufferers in the cerebrovascular group were more likely than non-migrainous to have hypertension (OR: 1.32; 95% CI: 1.22–1.5, $p < 0.01$). In the cardiovascular group, migraine sufferers were also more likely than non-migrainous to have hypertension (OR: 1.6; 95% CI: 1.42–1.9, $p < 0.01$) and higher cholesterol levels ($p < 0.01$).

Migraine severity as assessed by MIDAS score showed significantly positive correlation with stroke severity

**Table 5** Comparison of lipid profile in cerebrovascular and cardiovascular groups

| Parameter studied | Cerebrovascular group (mean in mg/dl ± SD) | Cardiovascular group (mean in mg/dl ± SD) | *p* value |
|---|---|---|---|
| Total Cholesterol | 231.15 ± 87.53 | 317.93 ± 70.59 | 0.001 |
| TG | 146 ± 53.004 | 220.44 ± 71.54 | 0.001 |
| LDL | 123.6 ± 39.54 | 145.3 ± 68.33 | 0.01 |
| HDL | 45.27 ± 7.93 | 43.75 ± 6.83 | 0.3 |

*TG* triglyceride, *LDL* low density lipoprotein, *HDL* high density lipoprotein

in the cerebrovascular group as evaluated by NIHHS ($r=0.83$, $p<0.001$). In the cardiovascular group, a positive correlation, though insignificant, was found between MIDAS score and severity of cardiac affection as assessed by ejection fraction ($r=0.153$, $p<0.618$).

There was no significant statistical difference in mortality at discharge in patients with migraine with and without aura compared to patients without migraine in both cerebrovascular and cardiovascular groups; Table 6.

## Discussion

In recent years, numerous studies have suggested that migraine, particularly migraine with aura, is a risk factor for ischemic stroke [2–4]. Recent evidence has also linked migraine to a broader range of ischemic vascular disorders including angina, myocardial infarction, coronary revascularization, claudication, and cardiovascular mortality [1, 5–9]. In this study, all patients with migraine had 3.3 folds increased risk of ischemic stroke compared to non-migrainous patients. The increased risk was further magnified to 5 folds in patients with migraine with aura and was roughly 2 folds, after adjusting for other risk factors, in patients with MO highlighting that all migraineurs had higher risk.

Many studies demonstrated a wide range of relative risk of migraine in stroke patients. In Carolei study [15], adjusted odds ratio was 1.9 for all patients with migraine and the risk was increased to 8.6 folds in the subgroup of patients with MA compared to control. In another study, adjusted odds ratio was 3 and 6.2 for MO and MA, respectively [16]. On the other hand, some studies revealed increased risk of stroke only in MA, whereas this was inconsistent in MO [10, 17]. Nonetheless, other studies disputed this association in both MA and MO [10, 17].

Migrainous patients had 2.75 folds increased risk of acute coronary syndrome after adjusting for many cardiovascular risk factors. The risk was also magnified to 4.12 in patients with MA compared to 1.88 in patients with MO.

Although some studies yielded negative or conflicting results for overall migraine [18], case reports [19] and large-scale cohort studies [1] found an association between migraine and chest pain. In some cases, migraine was associated with ischemic electrocardiographic changes [20].

In the Atherosclerosis Risk in Communities study [1], patients with headache were roughly twice as likely to have a history of angina as compared to controls, with the risk most elevated in the group with MA.

In the Women's Health Study, MA but not MO approximately doubled the relative risk of major CVD (ischemic stroke, myocardial infarction, coronary revascularization procedures, angina, as well as death related to ischemic cardiovascular events) [21, 22].

Finally, as part of Scher and colleagues study [23], men with migraine were at increased risk for major CVD (OR = 2.05 for MA and 1.51 for all migrainous patients), which increased to 4.01 for MA and 2.25 for MO in a subgroup of patients with Framingham 10-year risk of more than 20%.

The mechanisms that link migraine, especially MA, to ischemic vascular disease remain uncertain and are likely to be complex. Cortical spreading depression (CSD) may predispose to brain lesions by reducing cerebral blood flow and by activating a cascade of inflammatory events [24]. It may be suggested to implicate CSD in vascular events outside the brain (as in ischemic heart disease), and other mechanisms may be of importance.

Studies on the pathophysiology of migraine suggest that migraine can also be viewed in part as a systemic disorder that is affecting the vasculature, and migraineurs might have reduced number and function of endothelial progenitor cells, a surrogate for marker for impaired vascular function [24]. Even in the absence of vascular risk factors, people with migraine have decreased cerebral [25] and peripheral vascular resistance [26] and increased likelihood of retinal microvascular signs [27], hypercoagulability [28], and inflammation [29].

Moreover, the altered vascular reactivity is already present among young patients with a recent onset of migraine [26]. This may explain our results of increased risk of both ischemic stroke and acute coronary syndrome in migrainous patients as both share many pathophysiological processes. However, the increased risk of ischemic stroke than that of acute coronary syndrome in

**Table 6** Relation of migraine and immediate outcome in the studied groups

| Parameter | Cerebrovascular group I ($n=114$) | | | Cardiovascular group II ($n=86$) | | |
|---|---|---|---|---|---|---|
| | Number | Survived | Died | Number | Survived | Died |
| Migraine with aura | 42 | 36 | 6 | 26 | 22 | 4 |
| Migraine without aura | 17 | 14 | 3 | 7 | 6 | 1 |
| No migraine | 55 | 49 | 6 | 53 | 48 | 5 |
| *p* value | 0.45 | 0.48 | 0.25 | 0.92 | 0.65 | 0.32 |

migrainous patients may be explained by the suggested cortical spreading depression (CSD) in migraine pathogenesis. CSD, which is supposed to reduce cerebral blood flow and activate a cascade of inflammatory events, can affect cerebral arteries and is also suggested to affect coronary vessels as well as peripheral vessel [26]. CSD is also suggested in pathogenesis of aura in migraine and this can explain our results of increased risk in MA more than MO in both IS and ACS. It should be highlighted that migraine is biologically heterogeneous [26], and migraine with or without aura are extremes of a disease continuum, which cannot be sharply separated as two distinct entities, and this can explain our results of increased risk in all migrainous patients in variable degrees.

Coronary vasospasm represents one of the important causes of myocardial infarction with nonobstructive coronary arteries (MINOCA) which is a heterogeneous clinical entity, characterized by clinical evidence of myocardial infarction (MI) with nonobstructive coronary arteries on angiography ($\leq$50% stenosis) and without an overt cause for the MI, such as cardiac trauma or injury. MINOCA is not uncommon and has been reported in 5–15% of individuals presenting with MI, depending on the population studied [30]. In addition to coronary vasospasm, coronary microangiopathy and hypercoagulability are included. Considering migraine as a vasospastic disorder that is associated with hypercoagulability [28], microvascular signs [27], as well as affection of peripheral vessel [26] and inflammation [29] strongly support its link with acute coronary syndrome especially accompanied with coronary vasospasm.

In this context, the link between migraine prophylaxis and prophylaxis of acute coronary events was highlighted. Beta-blockers, which are the first line therapy for migraine prophylaxis [31, 32] yield prophylaxis in certain situations for acute coronary events. Calcium channel blockers [33], had been previously studied in migraine prophylaxis and revealed lesser benefit than β blockers. In addition, few data demonstrated some effectiveness of the use of angiotensin-converting enzyme inhibitors [34] and angiotensin receptor blockers [35] for migraine prophylaxis along with recent recommendations for their use in secondary prophylaxis of coronary events in variable situations. On the other hand, ergot that is commonly used in acute migrainous attack management is considered as carrying more risk for type 2 myocardial infarction that is associated with coronary vasospasm [30]. This "therapeutic link" should be considered, and suggests sharing of considerable pathophysiological mechanisms in the disease process of both migraine and coronary artery disease.

It has also been suggested that persons with MA have a higher prevalence of risk factors known to be associated with cardiovascular disease (CVD), including hypertension, diabetes, and hyperlipidemia [23].

Our study found that all migrainous patients with ischemic stroke were 1.32 more likely than non-migrainous to have hypertension. In migrainous cardiovascular patients, the risk of hypertension was stronger (RR 1.6) in addition to the higher cholesterol level compared with non-migrainous patients.

The results in this study emphasize the role of the traditional risk factors shared in both cerebrovascular and cardiovascular disease. Hypertension was a stronger risk factor in IS than ACS. TIAs had markedly stronger risk in IS compared to ACS. On the other hand, smoking, diabetes mellitus and physical inactivity were also independent risk factors for both ACS and IS though showed higher risk in patients with ACS. Total cholesterol, LDL and TG were elevated in both groups but were significantly elevated in the cardiovascular group compared to the cerebrovascular group. This supports the role of these risk factors in pathogenesis of atherosclerosis as a systemic disease in which both cerebral and coronary vessels are comparably affected.

Comparing risk of migraine with other studied risk factors, we found that in patients with IS, migraine had a risk ratio 3.3 which was roughly equal to smoking, uncontrolled hypertension and greater than diabetes mellitus and physical inactivity but still far lesser than the risk of TIA. The subgroup patients with MA showed a parallel greater risk. In patients with ACS, migraine had a risk ratio of 2.75, which was greater than that of physical inactivity and TIA but still lesser than hypertension, smoking and diabetes mellitus. As in IS, the subgroup patients with MA had a parallel greater risk of ACS.

Our results revealed that migraine severity had a significant positive correlation with stroke severity, whereas the correlation with cardiac severity was insignificant. This may suggest a possible role of migraine in pathogenesis of acute IS more prominently than its role in ACS in addition to its chronic effect in both cerebral and coronary vessels. However, there was no significant difference in mortality in migrainous and non-migrainous patients in both groups.

Based on these findings, clinicians should have heightened vigilance for considering migraine in risk stratification of cerebrovascular and cardiovascular diseases. In the same context, modifiable cerebrovascular and cardiovascular risk factors in migraineurs, which has been associated with magnifying risk for IS and ACS should be meticulously considered. In addition, studies should investigate the possibility that preventive medications for migraine or antiplatelet therapy might reduce the risk of cerebrovascular and cardiovascular diseases in patients with overall migraine and MA in particularr.

## Conclusions

Patients with migraine (with and without aura) have higher risk than non- migrainous patients for both cerebrovascular and coronary vascular diseases. Risk is stronger in MA in both conditions. Considering migraine in risk stratification of cerebrovascular and cardiovascular diseases is recommended. Adjusted migraine prophylactic therapy should be considered and advocated. Future studies are recommended to compare the risk of IS or ACS in naïve migrainous patients with those under treatment and study the effect of treatment on the prognosis of cerebrocardiovascular diseases.

## Limitations

The following limitations needs to be acknowledged and addressed regarding the present study. The migraine is biologically heterogenous, its incidence shows differences in age, sex and has familial variations and hence, a larger patient and control sample are needed. In this study, migraine was studied as a risk factor of IS and ACS but the risk factors of migraine (e.g., hormonal contraceptive pills) was not studied. Moreover, magnetic resonance imaging (MRI) was not performed to all studied patient because of its unavailability in the insurance hospital at this time.

## Recommendations

We recommend to study and compare the effect of anti- migrainous treatment including sumatriptan and CGRP as well as antiplatelet treatment in migraine with IS or ACS (either on treatment or naïve) regarding risk factors and prognosis.

### Abbreviations

ACS: Acute coronary syndrome; CHD: Coronary heart disease; CVD: Cardiovascular disease; HIS: Headache International Society; IS: Ischemic stroke; MA: Migraine with aura; MIDAS: Migraine Disability Assessment Scale; MO: Migraine without aura; MRI: Magnetic resonance imaging; TIA: Transient ischemic attack.

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### Author contributions

EM: Study Design,, shared in writing the manuscript. O.M.: Interpretation of data, recruiting control subjects, statistical analysis, shared in discussion. N.A.: Study design, shared in writing the manuscript. M.A.: Study design, shared in writing the manuscript. M.K.: Recruiting patients, shared in writing the manuscript. All authors have read and approved the manuscript.

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Authors did not receive any funds.

### Availability of data and materials

Data are available with authors, It is not possible to share research data publicly, as it includes patient's information.

## Declarations

### Ethics approval and consent to participate

Approval to conduct this study was obtained from Neurology and Psychiatry Dept. Ethics committee, as the faculty ethics committee was not fully activated. Approval to publish the study was obtained from Faculty of Medicine Research Ethics Committee (FMREC) in Minia University, who confirmed that the study conformed to the principles of "Declaration of Helsinki". written consents were taken from all patients or their relatives.

### Consent for publication

Not applicable.

### Competing interests

Authors declare no competing interests.

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## Publisher's Note