Is migraine a risk factor for stroke?
Migraine and stroke: “vascular” comorbidity

Donata Guidetti, Eugenia Rota*, Nicola Morelli and Paolo Immovilli

Meta-analyses addressing the migraine-stroke association

<table>
<thead>
<tr>
<th>Study</th>
<th>Stroke type</th>
<th>Migraine</th>
<th>MA</th>
<th>MO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elminan M et al. Br Med J 2005; 330:63–5</td>
<td>Ischaemic</td>
<td>RR 2.16, (95% CI)</td>
<td>RR, 2.27; 95% CI</td>
<td>RR 1.83; 95% CI</td>
</tr>
<tr>
<td>Schurks M et al. BMJ (2009) 339:b3914.</td>
<td>Ischaemic</td>
<td>RR 1.73 (95% CI)</td>
<td>RR 2.16 95% CI</td>
<td>RR 1.23 95% CI</td>
</tr>
<tr>
<td>SpectorJT et al. Am J Med (2010) 123:612–24</td>
<td>Ischemic</td>
<td>OR 2.04(95% CI)</td>
<td>OR 2.25, 95% CI</td>
<td>OR 1.24, 95% CI</td>
</tr>
<tr>
<td>Sacco S et al. Stroke (2013) 44 (11):3032–8.</td>
<td>Haemorrhagic</td>
<td>OR 1.48 (9% CI)</td>
<td>OR 1.62 (95% CI)</td>
<td>OR 1.39 (95% CI)</td>
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</table>
The association between stroke and migraine

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<td>Kurth T., Cephalalgia, 2007, 27, 967–975</td>
<td>meta-analysis of 11 case-control and 3 cohort</td>
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<td>RR 1.83; 95% CI</td>
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<tr>
<td>Kuo C-Y, et al. 2013. PLoS ONE 8(1): e55253</td>
<td>population-based cohort Age-sex match (NHI Taiwan)</td>
<td>Hemorrhagic stroke</td>
<td>adjusted HR 2.13 (95% CI) p 0.0001</td>
<td></td>
</tr>
<tr>
<td>Mawet J.et al Cephalalgia 2015, Vol. 35 (2) 165–181</td>
<td>Meta analysis 13 case-control and 8 cohort</td>
<td>Ischemic</td>
<td>OR 2.04(95% CI)</td>
<td>OR 2.51, 95% CI P 0.0001</td>
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<td></td>
<td>Woman younger than 45 OR 2.89, 95% CI</td>
<td>OR 1.29, 95% CI p&gt;0.0001</td>
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</tbody>
</table>

Increased Risk of Hemorrhagic Stroke in Patients with Migraine: A Population-Based Cohort Study

Cheng-Ya Kuo, Ming-Fang Yen, Li-Sheng Chen, Ching-Yuan Fann, Yueh-Hsia Chiu, Hsiu-Hsi Chen, Shin-Liang Pan

The data used in this study were obtained from the complete National Health Insurance (NHI) claim database in Taiwan for the period 2000 to 2003.

- The migraine group (compare with non migraine) had a higher prevalence of
  - hypertension (P,0.0001),
  - hyperlipidemia (P,0.0001),
  - coronary heart disease (P,0.0001),
  - chronic rheumatic heart disease (P = 0.0001), and
  - other heart disease (P,0.0001) than the non-migraine group.
Migraine and stroke: “vascular” comorbidity

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MA patients tended to have

- high-blood pressure (OR = 1.76 95% CI 1.04–3.0),
- a worse cholesterol profile (total cholesterol ≥240 mg/dL: OR = 1.43 95% CI 0.97–2.1),
- an earlier onset of coronary heart disease or stroke (OR = 3.96; 95% CI 1.1–14.3), with a twofold probability of having an elevated Framingham risk, resulting in a higher cardiovascular risk profile.

Guidetti B et al. frontiers in Neurology 2014

Migraine, cardiovascular disease, and stroke during pregnancy: Systematic review of the literature

Wabnitz A and Bushnell C. Cephalalgia 2015, Vol. 35(2) 132–139

there is an increased risk of (pregnant migraineurs compared to nonmigraineurs).

- gestational hypertension (OR range from 1.23 to 1.68) and preeclampsia (OR range 1.08 to 3.5)
- acute myocardial infarction and heart disease (OR 4.9; 95% CI 1.7-14.),
- thromboembolic events during pregnancy (deep venous thrombosis (OR 2.4; 95% CI 1.3 - 4.2)
- pulmonary embolus (OR 3.1; 95% CI 1.7 - 5.6).
correlation between migraine with stroke and coronary heart disease

- Cross sectional study, 90 patients, July - September 2017
- Migraine and stroke PR= 1.21 (95% CI 0.80-1.84)
- Migraine and Coronary heart Disease PR =0.83 (95% CI 0.51- 1.40)

Harizah Q.E, Sjahrir H, Nasution IK. Presented at National Annual Meeting of Indonesian Neurological Association, Pekan Baru Indonesia Oct 2017

### The association between stroke and migraine

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<tr>
<td>Wabnitz A Cephalalgia 2015, Vol. 35(2) 132–139</td>
<td>Systematic review ischemic</td>
<td>pregnancy (OR range 7.9-30.7)</td>
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<td></td>
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<td>ICH</td>
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<td></td>
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<td>Pregnancy OR 9.1</td>
<td></td>
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</tr>
<tr>
<td>Mawet J.et al Cephalalgia 2015, Vol. 35(2) 165–181</td>
<td>Meta analysis 13 case-control and 8 cohort ischemic</td>
<td>Smokers (OR 9.03, 95% CI)</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>meta analysis case control</td>
<td>white matter MRI hyperintens</td>
<td>OR 3.9, 95% CI</td>
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</table>
A nationwide cohort study was conducted using data from the Taiwan National Health Insurance Research Database. Two cohorts were extracted: a neurologist-diagnosed migraine cohort, and a non-headache, propensity score-matched comparison cohort.

### Results

- **Population-based cohorts (aHR: 3.24, 95% CI: 2.45–4.30, p<0.0001).**
- **Women aged <45 years (aHR: 1.38, 95% CI: 1.05–1.82, p=0.021).**
- **Men aged <45 years (aHR: 3.17, 95% CI: 2.01–5.02, p<0.001).**
- **Subgroup analysis by age and sex revealed the highest risk in women aged <45 years and men aged <45 years.**

### Conclusion

The association between migraine and ischemic stroke varies in different subgroups of patients. Women with migraine, especially those aged <45 years, are at increased risk of ischemic stroke compared to men and older women.

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### The association between stroke and migraine

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<th>Migraine</th>
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<th>MO</th>
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<tr>
<td>Monteith TS et al. 2015;85:715–721</td>
<td>population-based cohort study in older Northern Manhattan</td>
<td>ischemic</td>
<td>Smokers</td>
<td>HR 3.17 95% CI</td>
</tr>
<tr>
<td>Linxin Li et al. Neurology® 2015;85:1444–1451</td>
<td>a population-based cohort study</td>
<td>cryptogenic</td>
<td>OR 1.73 95% CI</td>
<td>Oxford Vascular study</td>
</tr>
<tr>
<td>Peng KP et al. Cephalalgia 2017, Vol. 37(4) 327–335</td>
<td>Population based cohort study</td>
<td>ischemic</td>
<td>aHR: 1.24, 95% CI p&lt;0.001</td>
<td>aHR: 1.08, 95% CI</td>
</tr>
<tr>
<td>NIH Taiwan</td>
<td>women aged &lt;45 years</td>
<td>HR: 4.58, 95% CI</td>
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</table>

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### Migraine and incidence of ischemic stroke: A nationwide population-based study


Cohort study was conducted using data from the Taiwan National Health Insurance 2004-2009

- **This study with short duration of 3.6 years compared to 10 years in the WHS, still identified an association between migraine and ischemic stroke (aHR 1.24 95% CI).**

- **found an increased risk of ischemic stroke in men with migraine (aHR: 1.20, 95% CI: 1.01–1.42, p =0.036).**

- **Subgroup analyses by age and migraine sub-type revealed a trend toward the development of ischemic stroke in younger (age <45 years) male patients (aHR: 1.54, 95% CI: 0.96–2.48, p =0.075).**
Migraine and stroke: In search of shared mechanisms

Jerome Mawet, Tobias Kurth and Cenk Ayata

Keywords

Migraine, ischemic stroke, cerebrovascular disease, spreading depression, migrainous infarct

The underlying mechanisms are poorly understood and probably multifactorial.

Background:

We carried out an extended literature review of experimental and clinical evidence supporting the association between migraine and ischemic stroke. Based on clinical and experimental data, we propose mechanistic hypotheses to explain the link, such as microembolic triggers of ischemic stroke in migraineurs.

Abstract

We discuss the possible practical implications of clinical and experimental data, such as aggressive risk factor screening and management, stroke prophylaxis and specific acute stroke management in migraineurs. However, evidence from prospective clinical trials is required before modifying the practice in this patient population.

Results

Migraine, particularly with aura, increases the risk for ischemic stroke, at least in a subset of patients. Evidence suggests that migraine, particularly with aura, increases the risk for ischemic stroke, at least in a subset of patients.

The population-based Epidemiology of Vascular Aging study (780 participants, mean age of 69) also found an increased risk of cerebral infarcts in migraineurs with aura only (Kurth T BMJ 2011).

Cerebral Abnormalities in Migraine and Epidemiological Risk Analysis (CAMERA) population-based MRI lesion prevalence study

- Results: increased risk of subclinical posterior circulation infarct-like lesions, mostly located in the cerebellum, in migraineurs compared to controls (OR 7.1, 95% CI ).
- The risk was substantially higher in MA (OR 13.7, 95% CI), especially with frequent migraine attacks (>1 attack/ month) (OR 15.8, 95% CI 1.8–140), (Kruit MT 2015)

The population-based Epidemiology of Vascular Aging study (780 participants, mean age of 69) also found an increased risk of cerebral infarcts in migraineurs with aura only (Kurth T BMJ 2011).
Migraine with aura may be a direct cause of migrainous infarction (the classification made by the International Headache Society (IHS) in 2013)

(Guidetti B et al. frontiers in Neurology 2014)

- Migrainous infarction is defined as a stroke that occurs during an attack of migraine with aura in which aura symptoms persist for > 60 minutes.
- Migrainous infarction accounts for 0.2% to 0.5% of all ischemic strokes in cross-sectional studies using large stroke registries.


MIGRAINE WITH AURA
aura visual
The concept of "cortical spreading depression (CSD)" has been accepted as the main pathogenetic mechanism of migraine aura.

CSD, can cause severe vasoconstriction which is a unique pathophysiologic mechanism of migraine aura, may precipitate an ischemic stroke


Potential mechanisms of migrainous infarction include vasospasm, hypercoagulability, and vascular changes related to cortical spreading depression.

(Tietjen GE. Cephalalgia, 2007, 27, 981–987)

Spreading depolarizations in a case of migraine-related stroke

Edgar Santos³, Renán Sánchez-Porras¹, Christian Dohmen², Daniel Hertel¹, Andreas W Unterberg¹ and Oliver W Sakowitz¹

endothelin-1-induced vasospasm and microembolism may be a link between CSDs and MA,

a continuum of CSDs, hypoxic-ischaemic episodes can induce MA attacks and hypoperfusion was established

the intense reduction of CBF enabled turbulence and the subsequent stagnation of blood flow, severe enough for a thrombosis to develop
Migraine, cardiovascular disease, and stroke during pregnancy: Systematic review of the literature

Wabnitz A and Bushnell C. Cephalalgia 2015, Vol. 35(2) 132–139

- migraine can also contribute to a hypercoagulable state of pregnancy
- Estrogen is responsible for increased procoagulants during pregnancy through stimulation of hepatic synthesis of clotting factors.
- The rising blood pressures in migraineurs during preeclampsia have a link with stroke

Active migraine places women at significantly higher risk for ischemic stroke during pregnancy.

- reversible cerebral vasoconstriction syndrome (RCVS), a clinical and radiological syndrome characterized by severe unusual headache and transient multifocal cerebral vasoconstriction
- the link between RCVS and migraine may also contribute to the higher risk of HS in migraineurs.

Mawet J, Kurth T and Ayata C. Cephalalgia 2015, Vol. 35(2) 165–181
**Oral contraceptive/hormonal and stroke**

- Oral contraceptives, even at low doses, significantly increase the risk of cerebral venous thrombosis
- Migraine is a contraindication for OC use. (a progestogen-only OC might be recommended)
- There are no data on the relationship between hormone replacement therapy, migraine and stroke.
- However, there are reasons to be concerned that HRT may contribute to stroke risk


**Migraine in women: the role of hormones and their impact on vascular diseases**

**Risk of ischemic stroke OR; 95% CI**

<table>
<thead>
<tr>
<th>Collaborative Group</th>
<th>Women with migraine using COCs vs. women with migraine not using COCs</th>
<th>Women without migraine using COCs vs. women without migraine not using COCs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5.9; 2.9–12.2</td>
<td>4.9; 2.9–8.3</td>
</tr>
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</table>

Migraine is associated with endothelial dysfunction, a process: 1) mediated by oxidative stress, 2) causing thrombosis, inflammation, and arterial dissection, 3) and associated with vascular reactivity, 3) and associated with vascular reactivity.

Potential Mechanism of Ischemia in Migraine.

- PAF is released from cerebral endothelial cells, platelets and mast cells in response to hypoxia and calcitonin gene-related peptide (CGRP), and in turn, prompts the release of von Willebrand Factor.
- vWF, a large endothelial-derived glycoprotein, indirectly activates the platelet IIb/IIIa receptor, crucial for binding fibrinogen, similarly affects platelets aggregation.

Tietjen GE. Cephalalgia, 2007, 27, 981–987

AC-DD: angiotensin-converting enzyme gene deletion polymorphism increased frequency of attacks.
MTHFR: methylenetetrahydrofolate reductase associated with susceptibility to MA.
Biomarkers of endothelial dysfunction, i.e., elevated vWF antigen, vWF activity, high-sensitivity C-reactive protein and reduced nitrate/nitrite levels.

**Endothelial dysfunction in Migraineurs**

- Increase in endothelial-derived vasoconstrictors (endothelin & serotonin)
- Endothelial progenitor cell (EPC) decrease
- Endothelial microparticles increased

lead to a procoagulatory, proinflammatory and proliferative state, which predisposes to atherosclerosis

**THROMBOSIS**


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**Laboratory analyses in migraine and non-migraine patients**

(a prospective study of patients < 55 years of age with brain ischemia.)

<table>
<thead>
<tr>
<th>Variable</th>
<th>All patients (N=154)</th>
<th>Brain infarction &lt;50 years old</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Migraine (n=44)</td>
<td>Non-migraine (n=110)</td>
</tr>
<tr>
<td></td>
<td>Migraine (n=18)</td>
<td>Non-migraine (n=61)</td>
</tr>
<tr>
<td>Hypercoagulable states*, n (%)</td>
<td>19 (38.6)</td>
<td>18 (16.4)</td>
</tr>
<tr>
<td></td>
<td>8 (44.4)</td>
<td>11 (18)</td>
</tr>
<tr>
<td>Protein C or S deficiency</td>
<td>6 (13.6)</td>
<td>3 (2.7)</td>
</tr>
<tr>
<td></td>
<td>2 (11.1)</td>
<td>3 (4.9)</td>
</tr>
<tr>
<td>Prothrombin G20210A mutation**, n (%)</td>
<td>5 (11.4)</td>
<td>3 (2.7)</td>
</tr>
<tr>
<td></td>
<td>2 (11.1)</td>
<td>2 (3.3)</td>
</tr>
</tbody>
</table>

- HS more frequent in the migraine than non-migraine (38.6% vs. 16.4%, \( p < 0.01 \)), as well as in the group of brain infarction patients under 50 years old (44.4% vs. 18%, \( p < 0.03 \))
- MA patients presented a higher HS frequency than MO although this difference was NS

Sañchez PM et al. Cephalalgia 2011. 31(16) 1609–1617
A recent study in 1456 women MA (mean age 34)

- carriers of factor V Leiden or factor II G20210A mutations (OR 1.76, 95% CI 1.02–3.06)
- elevated pro-thrombin factor,
- decreased resistance to activated protein C,
- protein S deficiency

Mawet J, Kurth T and Ayata C. Cephalalgia 2015, Vol. 35(2) 165–181

A meta-analysis of case-control studies of PFO

PFO

RISK OR 5.13
MIGRAINE

RISK OR 2.54

- The basis for the association of PFO and migraine with aura is uncertain, but there is evidence that both migraine and PFO have a genetic predisposition.
- PFO closure in reducing migraine attack frequency, such as headache resolution in up to 80% of patients

Tietjen GE. Cephalalgia, 2007, 27, 981–987
Mawet J, Kurth T and Ayata C. Cephalalgia 2015, Vol. 35(2) 165–181
Wabnitz A and Bushnell C. Cephalalgia 2015, Vol. 35(2) 132–139
Cervical Arterial dissection

- In a metaanalysis, migraine (MO) is associated with a two-fold increased risk of cervical artery dissection (OR = 2.06, 95% CI).
- Arterial dissection, a well-recognized cause of stroke in the young more common in migraineurs.
- Elevations of serum elastase activity and shared genetic alterations such as MTHFR polymorphism are possible mechanisms.
- A recent genome-wide association study of cervical arterial dissection identified a significant association of the PHACTR1 (Phosphatase and actin regulator 1) locus, which is also associated with migraine.


There are 2 genetic mutations that show a stroke with migraine symp

- Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL), is Notch-3 mutation is the gene involved in encoding a transmembrane receptor primarily expressed in systemic small cerebral arterial smooth-muscle cells.
  - TIA and ischemic strokes are the most frequent occurring in 60%-85% of patients CADASIL with migraine features.
- Mitochondrial Encephalopathy, Lactic Acidosis and Stroke-like episodes (MELAS) is a genetically heterogeneous mitochondrial disorder characterized by features of central nervous system involvement (seizures, hemiparesis, hemianopia, cortical blindness, sensori-neural deafness, and/or episodic vomiting).
  - Headache is a common manifestation, which is either a recurrent migraine-like attack or a presenting symptom of stroke-like episodes.

Independent risk factors of ischemic stroke in migraineurs

- Migraine with Aura (OR 2.3 95% CI)
- Woman Age < 45 years (OR 2.6 95% CI)
- Oral contraceptive use (OR 5.9 95% CI)
- Smoking (HR 3.2-9.3 95% CI)

- Migraine with aura may be a direct cause of migrainous infarction
- Migraine particularly MA, were at increased risk of death from coronary heart disease and stroke (Gudmundsson LS et al. BMJ 2010)
Migraineurs men have an increased risk of ischemic stroke compared with men without migraine. HR 1.12

Found an increased risk of ischemic stroke in men with migraine (aHR: 1.20, 95% CI: 1.01–1.42, p = 0.036).


The migraine group had a higher prevalence of
- hypertension (P ≤ 0.0001),
- hyperlipidemia (P ≤ 0.0001),
- coronary heart disease (P ≤ 0.0001),

Prevention & treatment of stroke in migraineurs

1. Triptans and ergotamine are not recommended in patients with MA
2. Smoking cessation
3. Antithrombotics are not recommended to reduce a risk of stroke in migraineurs.
4. Headache specialists should take care not only of relieving pain but also of assessing and treating concurrent vascular risk factors
5. Gynecologists should consider prescribing oral contraceptives.

Sacco S et al. Cephalalgia 2012, 32(10) 785
Mawet J, Kurth T and Ayata C. Cephalalgia 2015, Vol. 35(2) 165–181
Thank you