Migraine as a cardiovascular risk factor for women

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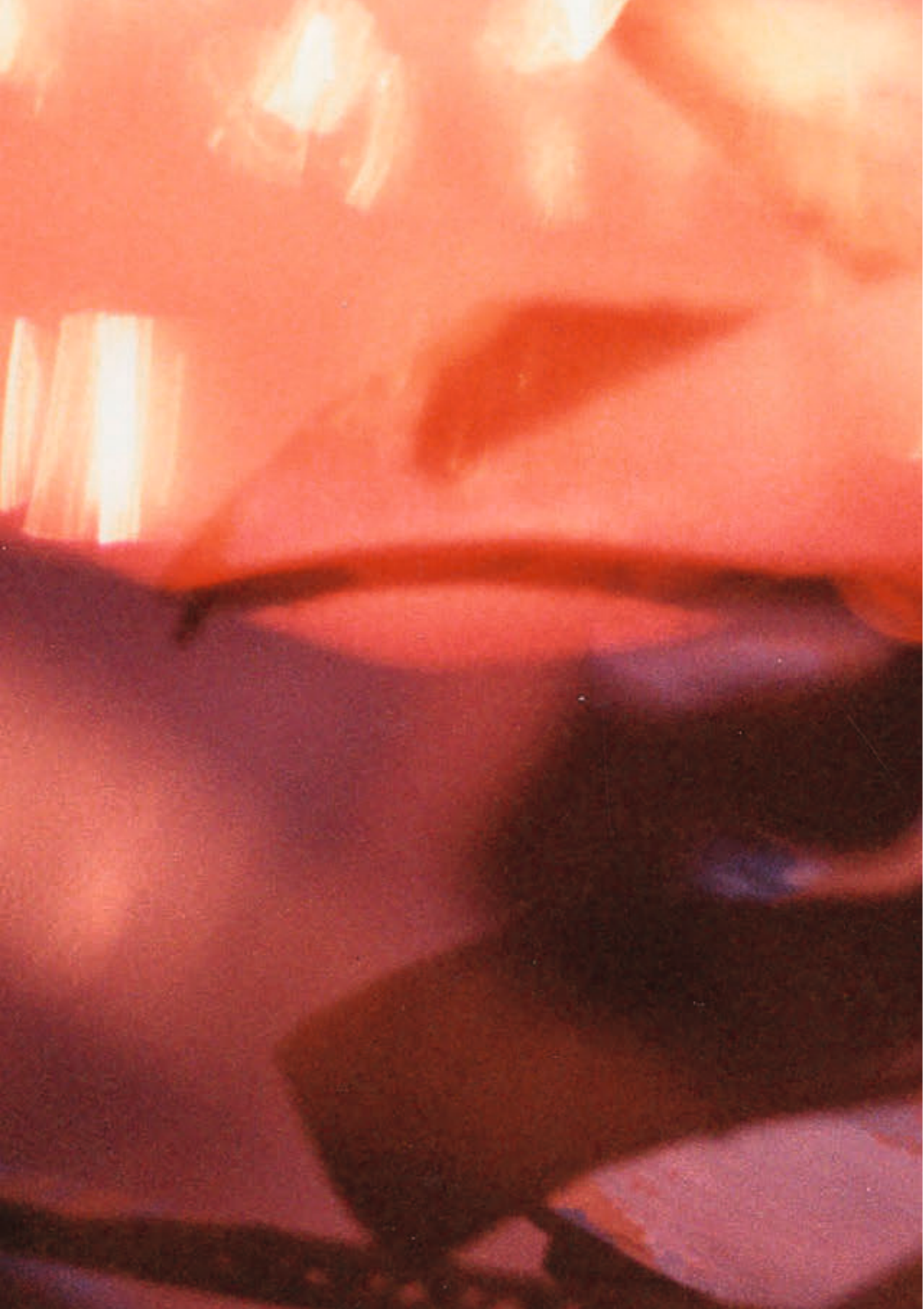

CHAPTER 2

Migraine and cardiovascular disease in women

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ABSTRACT

Migraine is responsible for high rates of disability. In addition, it is associated with an increased risk of cardiovascular disease. This association is not limited to the brain in the form of stroke, but includes cardiac ischemia. The increased risk is most consistently described in the female population and in particular for migraine with aura. This article reviews the current knowledge on migraine and the associated risk of cardiovascular disease, with a focus on female-specific factors.

1.EPIDEMIOLOGY AND PATHOPHYSIOLOGY OF MIGRAINE

Migraine is a chronic neurovascular disorder characterized by attacks of severe pulsating one-sided headache, often accompanied by nausea and photophobia, that may last up to 72 h. One third of migraine patients experiences migraine auras; most commonly transient visual or sensory neurological disturbances. Due to the frequent, debilitating attacks and the high prevalence of 11% in the general population and up to 25% in young women[1] migraine is firmly placed as the seventh cause of years lost to disability worldwide.[2] Migraine pathophysiology involves an incompletely understood mechanism originating from neural activation in the brainstem and subsequent release of neuropeptides associated with vasodilation, inflammation and pain. Interestingly, it appears that migraine pathophysiology may be linked to long term cardiovascular complications.

2. MIGRAINE INCREASES CARDIOVASCULAR RISK

2.1 EPIDEMIOLOGY

There is increasing evidence that migraine, especially migraine with aura, increases the risk of cardiovascular disease (CVD) (HR 1.5, CI 1.33–1.69) and cardiovascular mortality (HR 1.37, 1.02–1.83).[3] The increased risk of stroke (RR ~2.0) has been demonstrated in a considerable amount of literature.[4] Especially when combined with other cardiovascular risk factors, such as use of oral contraceptives and smoking, the risk of ischemic stroke may be increased over 30 times in women.[5] Besides ischemic stroke there is also an increased risk for hemorrhagic stroke.[6] The involvement of cardiac disease such as myocardial infarction (HR 1.39, 1.18–1.64) has not yet been reported extensively and with inconsistent outcomes as can be seen in Table 1.[3] The association of CVD (including stroke) and migraine is described more often in women than in men.[4] Those studies that reportincreased risks in both genders, mostly describe a higher risk in women. [4] Partly, this difference may be a result of bias caused by the higher prevalence of migraine in women. Currently, there is no explanation for the gender difference in migraine prevalence, severity and the consequences in the form of CVD risk. It is important to specify that despite the increased relative risk, the absolute risk for CVD in young women remains low. However, the high prevalence of migraine in this population in combination with the increased awareness of the impact of CVD in women make understanding the pathophysiological mechanisms behind migraine and other (female specific) risk factors and their interaction all the more urgent. A good example of female specific CVD related factors are gestational hypertension and preeclampsia, which interestingly occur more often in women with migraine.[7] Whether a history of both migraine and preeclampsia gives rise to a multiplicative increase in CVD risk is yet unknown, but certainly worthwhile to explore because of the high prevalence of both conditions.

2.2. PATHOPHYSIOLOGY

The mechanism behind the association between migraine and cerebrovascular damage is a widely explored topic. Dysregulation of the neurovascular system is triggered during a migraine attack and may be a manifestation, or a cause, of cerebrovascular damage. Subclinical damage, presented as white matter hyperintensities and silent brain lesions on MRI, is found to be more prevalent in female migraineurs when compared with healthy controls and male migraineurs.[8] There is no clear proof that an increased frequency of migraine attacks gives rise to more extensive damage.[9] Interestingly, the risk for strokes seems to be especially increased for migraine with aura (OR 2.16, CI 1.53–3.03).[4] It is suggested that cortical spreading depression (CSD) is involved in this interaction. This wave of depolarization and neurovascular uncoupling spreads over the posterior cortex during migraine aura and is involved in stroke where it is connected to the extent of ischemic tissue damage.[10] In mouse

Table 1: Cohort studies reporting association migraine – CVD other than stroke

Author	Study type	Population (N=)	Age	Migraine type (diagnosis)	CVD specification	Associated risk (95 %CI)
Kurth 2016	Prospective cohort (FU >20 years)	Women (115,541)	25-42	All migraine (Self reported physisican's diagnosis)	Major CVD (MI, stroke, fatal CVD) MI CV mortality	HR 1.50 (1.33-1.69) HR 1.39 (1.18-1.64) HR 1.37 (1.02-1.83)
Wang 2014	Retrospective cohort	Both (23,082)	18-45	All migraine (Medical records)	IHD	HR 2.50 (1.78-3.52)
Bigal 2010	Case-control	Both (11,345)		All migraine MA MO (Validated questionnaire IHS2 criteria)	MI MI MI	OR 2.19 (1.73-2.77) OR 2.99 (2.27-3.95) OR 1.80 (1.39-2.34)
Gudmundsson 2010	Prospective cohort	Both (18,725)	33-81	All MA MO (Interview IHS 2 criteria)	CV mortality CV mortality CV mortality	HR 1.19 (1.07-1.32) HR 1.27 (1.13-1.43) HR 1.10 (0.91-1.34)
Schürks 2009	Meta-analysis	Both	Any	Heterogenous	MI CV mortality	Pooled 1.12 (0.95-1.32) Pooled 1.03 (0.79-1.34)

Table 1: Continued

Author	Study type	Population (N=)	Age	Migraine type (diagnosis)	CVD specification	Associated risk (95 %CI)
Kurth 2007	Prospective cohort (FU 16 years)	Men (20,084)	40-84	All migraine (Self report migraine attack)	Major CVD (MI, stroke, fatal CVD) CV mortality	HR 1.12 (0.84-1.50) HR 1.07 (0.80-1.43)
Ahmed 2006	Retrospective cohort	Women (873)	Any	All migraine (Self report questionnaire)	CV event CV mortality	HR 1.21 (0.93-1.58) HR 1.16 (0.20-6.7)
Velentgas 2004	Retrospective cohort	Both (260,822)	Any	All migraine (Triptan use or based on medical record)	MI CV mortality	RR 0.96 (0.80-1.15) RR 0.60 (0.33-1.09)
Hall 2004	Retrospective cohort	Both (140,814)	Any	All migraine (Medical record)	MI CV mortality	HR 1.15 (0.96-1.38) HR 0.93 (0.76-1.13)
Sternfeld 1995	Retrospective cohort	Both (79,588) Men Women Men Women	Any	All migraine Frequent unilateral headaches with nausea or affected vision Self reported physician's diagnosis or treatment	MI MI MI MI	RR 0.8 (0.5-1.2) RR 0.7 (0.4-1.0) RR 1.2 (0.7-1.9) RR 1.4 (0.9-2.1)
		Men Women Men Women	<40	Frequent unilateral headaches with nausea or affected vision Self reported physician's diagnosis or treatment	MI MI MI MI	RR 0.3 (0.1-2.4) RR 1.5 (0.5-5.1) RR 0.6 (0.1-4.4) RR 2.1 (0.5-9.5)

models with CADASIL (a severe monogenic stroke type with migraine with aura), increased vulnerability for CSD has been shown.[11]The connection of migraine with non-cerebral vascular damage, such as coronary heart disease, is more difficult to comprehend. It is suggested that a certain systemic 'vascular vulnerability' may be involved.[10] Migraine could be regarded as an expression of this underlying condition which, when combined with other modifiers of vascular health, may lead to a synergistic increase in CVD risk. This hypothesis could explain the multiplicative risk seen in young female migraineurs who smoke and use oral contraceptives.

Ongoing research is aiming to define this vascular vulnerability. Migraine is associated with classical cardiovascular risk factors, such as hypertension and hypercholesterolemia, as well as increased levels of factors associated with CVD risk such as prothrombin, von Willebrand factor and endothelin.[12,13] However, migraine is not associated with enhanced atherosclerosis, which illustrates the complexity.[14] Increased thrombogenicity, inflammation and altered vasodilatory reaction are found in migraineurs and can be seen as markers of dysfunction of the endothelium, the inner lining of the blood vessels that normally has vasoprotective properties.[15] Endothelial dysfunction might be the vascular vulnerability of which both migraine and CVD are expressions, but high quality studies taking into account endothelium-dependent as well as – independent vascular function measurements are lacking. Interestingly, in preeclampsia similar abnormal vasoreactivity, altered platelet activity and other signs of endothelial dysfunction are found.[7] A search for shared mechanisms between preeclampsia and migraine may lead to interesting discoveries. For the time being, the pathological basis behind the migraine - CVD association remains puzzling, especially when regarded in the context of female health.

3. HORMONES AS PART OF PATHOPHYSIOLOGY

Sex hormone levels are closely linked to both migraine and cardiovascular disease and could account for gender differences. In the case of migraine, a steady rise in prevalence and attack frequency occurs right after menarche and a decline is seen after menopause. Throughout the fertile years, migraine may be partly linked to the menstrual cycle (menstrually related migraine, in this case migraine attacks also occur outside the perimenstrual period) or may occur exclusively during the menstruation (pure menstrual migraine). Especially around fluctuations in hormone levels the sensitivity for migraine seems to increase. Possibly, this marks the influence of estrogen on factors involved in pain transmission and migraine pathophysiology. Indeed, recently the peak estradiol levels in women with menstrually related migraine were reported to be lower than those in healthy women.[16] In another study, women with migraine had faster late luteal estrogen withdrawal rates compared to healthy controls although this did not correlate with occurrence of perimenstrual headache.[17] Additionally, vasoreactivity mediated by the trigeminal nerve, which is part of the neurovascular system involved in migraine attacks, responds differently to hormone fluctuations in women with menstrually related migraine.[16] Estrogen, in relation to progesterone and low leveltestosterone, has a major influence on vascular health in a multitude of ways. Estrogen is involved in different modalities such as thrombotic propensity, vasodilatory response and is thought to act protective against CVD risk until menopause, when hormone balance shifts and CVD prevalence surges. This may partly explain the higher CVD risk of migraine observed in younger women. After menopause, major CVD risk factors such as hypertension and hypercholesterolemia may outweigh migraine as a risk factor. However, because of the complexity of the effects and interactions of estrogen in the vascular system, its role in the migraine – CVD connection remains ambiguous.

4. CLINICAL ADVICE BASED ON THE EXISTING LITERATURE

Clinical trials on management to decrease CVD risk in migraine patients are nonexistent. There is no evidence that prophylactic treatment in the form of statins or antiplatelets is of benefit for otherwise healthy female migraine patients, especially when considering side-effects, costs and burden. Caution is warranted with the use of triptans after a cardiovascular event because of their vasoconstrictive properties, however, there is no real evidence that the use of this medication in migraineurs is in itself related to CVD risk.[18] This might be the case for 'older generation' migraine drugs such as ergotamines.[19] Whereas the AHA stroke association recommends caution when prescribing oral contraceptives (OC) to women with migraine, it is also stated that this recommendation is based on very limited evidence.[20] More targeted research on this topic would be of great use in the clinical setting, especially since quitting OC use can be unfavorable for migraine frequency and severity. To conclude, there is currently no evidence for changes in medication use that may be beneficial to the CVD risk in women with migraine. However, the importance of awareness and lifestyle advice is evident. Smoking should be quitted, as the already increased risk of stroke shows a dramatic rise, especially in those suffering from migraine with aura.

5. SUMMARY

Migraine is associated with an increased risk of CVD. This association is described especially in young women suffering from migraine with aura. Though the precise mechanisms behind this association remain unknown, it is hypothesized that a vascular vulnerability is at the basis of both migraine and CVD. Limited knowledge exists on why this risk is possibly gender specific, and how it relates to sex hormones and to other female specific cardiovascular risk factors. How much caution is warranted in women with migraine in combination with other female specific events associated with CVD, such as preeclampsia, is yet unknown. Clinical recommendations are currently limited to raising awareness and giving lifestyle advice.

PRACTICE POINTS

- Although overall cardiovascular risk in young women remains low, migraine with aura should be regarded as an important risk factor in clinical assessment.
- Careful lifestyle advise is warranted, with a focus on the importance of quitting smoking.
- As of yet, there is not enough evidence to support changes in medication use, such as quitting OC, prescribing antiplatelets, or preventing migraine attacks, in order to decrease CVD risk in young women with migraine

RESEARCH AGENDA

- Physiological basis for gender differences in CVD risk in migraine patients.
- Further explore the interaction between migraine and other, female specific, risk factors.
- Useful preventative measures, benefits of altering prescription of migraine specific medication, oral contraceptives and statins/anticoagulation.

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