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Review

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.

Contents

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

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

Author	Study type	Population (N=)	Age range	Migraine type (diagnosis)	CVD specification	Associated risk (95%CI)
Kurth [3]	Prospective cohort (FU > 20 years)	Women (115,541)	25–42	All migraine (Self-reported physician'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 [10]	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 [4]	Meta-analysis	Both	Any	Heterogenous	MI CV mortality	Pooled 1.12 (0.95–1.32) Pooled 1.03 (0.79–1.34)
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)

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) [3] has not yet been reported extensively and with inconsistent outcomes as can be seen in Table 1.

The association of CVD (including stroke) and migraine is described more often in women than in men [4]. Those studies that report increased 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 models with CADASIL (a severe monogenic stroke type with migraine with aura), increased vulnerability for CSD has been shown [11].