Relationship between migraine and stroke: how true and how close

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Migraine is a common chronic disorder with episodic headache. Up to one third of patients with migraine experience headache characterized by neurological symptoms most often involving the visual fields and less often the sensory or speech. Migraine physiology has been well elucidated but several lacunae still remain. Several mechanisms have been implicated to explain the link between migraine and the occurrence of stroke and cardiovascular disease. None have been definitively proven. In the absence of robust evidence, the best possible advice will be: in an otherwise healthy young person with migraine, no cause for concern exists because of the very low absolute risk of stroke. Advice to stop smoking seems prudent, as does oestrogen or only progesterone to young women with migraine. Further research is imperative on the association between migraine and mortality from stroke and cardiovascular disease and all causes including studies to identify whether there are specific subgroups of people with migraine who are at enhance risk because of genetic or environmental factors.

Keywords: Cardiovascular disease, chronic disorder, migraine, myocardial ischaemia, stroke.

Introduction

MIGRAINE is a common chronic disorder with episodic headache. It affects 10–20% of the population during the most productive years of life[1]. Women are affected more often than men[1]. Clinically, migraine is characterized by recurrent attacks of headache and various combinations of symptoms related to the gastrointestinal and autonomic nervous system. Up to one third of patients with migraine experience headache characterized by neurological symptoms most often involving the visual fields and less often the sensory or speech[1]. It is not a disease but a syndrome that is characterized by paroxysmal headache associated with other signs and symptoms. About 80% of migraineurs have migraine without aura, whereas migraine with typical aura accounts for 15–20% of cases. Isolated migraine aura without headache (acephalalgic migraine) may be encountered in 5% of patients[2]. Migraine variant (or migraine equivalent) is the term applied to a migraine that exhibits itself in a form other than head pain. Such conditions are less recognized, less common and less well understood than the typical migraines. Migraine variants may be characterized by the following: (1) Paroxysmal episodes of prolonged visual auras; (2) Atypical sensory, motor or visual aura; (3) Confusion; (4) Dysarthria; (5) Focal neurological deficits; (6) Gastrointestinal manifestations; (7) Other constitutional symptoms with or without headache.

The diagnosis of migraine variant is determined by a history of paroxysmal signs and symptoms with or without cephalalgia and a previous history of migraine with aura, in the absence of other medical disorders that may contribute to the symptoms. Many of these patients usually have a family history of migraine.

Many migraine variants have been defined by the International Classification of Headache Disorders 2004 classification (ICHD-II), including the following: Hemiplegic migraine; Basilar migraine; Childhood periodic syndromes; Retinal migraine; Ophthalmoplegic migraine and Complicated migraine.

Migraine physiology has been well elucidated but several lacunae still remain. The condition is viewed as an inherited disorder of the brain, but vascular mechanisms are clearly implicated. Endothelial dysfunction, hypercoagulability and pathological vascular reactivity have all been implicated in various studies. Migraine is associated with a neuronal network excitability, with activation and sensitization of the trigeminovascular system. Cortical spreading depression (CSD), recognized as the neuronal phenomenon underlying visual aura, is believed to begin in the occipital region and gradually spreads anteriorly[3]. This phenomenon is accompanied by a transient oligaemia, followed by hyperaemia in other parts of the cortex[4].

Various molecular and cellular mechanisms may lead to the increased susceptibility to CSD in migraineurs, which could potentially play an important role in the pathophysiology of migraine variants. A vasogenic leakage from leptomeningeal vessels, with activation of the trigeminovascular system, probably contribute to the prolonged aura in patients with hemiplegic migraine.

Hemiplegic migraine is a rare but well-described form of migraine variant. It was initially described in 1910 as a type of migraine consisting of recurrent headaches associated with temporary unilateral hemiparesis or hemiple-

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gia, at times accompanied by ipsilateral numbness or tingling, with or without a speech disturbance. Thus, a history of recurrent transient hemiplegia or hemiparesis that occurs during an attack of migraine headache suggests hemiplegic migraine. The hemiparesis may resolve before the headache or may persist for days to weeks. The focal neurologic deficit may precede or accompany the headache, which is usually less dramatic than the motor deficit. Other migraine symptoms may be present to varying degrees. Patients may also experience disturbance of consciousness and rarely coma. The neurologic deficit is transient and usually clears in minute to hours, or it may resolve with the beginning of the headache phase[5–7].

Two forms of hemiplegic migraine are known: familial hemiplegic migraine (FHM) and sporadic hemiplegic migraine (SHM). The two forms are phenotypically similar subtypes of migraine with aura, differentiated only by the unilateral motor symptoms[8].

FHM is a genetically heterogenous autosomal dominant disorder and a channelopathy; most of the affected families (FHM1) bear mutations in the *CACNA1A* gene (a defect linked to abnormal voltage-dependent P/Q-type calcium channel alpha-1A on 19p13)[9]. In FHM type 2 (FHM2), mutation in ATP1A2 (R548H) ON 1q23 was identified, encoding the alpha2-subunit of sodium/potassium pumps[10]. A third novel mutation in sodium channel gene *SCN1A* has also been identified in FHM3. Genetic testing is available for FHM by using polymerase chain reaction (PCR) testing to detect point mutations in CACNA1A and ATP1A2 (ref. 11). DNA sequencing is also available. Positron emission tomography (PET) studies have shown glucose hypometabolism in the contralateral perisylvian region early during a hemiplegic migraine[12]. Alternating hemiplegic migraine primarily occurs in childhood and is a chronic progressive disorder, associated with a high prevalence of neurologic deficit[13].

Sporadic hemiplegic migraine is defined as migraine attacks associated with motor weakness in the absence of a family history of similar attacks. Cases of SHM have also been linked to the *CACNA1A* and *ATP1A2* genes[14].

In addition, several population-based and clinic-based studies have established a link between migraine and ischaemic stroke[15–19]. Increasing evidence also suggests association between migraine and other ischaemic vascular events, including myocardial infarction, angina, or death due to cardiovascular disease[20–23].

We discuss here the current evidence on the association between migraine and cardiovascular disease including stroke, stroke subtypes, myocardial infarction, angina and death due to cardiovascular disease. We report on the potential modifying factors of the association between migraine and cardiovascular disease, including migraine aura, sex, age, smoking and use of oral contraceptives. We also discuss the clinical implications of these findings and the future avenues of research.

Recent association between migraine and stroke

Recent meta-analysis of studies which analysed the association of migraine and stroke, gave a pooled relative risks of 1.73 (95% confidence interval of 1.31 to 2.20) for all studies, 1.96 (1.39–2.76) for the case control studies and 1.47 (0.95–2.27) for the cohort studies. Further analysis suggested an increased risk of ischaemic stroke among women (pooled relative risk 2.08, 95% confidence interval 1.13–3.84) but not among men (1.37, 0.89–2.11). The risk for people with migraine aged less than 45 (2.65, 1.41–4.97) was higher than the overall group, which was more pronounced in women (3.65, 2.21–6.04). The risk of ischaemic stroke increased among smokers (9.03, 4.22–19.34) and women currently using oral contraceptives (7.02, 1.51–32.68)[24,25].

Association between migraine and ischaemic stroke[23–25] stratified by migraine aura status suggested a significantly increased risk of ischaemic stroke among people who had migraine with aura (16, 1.53–3.03) but not those who had migraine without aura (1.23, 0.90–1.69). In the meta-analysis, the risk of transient ischaemic attacks seem to increase more than two-fold (2.34, 1.90–2.88) but there was no association with haemorrhagic stroke (1.18, 0.87–1.60). However, Kurth *et al.*[26] reported migraine with aura, in addition to ischaemic events, also to be a risk factor for haemorrhagic stroke. Data on association between migraine and haemorrhagic stroke, however, are sparse. Two case control studies and large population-based study with health insurance data indicated an association between peripartum migraine and increased risk of intracerebral haemorrhage. A earlier study[26] did not find any association between migraine and increased risk of haemorrhagic stroke. Kurth *et al.* in a prospective study of middle aged and initially apparently healthy women, found an association between migraine with aura and an increased risk of haemorrhagic stroke. Compared with women with no history of migraine and after adjustment for many potential confounders through a propensity score weighting, women who reported active migraine with aura had over twice the risk of haemorrhagic stroke. In contrast with the association between migraine with aura and ischaemic stroke, which is stronger among younger women, the association with haemorrhagic stroke seems more apparent in the older age group. This study contrasts with the previous report[26] in which migraine with aura was not associated with increased risk of haemorrhagic stroke after a mean follow up of nine years. The pattern of association suggests that this discrepancy is caused by the difference in length of follow-up. The increased risk for haemorrhagic stroke among women with migraine with aura becomes clear only after longer follow-up (mean 13.6 years) in study by Kurth *et al.*[26]).

Kruit *et al.*[27] found a higher prevalence of subclinical infarcts in the posterior circulation (OR 13.7; 95% CI 1.7,

112). Female migraineurs were at independent increased risk of white matter lesions (WML; OR 2.1; CI 1.0, 4.1) and migraineurs had a higher prevalence of brainstem hyperintense lesions (4.4% versus 0.7%, $P = 0.04$). They also observed a higher life time prevalence of frequent syncope and orthostatic insufficiency in migraineurs. They also found evidence of increased iron concentrations in putamen ($P = 0.02$), globus pallidus ($P = 0.03$) and red nucleus ($P = 0.03$). The Italian Project on Stroke in Young Adults studied the predictors of migraine subtypes in young adults with ischaemic stroke. Of 981 patients, low cardiovascular risk profile, right-to-left shunt and an underlying procoagulant state are predictors of migraine with aura.

Association between migraine and myocardial ischaemia

Migraine with aura (relative risk 2.08, CI 1.3 to 3.31) seemed to be associated with a two-fold increased risk of myocardial infarction. Among participants with any migraine, the risk of angina seemed to be slightly but significantly increased (pooled relative risk 1.29, CI 1.12 to 1.47)[16–18].

Association between migraine and death due to cardiovascular disease[28]

Pooled analysis of five studies on the association between any migraine and death due to cardiovascular disease did not suggest an overall association (pooled relative risk 1.03, CI 0.79 to 1.34). The study on the association among women found an increased risk (1.60, CI 1.06 to 2.42), which was not found in among men. The study on aura specific associations found an increased risk among people who had migraine with aura (relative risk 2.33, CI 1.21 to 4.51)[19–21].

In a cohort study by Gudmundsson *et al*.[29,30], with over 470,000 person years and a median follow up of 26 years, men and women with migraine with aura were shown to be at increased risk of mortality from all causes and cardiovascular disease, whereas those with migraine without aura were not at increased risk. Risk of mortality from cardiovascular disease was marginally more increased in men than in women with migraine and aura. Migraine with aura is an independent risk factor for cardiovascular and all cause mortality in men and women but weaker than major established risk factors such as cigarette smoking, diabetes and high blood pressure[31,32].

Potential mechanisms[33–40]

Several mechanisms have been implicated to explain the link between migraine and the occurrence of stroke and cardiovascular disease. None have been definitively proven the link.

- Migraine and ischaemic events have been linked through a genetic component. They might reflect associations among migraine with aura and vasculopathy and mitochondrial myopathy, encephalopathy, lactic acidosis and stroke (MELAS), methylenetetrahydrofolate reductase (M-THFR) is an important enzyme in the metabolism of homocysteine, derived from the amino acid methionine and a risk factor for cerebral small vessel disease and migraine.
- Migraine could directly cause an ischaemic event that is from a migrainous infarct, but such events are rare and can therefore account for only a small proportion of all strokes in people with migraine.
- There is increasing evidence that migraine is associated with coronary heart disease and a study reported an association between migraine and an increased prevalence of conventional vascular risk factors. The current data show little difference in risk factors between those with migraine and without migraine, which is in line with previous studies on people with migraine in the Reykjavik Study.
- Others have reported that people with migraine even in the absence of conventional risk factors are at increased risk of stroke and have decreased cerebral and peripheral vascular resistance, retinal microvascular signs, hypercoagulability and inflammation, supporting the hypothesis that migraine might be a systemic disorder that affects vasculature. People with migraine have been shown to have altered vascular reactivity at a young age (under 25 years), which indicates that there might be a factor affecting both the onset of migraine and progression of cardiovascular disease early in life.
- A recent study reported that people with migraine without aura had reduced function and number of endothelial progenitor cells, which has been associated with higher Framingham risk scores in people with coronary heart disease and increased risk of mortality from cardiovascular disease[28].
- There is an increased prevalence of persistent foramen ovale in patients with migraine with aura. Patent foramen ovale has been cited as a risk factor for the occurrence of cryptogenic strokes. Till date though, there is no consensus on this association[40].
- There is also an increased risk for cervical artery dissection in patients with migraine with aura.

Clinical implications

Migraine and stroke are both common conditions. It is hardly surprising therefore, that the two can coexist in the same patient.

Age is the most important risk factor for stroke. In young individuals, the absolute risk of stroke is relatively lower and hence the increased relative risks reported above even in women taking oral contraceptive pills, need not be alarming[41]. The association of increased risk of stroke in older men with migraine is not clear. Confirmation of another suspected risk factor may perhaps offer the hope of further prevention. The risk of stroke in older people is due to the influence of several risk factors and may exceed the sum of their individual relative risks.

Migraine is not an uniform condition. Subtypes include migraine with aura, hemiplegic migraine and migraine recurring in elderly after years of being migraine free. Some medical conditions are associated with an increase in the risk of stroke and migraine – for example, cerebral autosomal dominant leucoaraiosis (CADASIL)[42] and the antiphospholipid syndrome. Others such as acute dissection of the carotid or vertebral artery, subarachnoid haemorrhage, cranial arteritis and occasionally cerebral tumours may produce migrainous symptoms.

Stroke is also not a single disease. Small or/and large vessels may be affected, with local thrombosis or thromboembolism from artery to artery or cardioembolism. In migraine, cerebral blood flow has been shown to be reduced in certain regions and platelet activity is thought to be increased. These two factors may contribute to increased risk of thrombosis.

The possibility that treatments used in acute migraine may affect the risk of stroke especially when vasoconstrictors such as ergotamine and triptans are used. However, we have no evidence that such treatments have increased the risk of stroke. One would also expect that some agents used in the prophylaxis of migraine such as b-blockers and aspirin should reduce the risk of stroke[43,44].

Neurological deficit persisting after migraine is rare. In some instances, the ischaemic event is not related to an obvious acute attack of migraine with cephalalgia. In such a situation, another condition may possibly cause both ischaemic and migraine.

People with migraine, particularly those with aura are at a modestly increased risk of mortality, independent of classic risk factors for cardiovascular disease measured in mid-life. The absolute risk is low and the focus should be on conventional risk factors, such as hypertension, smoking and adverse lipid profile, for reducing the risk of cardiovascular disease regardless of migraine status.

In an otherwise healthy young person with migraine, no cause for concern exists because of low absolute risk of stroke. Quitting smoking seems prudent, as does oestrogen or only progesterone to young women with migraine. Neurologists to stop oral contraceptive pills if migraine becomes more frequent or changes in character with a more prominent or prolonged aura. If a middle aged woman with migraine continuous to smoke or if other risk factors such as hypertension exist, contraceptive pills are advised.

Future avenues of research

Further research is needed on the association between migraine and mortality from stroke and cardiovascular disease and all causes including studies to identify whether there are specific subgroups of people with migraine who are at enhanced risk because of genetic or environmental factors. Future studies must also assess aura status and frequency of attacks and prospective studies can monitor changes in the risk profile for stroke and cardiovascular disease to better understand the aetiology and pathophysiology of migraine in its development. Studies are also needed to determine if reducing the frequency of attacks with migraine preventive treatment reduces the risk of stroke and cardiovascular disease.

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