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REVIEW

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Headache and ischemic stroke

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Abstract Migraine is a common neurological condition affecting yearly 1%–10% of all men and 3%–20% of all women. Focal neurological symptoms (auras), most commonly visual and sensory, occur in 4% of migraine attacks. Migraine with and without aura seems to be associated with an increased stroke risk. Migraine with aura may mimic transient ischemic attacks and may induce stroke (migrainous stroke). Headache is also a common symptom during ischemic stroke In this review, we present the evidence about each of these circumstances to better understand the relationship between headache, especially migraine, and ischemic stroke

Key words Headache • Stroke • Migraine • Cerebrovascular diseases

Migraine and subsequent risk of ischemic stroke

Large-scale prospective epidemiological studies have identified major risk factors for stroke, including advanced age, race, family history of stroke, hypertension, diabetes mellitus, heart disease, elevated cholesterol levels, current smoking, obesity, heavy alcohol intake, sedentary lifestyle, use of exogenous hormones, and hyperhomocysteinemia [1, 2]. Although several clinical reports claim the existence of an association between migraine and stroke, only a few epidemiological studies have addressed this specific issue. The U.S. Physicians' Health Study showed that physicians aged 40–84 years with a history of migraine had increased risk of stroke; after adjustment for age and other cardiovascular risk factors, the relative risk was 1.84 (95% CI, 1.06 to 3.20) for total strokes and 2.0 (95% CI, 1.10 to 3.64) for ischemic strokes [3]. Merikangas et al. [4] also found that, after controlling for established risk factors for stroke (e.g. hypertension, diabetes, heart disease, gender), both migraine and severe nonspecific headache were associated with a significantly increased risk for stroke (RR, 1.5) that was higher in young patients: at the age of 40 years, the relative risk was 2.81 (95% CI, 1.45–5.43), at 50 years it was 2.07 (95% CI, 1.30–3.30), at 60 years it was 1.69 (95% CI, 1.10–2.60), and at 90 years it was 1.16 (95% CI, 0.63–2.11). Therefore,

migraine plays a more critical role in stroke of the young. In other studies the risk of ischemic stroke was not excessive among migraineurs aged ≥60 years [5, 6].

In recent years, several studies have been published on the association between migraine and stroke in young women under 45 years of age. Tzourio et al. [7] found that stroke was strongly associated with migraine, both without aura (odds ratio, 3.0; 95% CI, 1.5–5.8) and with aura (odds ratio, 6.2; 95% CI, 2.1–1.80). In another study [8], a history of migraine was more frequent in stroke patients than in controls (odds ratio, 1.9; 95% CI, 1.1–1.3). In the prospectively designed subgroup analyses, a history of migraine reached the highest odds ratio (3.7; 95% CI, 1.5–9.0) and was the only significant risk factor in women below age 35 years. Chang et al. [9] reported that in young women (20–44 years of age) a personal history of migraine was strongly associated with stroke (for all stroke: adjusted OR, 1.78; 95% CI, 1.14–2.77; for ischemic stroke: OR, 3.54; 95% CI, 1.30–9.61). In agreement with previous studies [5, 10], ischemic stroke was associated with both migraine with aura (OR, 3.81; 95% CI, 1.26–1.15) and migraine without aura (OR, 2.97; 95% CI, 0.66–1.35).

The risk of stroke in young migrainous women seems to apply not only to ischemic stroke, but also to hemorrhagic stroke, although hemorragic stroke has been not extensively studied and the results are less consistent [11].

In this category of patients, the risk of ischemic stroke was substantially increased by the use of oral contraceptives (OR, 13.9), for which a dose-effect relationship between risk of stroke and dose of estrogen was found (for pills containing 50 μg estrogen: OR, 4.8; for pills with 30–40 μg: OR, 2.7; pills with 20 μg: OR, 1.7; pills with progesterone; OR, 1) [7]; the risk of ischemic stroke was also elevated in heavy smokers (≥20 cigarettes per day: OR, 10.2). In migrainous women, coexistent use of oral contraceptives, history of high blood pressure and smoking habit had greater than multiplicative effects on the odds ratio for ischemic stroke (OR, 34.4; 95% CI, 3.27–3.61). However, this dramatic increase was based on only nine cases and two controls [9]. Other conditions predisposing to stroke, namely minor cardiac abnormalities like patent foramen ovale [12] and mitral valve prolapse [13] or the presence of anti-cardiolipin antibodies [14], may cause a stroke when combined with migraine, but this has not been definitely established [11].

Several hypotheses have been raised to explain the association between migraine and stroke: vasospasm, endothelial dysfunction, congenital thrombophilia, platelet hyperaggregability, and association with cardiac abnormalities predisposing to ischemic stroke. However, no fully convincing evidence has been produced [11].

The strength of the association should not, however, lead to the conclusion that all young women with migraine are at high risk of stroke. The incidence of ischemic stroke in young women is low (approximately 10 cases in 100 000 women/years) [15, 16], and the risk of ischemic stroke is only 17–19 per 100 000 women with migraine per year [7]. Furthermore, it is not known whether this increased risk relates to all young migrainous women or only to a subgroup of them (i.e. patients with MELAS, cardiac abnormalities or antiphospholipid antibodies syndrome) [17–19]. However, young women, especially those <35 years of age, should be firmly advised to avoid smoking, and if they use oral contraceptives, to choose pills with a low estrogen content or only progesterone [11].

Migrainous stroke

Stroke is a rare but potentially devastating complication of migraine. In 1988, the International Headache Society [20] classified migrainous infarction under the complications of migraine with aura (IHS 1.6.2), where the diagnosis of migraine-induced stroke in patients with migraine without aura is not allowed. To meet this definition, patients must have: (i) neurological symptoms and signs that are identical or similar to those of other migraine attacks and not completely reversible within 7 days and/or neuroimaging evidence of ischemic infarction in a relevant area; (ii) the stroke must have occurred during a typical migraine attack; (iii) other causes of stroke must be excluded, although stroke risk factors may be present. Several authors [21, 22] proposed that migrainous infarction should be redefined in the IHS classification as a possible complication of both migraine with and without aura because they described patients who had an ischemic stroke during a typical migraine attack (even if migraine with aura is substantially present (80%) in patients with migrainous stroke) [23]. In the WHO study [9], migrainous stroke was defined as any stroke occurring in presence of headaches in the 3 days before the stroke; following this rule, up to 40% of the strokes in migrainous women can be considered migrainous stroke.

The incidence of migrainous infarction has been estimated to be 3.36 per 100 000 persons per year, but in the absence of other stroke risk factors, this was reduced to 1.44 per 100 000 persons per year [24]. Migraine-induced stroke accounts for 0.8% of all strokes and accounts for as few as 4% [25] to as many as 20% of ischemic strokes in the young [26, 27].

Bogousslavsky et al. [28] found a marked female preponderance in the migrainous stroke group with respect to controls, and Iglesias et al. [29] claimed that the combination of smoking and migraine was highly associated with stroke. Oral contraceptives are also recognized to increase stroke risk in migraine sufferers [7]. Usually, headache fre-

quency and severity decrease after stroke, probably due to reduced nociceptive transmission as a result of loss in vasoreactivity of the affected cerebral blood vessel [30].

The prognosis of cerebral infarction associated with migraine is generally good. Hoekstra-van Dalen et al. [31] found that no patient had recurrent stroke during an average follow-up period of 5.8 years. Strokes related to migraine are commonly found in the territory of the posterior cerebral artery [27, 32]. The mechanism by which migraine causes a cerebral infarction is unknown; it has been proposed that during migraine attack there is a reduction of cerebral blood flow secondary to arteriolar vasoconstriction [33–35]. A slowly spreading wave of cortical neuronal depression with spreading oligoemia is also possible. Prolonged vasoconstriction and oligoemia may lead to hemostasis and predispose to intravascular thrombosis and migraine-induced cerebral infarction Increased platelet aggregability, presence of antiphospholipid antibodies and use of oral contraceptives may contribute to the risk of enhanced coagulation [36–38]. The increase in procoagulant effects, the decrease in anticoagulant effects, and the hyperactivation of the antifibrinolytic system indicate that oral contraceptives do have a net prothrombotic effect [39]. In his model of neurogenic inflammation due to pathological activation of the trigeminovascular system during migraine attack, Moskowitz [40] showed that platelet aggregation occurs in the lumen of blood vessels. Another hypothesis suggests that repeated episodes of migraine-induced vasoconstriction may weaken the internal elastic lamina of cerebral vessels and predispose to arterial dissection [41]. Paradoxical embolism is another postuled cause [42]. Both migraine and stroke may also result from underlying genetic disorders such as MELAS or CADASIL [43, 44].

Headache during ischemic stroke

Headache occurs frequently in acute ischemic stroke (IHS 6.1.2) or during a transient ischemic attack (IHS 6.1.1), but its frequency varies widely among different studies, ranging from 18% to 41% [45–55]. Overall, an underestimation of the frequency of headache in ischemic stroke patients can be claimed, as patients with language dysfunction, altered mental status or other factors impeding reliable determination of a headache complaint are excluded from most studies. In our series, headache was present in more than one-third of the patients with ischemic stroke and was much more common among patients with infarct in the posterior circulation (73.3%) than in those in whom the anterior circulation was involved (25.8%) [55]; this finding has also been described in other reports and may be due to the rich innervation by nociceptive afferents of vessels in the posterior circulation [40, 51]. Stroke-related headache was frequently associated with large artery disease (40.7%) and was higher in patients with carotid artery occlusion. Similar results have been obtained by other authors, who reported headache frequencies ranging from 26% to 35% in patients with symptomatic carotid artery disease [46, 48]. Gorelick et al. [48] reported that there is no significant difference in the frequency of onset headache between patients with extracranial carotid artery disease, disease of the carotid siphon, middle cerebral artery, or carotid siphon and middle cerebral artery in tandem. As already reported, in the great majority of papers, headache is less common in lacunar infarction. In our series, the frequency of headache in lacunar infarction was 12.9%; similar frequencies have been observed by others [47, 49, 51, 56]. A history of headache, was present only in stroke patients with headache, and headache anticipated (on average by 2 days) the stroke in 24% of subjects. This observation is in agreement with previous studies and demonstrates that stroke in many cases is the result of a long-lasting pathological vascular process, in which headache merely serves as a warning sign of ischemic stroke [48, 51]. In several series, a higher frequency of onset headache was present in women and young people [57, 58], who generally have a higher frequency of headaches. The mechanisms underlying headache are not known. Several studies have suggested that headache is associated with dilation of some arteries at the base of the brain [59]. Headache is probably related to activation of nociceptive trigeminovascular afferents; pain ensues when a sufficient amount of nociceptors have been recruited [60]. The release of amino-acid neurotransmitters [61] and platelet activation [62] may also play a role in the pathogenesis of headache occurring at the onset of ischemic stroke.

Headache is also common in patients with cervical artery dissection [63]. Unilateral facial or orbital pain is present in half of patients with internal carotid artery dissection. The characteristic unilateral headache develops in two-thirds of patients, most commonly in the frontotemporal area, but it occasionally involves the hemicranium or the occipital area [64]. The onset of headache is usually gradual, but it may be an instantaneous, excruciating, “thunderclap” headache that mimics a subarachnoid hemorrhage [64, 65]. The headache is most commonly described as a constant steady aching, but it may also be throbbing or steady and sharp [63, 64]. About one-fourth of patients with a history of migraine claim that the headache is similar to a migraine attack. In case of vertebral artery dissection, headache occurs in two-thirds of patients, almost always in the occipital area, but in rare cases it involves the hemicranium or the frontal area or is bilateral [64]. Pain is usually the initial manifestation of cervical artery dissection and the mean time to the appearance of other symptoms is four days for carotid dissection and 15 hours for vertebral dissection [63]. In our experience [66],

headache was present in 10% of patients with cervical artery dissection before the focal neurological deficits, while 66.7% of the patients had headache during the dissection-related stroke.

Migraine syndromes that mimic stroke

Migrainous syndromes that may mimic conventional cerebrovascular syndromes include hemiplegic migraine and basilar artery migraine. The IHS classifies hemiplegic migraine under migraine with typical aura (IHS 1.2.1) or prolonged aura (IHS 1.2.2). Familial hemiplegic migraine is classified as a subgroup of migraine with aura (IHS 1.2.3) and the definition includes the criteria for migraine with aura with hemiplegic features and at least one first-degree relative with identical attacks. Hemiplegic migraine attacks are characterized by hemiparesis or hemiplegia. There is an autosomal dominant inheritance pattern of the disorder. Hemiplegic migraine attacks may also be part of other familial disorders, namely mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS), and cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL). Basilar migraine (IHS 1.2.4) is another disorder that may mimic a transient cerebrovascular accident. The diagnostic criteria include those for migraine with aura plus two or more aura symptoms of the following types: visual symptoms in both the temporal and nasal fields of both eyes, dysarthria, vertigo, tinnitus, decreasing hearing, double vision, ataxia, bilateral paresthesias, bilateral paresis, and decreased level of consciousness. The diagnosis of basilar migraine is supported by the pattern of evolution of the neurological deficit and the accompanying headache, the history of previous similar attacks, a positive family history and the often negative diagnostic workup [67]. It is not unusual for patients who have experienced migraine with aura to suffer identical auras at other times, but without headache, particularly as they get older [68, 69]. Diagnostic difficulty arises when a patient over 40 years of age with no previous history of classic migraine presents a first-ever episode of transient symptoms of focal neurological dysfunction that are typical of a migrainous aura, but without any associated headache [70]. The differential diagnosis of this circumstance is important especially for the prognosis: after 10 years of follow-up, the relative risk of a stroke occurring in a patient with a history of transient ischemic attack (TIA) compared with that in a patient with "migrainous aura without headache" was 7.6 (95% CI, 0.8–74), and the relative risk of any serious vascular event (e.g. stroke, myocardial infarction, or vascular death) was 3.8 (95% CI, 0.8–19) [71].

Conclusions

Headache is an underemphasized feature of ischemic cerebrovascular disease; the thorough evaluation of its clinical features can be of help in diagnosing correctly different cerebrovascular pathological conditions.

The relationship between headache, namely migraine, and stroke is difficult to disentangle. Epidemiological studies indicate that the comorbidity of migraine and stroke in the young is an important issue and has implications for patient management.

Migraine is associated with an increased incidence of stroke in young migraineur women who smoke or use oral contraceptives; these subjects should be strongly advised to discontinue smoking and they should be discouraged to use oral contraceptives; in any case, only pills with a low (<50 μg) estrogen content should be used.

No randomized study of primary stroke prevention in migraineurs or of secondary prevention in patients with a migraine-associated stroke has been performed. In patients who have had a migraine-induced stroke, daily use of an antiplatelet agent is reasonable although unproven, while the use of vasoconstrictive agents (e.g. ergotamine, triptans) for treating migraine attack should be avoided.

The mechanism by which migraine causes a cerebral infarction – i.e. why focal oligoemia sometime progresses to cerebral infarction – is substantially unknown. Pathophysiological studies aimed at identifying the role played by each different component (endothelium, platelets, leukocytes, coagulation factors, genetic susceptibility) in the ischemic cascade are highly recommended.

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