Estrogens, Migraine, and Stroke

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Abstract—Epidemiological studies suggest the existence of close but complex relationships between estrogens, migraine, and stroke in women before menopause. Migraine, particularly without aura, is strongly influenced by estrogens as illustrated by the frequency of onset at puberty, of menstrual migraine, and of improvement during pregnancy. Migraine, particularly with aura, is a risk factor for ischemic stroke with a relative risk of 3, further increased by tobacco smoking and oral contraceptive use. The pathophysiological mechanism underlying these close relationships remains unknown. In practice, given the very low absolute risk of stroke in young women, there is no systematic contraindication to oral contraceptive use in young female migraineurs but rather a firm recommendation for no smoking and for the use of low-estrogen-content pills or progestogens only, particularly in migraine with aura. (*Stroke.* 2004;35[suppl I]:2652-2656.)

Key Words: contraceptives, oral ■ estrogens ■ hormone replacement therapy ■ migraine ■ stroke

Migraine has long been recognized as a predominantly female condition, whereas stroke was thought to affect mostly men. Indeed, the incidence of stroke in men is twice that of women,¹ and a number of large cardiovascular prevention trials such as the Physicians' Health Study² or the British Doctor's Study³ were restricted to men. It is only recently that stroke in women has been recognized as a major health issue⁴ because (1) the prevalence of stroke is higher in women than in men as a result of their longer life expectancy and (2) the incidence of stroke in young women is rising,⁵ essentially as a result of the increase in tobacco smoking and obesity.

The study of the relationships between estrogens, migraine, and stroke encompasses 3 different subjects: estrogens and migraine, migraine and stroke, and estrogens and stroke; each would each merit a review on its own.⁶ Given that relationships between estrogens and stroke are dealt with in other presentations, this review will be devoted primarily to the relationships between estrogens and migraine and between migraine and stroke, particularly in women.

Estrogens and Migraine

The evidence is plentiful for a link between female hormones and migraine.^{7,8} The first evidence comes from epidemiological studies that show a higher female prevalence of migraine after puberty, with lifetime prevalence of 25% compared with 8% in men. This difference between sexes becomes greater with age, peaking early in the fifth decade of life and then declining.^{9,10} Other evidence includes the frequency of menstrual migraine, the improvement of migraine during pregnancy, and the effects of oral contraceptives (OC), menopause, and hormone replacement therapy (HRT) on the course of migraine. Overall, this hormonal influence is far more important for migraine without aura than for migraine with aura.

Menstrual migraine has recently been defined as attacks of migraine occurring between 2 days before and 3 days after menstruation.¹¹ Pure menstrual migraine is rare, at 5% to 8%, whereas menstrually related attacks are very frequent, up to 69% by self-assessment and 17% to 45% with the use of prospective diary cards.7,8 Menstrual migraine attacks are mostly without aura and are due to the abrupt fall in estradiol that occurs just before menstruation.¹²⁻¹⁵ The most effective preventive treatment is estrogen replacement before menstruation, and the best results have been obtained with percutaneous estradiol gel (1.5 mg), which has been found superior to placebo in 3 double-blind control studies.15-17 Treatment was started either 48 hours before the anticipated migraine attack and used daily for the next 7 days or 10 days after ovulation and continued daily until the second day of menstruation.

The effects of OC on migraine are variable,^{6–8,18} worsening has been reported in 18% to 55% of cases, with attacks usually occurring in drug-free intervals. However, in an almost equal number of cases (30% to 40%), no change or even an improvement has been described, and in a few cases (5% to 10%), the onset of migraine takes place in the first few months of OC use. Migraine without aura most commonly improves, whereas migraine with aura is more likely to worsen or even develop for the first time when OC are used.¹⁹ The effect of OC discontinuation on the course of migraine is also variable: improvement or no change has been reported in an almost equal number of cases. The role of the estrogen and progestogen contents is unknown.

Received June 15, 2004; accepted August 5, 2004.

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Migraine improves during pregnancy in a vast majority of women (55% to 90%),^{20,21} particularly in menstrual migraine, in migraine without aura, during the last 2 trimesters of pregnancy, and during the first pregnancy. However, in some women migraine remains unchanged (5% to 30%), worsens (3% to 7%), or even appears for the first time (5% to 10%) during pregnancy, usually as attacks of migraine with aura.^{22,23} In contrast to the usual improvement during pregnancy, there is a frequent recurrence of migraine attacks during the postpartum period (30% to 40% of cases).²¹

The relationships between menopause, HRT, and migraine are still debated. It was said classically that migraine worsens just before menopause and improves after menopause in approximately two thirds of cases, but recent studies have shown no change or even a worsening in up to 50% of cases.²⁴ The influence of HRT on migraine is variable: improvement, worsening, or no change have all been reported, but more data have indicated a worsening, particularly in migraine with aura, which can even develop for the first time when HRT is started.²⁵ If migraine worsens with HRT, the dose can be reduced, different estrogens can be used, or estrogens can be used continuously in the case of withdrawal migraine.²⁶

To summarize this discussion of estrogens and migraine, the female preponderance of migraine, frequency of menstrual migraine, improvement of migraine during pregnancy, recurrence of attacks during the postpartum period, frequent improvement after menopause, and worsening with HRT point to a major influence of estrogens on migraine. The pathophysiological mechanism underlying this close relationship remains unknown. The hormonal influence might be different on migraine without aura and on migraine with aura; there is good evidence for an association between estrogen withdrawal and attacks of migraine without aura but only weak evidence for an association between high estrogen states and attacks of migraine with aura.8 However, it is still unknown whether migraine without aura and migraine with aura represent 2 different conditions or 2 varieties of a single condition.

Migraine and Stroke

The relationships between migraine and stroke apply to ischemic stroke and are extremely complex, encompassing at least 4 issues: migraine as a cause of ischemic stroke (migrainous infarcts), migraine and ischemic stroke sharing a common cause (symptomatic migraine), migraine attacks triggered by cerebral ischemia, and migraine as a risk factor for ischemic stroke. There seems to be no sex difference regarding the first 3 issues, which will be briefly reviewed, in contrast to the fourth issue, migraine as a risk factor for ischemic stroke, which seems to apply mostly to young women.^{27,28}

Migrainous infarcts are said to be frequent causes of ischemic stroke in the young.^{29–31} However, true migrainous infarcts,¹¹ ie, infarcts due to an unusually severe hypoperfusion during the aura, are very rare and are vastly overdiagnosed. They occur in patients with migraine with aura, during an attack of migraine with aura, with symp-

toms that are those of the aura, with a documented infarct in the relevant area, and in the absence of other causes at an extensive workup.¹¹ They most frequently affect the posterior cerebral artery territory. They are more frequent in women, but less so than expected from the female preponderance of migraine.^{27,28}

Numerous conditions can cause both ischemic stroke and migraine attacks, usually with aura. In these disorders, migraine is no longer a primary headache condition but a mere symptom of the underlying vascular disease, which can be a blood disorder, a cardiac disorder, a mitochondrial disorder, or, more frequently, a vessel wall abnormality, as illustrated by cerebral autosomal dominant arteriopathy with subcortical infarct and leukoencephalopathy (CADA-SIL), a small-artery disease of the brain affecting smooth muscle cells and due to Notch 3 mutations. This condition is characterized by small deep infarcts, dementia, mood disorders and, in one third of cases, migraine with aura. When migraine is present, it is the first symptom of the disease, occurring 10 to 15 years before the first stroke.^{32,33} Another example of chronic small-artery disease of the brain causing migraine with aura is the recently identified syndrome of autosomal dominant vascular retinopathy, migraine, and Raynaud's phenomenon.³⁴ However, in all these conditions, there is no sex difference, so that estrogens are unlikely to play a major role in this variety of migraine-ischemic stroke connection.

A number of observations show that cerebral ischemia, particularly when due to severe carotid stenosis related to dissections, can trigger a migrainous aura. Olesen et al³⁵ have even suggested that such ischemia-induced migraine attacks were more frequent than migrainous infarctions. Whether this is related to the fact that migraine has been found to be a risk factor for cervical artery dissections remains unknown.^{36,37}

Numerous studies have been devoted to migraine as a risk factor for ischemic stroke. There are, at present, 2 large cohort studies, 9 case-control studies, and various CT and MRI studies.

The 2 large cohort studies are the Physicians' Health Study³⁸ and the NHANES,³⁹ based on 22 071 US male physicians and 12 220 subjects, respectively. Both studies found an increased risk of stroke in migraineurs, with a relative risk of 2 to 2.5, but the first was performed only in men, and the second found no sex difference. In regard to the 9 case-control studies,40-48 6 showed a statistically significant relationship between migraine and ischemic stroke in "young" women (usually aged <45 years) (Table).^{40–45} Among the 3 other studies, the first study also showed an increased risk of cerebral infarction in young migrainous women compared with neighbor controls but not with hospitalized controls.⁴⁶ The 2 other studies,^{47,48} performed in 89 patients aged 15 to 65 years and in 100 patients aged >60 years, respectively, did not show a significantly increased risk. Although numerous potential biases exist in case-control studies, particularly in a condition such as migraine for which there are no objective diagnostic criteria, these biases are unlikely to explain this consistent and homogeneous (relative risk \times 3) increase in

Authors	Subjects	Migraine Diagnosis	Stroke Risk in Migraineurs
Tzourio et al, ⁴⁰ 1993	212 patients with IS aged 15–80 y; 212 hospitalized controls matched for sex, age, hypertension	Direct interview by neurologist; IHS criteria	0R=4.3 (1.2, 6.3) for women aged ${<}45~\mathrm{y}$
Tzourio et al,42 1995	72 women hospitalized for IS aged 15–44 y; 173 controls matched for age	Direct interview by neurologist; IHS criteria	OR=3.0 (1.5, 5.8); OR=6.2 (2.1, 18) for migraine with aura
Lidegaard,41 1995	692 women with IS from national registry; 591 hospitalized controls matched for age and sex	Questionnaire	OR=2.8 (<i>P</i> <0.001)
Carolei et al, ⁴³ 1996	308 patients hospitalized for TIA or IS aged 15–44 y; 591 controls matched for age and sex	Direct interview by neurologist; IHS criteria	OR=3.7 (1.5, 9) in women aged ${<}35$ y; OR=8.6 (1, 75) for migraine with aura
Chang et al, ⁴⁴ 1999	291 women with IS aged 20-44 y; 736 controls matched for age	Direct interview by neurologist; IHS criteria	OR=3.5 (1.3, 9.6); OR=2.9 (0.6, 13.5) for migraine without aura; OR=3.8 (1.2, 11.5) for migraine with aura
Schwaag et al, ⁴⁵ 2003	160 patients with first IS or TIA aged ${<}46$ y; 160 controls matched for age and sex	Direct interview by neurologist; IHS criteria	OR=2.11 (1.16-3.82); OR=2.68 (1.25-5.75) in women

Recent Case-Control Studies of Migraine and Stroke in Young Women

IS indicates ischemic stroke; IHS, International Headache Society; and TIA, transient ischemic attack.

the ischemic stroke risk observed in young migrainous women. This increase is more marked for migraine with aura (relative risk, 3.8 to 6.2) than in migraine without aura, in which a statistically significant association was found in only 1 study.⁴² The risk is more than tripled by smoking (odds ratio [OR]=10)⁴² and quadrupled by OC use (OR=13.9 to 16.9).^{42.44} The triple combination of migraine, OC, and tobacco smoking further increases the risk, with OR of 34 to 35.^{42.44}

Neuroimaging (CT scan and MRI) studies in migraine patients have primarily shown a significant increase in white matter abnormalities compared with controls, but results are divergent and difficult to interpret because of many methodological shortcomings. The largest and most recent of these studies⁴⁹ was recently performed on 161 subjects with migraine with aura, 134 subjects with migraine without aura, and 140 controls aged 30 to 60 years. There was no significant difference in the overall prevalence of infarcts except in the cerebellum (5.4% versus 0.7%; OR=7.1). The risk of infarcts was increased in migraine with aura (OR=17.7) and when the frequency of attacks was >1 per month (OR=9.3). In regard to the white matter lesions load, there was no difference in periventricular white matter lesions, but there was an increase in deep white matter lesions in women (OR=2.1). The risk was similar in migraine with aura and without aura. There was a significant interaction with ergotamine use. The mechanism and prognostic significance of these abnormalities are at present unknown, but they suggest an increased risk of cerebral ischemia in migraineurs.

The mechanism of the increased risk of ischemic stroke in migraine, and particularly in young migrainous women, remains unknown. It does not seem to be due to an increase in conventional risk factors such as diabetes, hypertension, and dyslipidemia. Numerous abnormalities have been reported in migraineurs involving blood contents,⁵⁰ blood enzymes such as increased elastase activity,⁵¹ and cardiac abnormalities such as patent foramen ovale (PFO). The relationship between migraine, particularly migraine with aura, and PFO has recently attracted a great deal of interest^{52–55}: in patients with migraine with aura, PFO is twice as frequent (41% to 48%) as in controls (16% to 20%); in patients with cerebral infarction, migraine is twice as frequent in patients with PFO than in those without. Furthermore, closure of PFO was associated with a decrease in the frequency of migraine attacks in several studies.^{53–55} However, these abnormalities have not been found consistently, and they show no sex difference, so that they cannot explain why the increased risk of ischemic stroke in migraine affects young women so predominantly.

Whatever the underlying pathophysiological mechanism, the practical implications of the increased ischemic stroke risk in young migrainous women⁵⁶ are relatively clear: when the low absolute risk and its increase by cigarette smoking are taken into account, the first recommendation is to refrain from smoking. There is no systematic contraindication to combined OC use in the absence of migraine aura or of other vascular risk factors, but the use of low-estrogen-content OC or even of progestogen only is advised in those with migraine with aura. There is no indication for a systematic antithrombotic treatment.

Summary

In summary, the relationships between estrogens, migraine, and stroke differ according to age and can be summarized as follows.

Findings in women after menopause are as follows: (1) Migraine improves in 50% to 60% of cases but worsens with HRT. (2) Migraine is not proven as a risk factor for ischemic stroke. (3) Stroke is very frequent, affecting 1 of 5 women, and the risk is significantly increased by HRT. (4) There are no specific data thus far on the association between migraine and HRT in regard to the risk of stroke. Thus, migraine in itself is not a contraindication to the use of HRT, which should be decided on a case-by-case basis, with all the recent information gathered from randomized trials^{57–59} taken into account. Findings in women aged <50 years are as follows: (1) Thirty percent are affected by migraine, mostly without aura, which is strongly influenced by estrogens, eg, onset at puberty, menstrual migraine, improvement during pregnancy. (2) Migraine is a risk factor for ischemic stroke, with a relative risk of 3. The risk is higher in migraine with aura and is further increased by tobacco smoking and OC. (3) The absolute risk of ischemic stroke is very low, and therefore there is no systematic contraindication to OC use in migraineurs but rather a firm recommendation for no tobacco smoking and for the use of low-estrogen-content pills or progestogens only, particularly in cases of migraine with aura.

Despite this certainly not fortuitous connection between estrogen, migraine, and ischemic stroke, it must be emphasized that migraine, although painful and often incapacitating, remains an essentially benign condition.

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