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Migraine and risk of ischaemic stroke: a case-control study

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Abstract

Objectives—To determine whether migraine is a risk factor for ischaemic stroke.

Design—A case-control study.

Setting—Two hospitals in Paris.

Subjects—212 patients with stroke (137 men and 75 women) and 212 controls matched for sex, age (to within five years), and history of hypertension.

Main outcome measures—Ischaemic stroke, confirmed by brain computed tomography or magnetic resonance imaging, and history of headache, recorded with structured questionnaire during interview.

Results—Prevalence of migraine did not differ between patients with stroke and controls: 18/137 v 17/137 for men (odds ratio 1.1 (95% confidence interval 0.5 to 2.2), $p=0.86$); 23/75 v 17/75 for women (odds ratio 1.6 (0.7 to 3.5), $p=0.24$); and 41/212 v 34/212 for both sexes (odds ratio 1.3 (0.8 to 2.3), $p=0.33$). When subjects were split into two age groups, however, prevalence of migraine was significantly higher among younger women (aged <45) with stroke compared with their controls (13/20 v 6/20, odds ratio 4.3 (1.2 to 16.3), $p=0.03$). Furthermore, the risk of ischaemic stroke was higher among younger women who smoked (7/20 v 1/20, odds ratio 10.2 (1.1 to 93.3)).

Conclusions—Prevalence of migraine was not different between patients with stroke and matched controls except among women aged <45, when migraine and stroke were significantly associated.

Introduction

Besides being a rare but well documented cause of cerebral infarction—migrainous infarct—migraine has episodically been suggested as a risk factor for stroke. Indeed, the vasomotor changes¹ and modifications of platelet aggregability^{2,3} that occur during migraine

could cause an ischaemic stroke. Few epidemiological studies have addressed the question of the link between migraine and stroke, and their results are not consistent. As examples of the wide range of values observed, the risk of stroke associated with migraine was 1.2 for women aged under 45 not using oral contraceptives⁴ and was 31.3 for a subgroup of patients without vascular risk factors.⁵

The present study was performed to address this issue and was the first to be based on the diagnostic criteria for migraine recently proposed by the International Headache Society.⁶

Patients and methods

All patients aged 18–80 successively admitted to two Paris hospitals with a diagnosis of ischaemic stroke over 24 months were included in the study provided they were willing and able to answer the questionnaire. Ischaemic stroke was defined clinically, according to the World Health Organisation's criteria,⁷ and was confirmed in all patients by computed tomography or magnetic resonance imaging of the brain. Patients with transient ischaemic attacks or cerebral venous thrombosis were excluded. Controls were selected from patients admitted to the hospitals with benign rheumatological conditions or for routine surgical procedures excluding vascular surgery. Patients with a history of stroke were excluded. Controls were matched with patients with stroke for age (to within five years), sex, and history of hypertension.

Each subject's history of headache was recorded during an interview in hospital by a neurologist with a highly structured questionnaire. This covered all of the International Headache Society's diagnostic criteria for migraine with or without aura and different subtypes.⁶ The subjects were not aware of the final aim of the study: they were just asked if they wanted to participate in a neuroepidemiological study, and none

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refused. Other details were also recorded during the interview: past or current hypertension (blood pressure > 160 mm Hg systolic or > 95 mm Hg diastolic on at least two occasions), its duration, and whether it was treated; hypercholesterolaemia; diabetes mellitus; past or current smoking; past or current use of oral contraceptives; and chronic alcoholism (intake of ≥ 500 g alcohol per week for men and ≥ 250 g per week for women).

We calculated the number of subjects needed to demonstrate a twofold increase of stroke among the patients with migraine, assuming a 10% prevalence of migraine in the control group, a significance level of 5% (type I error), and a power of 80%: this required 220 patients in each group. Causes of stroke in young people are clearly different from those observed later in life: after an overall analysis, we therefore divided the sample into two age groups (<45 and ≥ 45) and compared the prevalence of migraine between cases and controls in the different subgroups.

We used Statistical Analysis System⁸ for all analyses except for unconditional multiple logistic regression, for which we used Biomedical Computer Programs.⁹ Categorical variables were compared by Fisher's test of exact probability (two tailed), Pearson's χ^2 test, or McNemar's test. When possible we used paired tests in the univariate analysis. Odds ratios were used as a close approximation to relative risk. The odds ratios after adjustment for possible confounding variables were calculated by unconditional multiple logistic regression.¹⁰ Hypothesis testing and estimation of the 95% confidence interval were carried out by using the estimated standard error for the estimated logistic coefficients.

Results

Although 228 patients with stroke were recruited, the results for 16 were excluded: eight because of inadequate data recording and eight because no matched control could be found. The analysis was therefore carried out with 212 patients with stroke (137 men and 75 women) and their matched controls. Table I shows the subjects' baseline characteristics: the two groups were similar in age, sex, and prevalence and duration of hypertension. Histories of cigarette smoking, hypercholesterolaemia, and diabetes mellitus were more common among the patients with stroke, and the differences were significant for smoking and diabetes in men and for hypercholesterolaemia in women.

In order to identify confounding factors—factors linked with both migraine and ischaemic stroke—we compared subjects with a history of migraine with those without (table II). Age and sex—two factors linked with the risk of stroke—were the only potential confounders: subjects with migraine were younger and

were more likely to be women than those without migraine. Table III shows the prevalence of migraine among the patients with stroke and the controls: no association was found between migraine and ischaemic stroke. This was also true for the different subtypes of migraine: migraine without aura was present in 19 of the 212 patients with stroke and 23 of the 212 controls (odds ratio 0.8 (95% confidence interval 0.4 to 1.5)); and migraine with typical aura was present in nine patients with stroke and seven controls (odds ratio 1.3 (0.5 to 3.8)). However, neurological symptoms that could be classified as migrainous aura without headache (code 1.2.5 of the International Headache Society's classification) were more common in the patients with stroke (13) than in the controls (four) (odds ratio 4.0 (1.1 to 14.2)).

TABLE II—Comparison of 75 subjects with a history of migraine and 349 subjects without by main risk factors for ischaemic stroke. Values are numbers (percentages) of subjects unless stated otherwise

	With migraine	Without migraine	p Value
Male:female ratio	35:40	239:110	0.001
Mean (SD) age (years)	49.3 (15.6)	57.6 (13.6)	0.001
History of hypertension	30 (40)	150 (43)	0.7
Cigarette smoking	27 (36)	101 (29)	0.3
Use of oral contraceptives in women aged < 45	14 (70)	16 (73)	0.9

TABLE III—Prevalence of migraine among 212 patients with ischaemic stroke (137 men and 75 women) and 212 matched controls. Values are numbers of subjects

	Patients with stroke	Controls	Odds ratio (95% confidence interval)	p Value
Men	18	17	1.1 (0.5 to 2.2)	0.86
Women	23	17	1.6 (0.7 to 3.5)	0.24
Both sexes	41	34	1.3 (0.8 to 2.3)	0.33

We performed separate analyses of people aged under and over 45. No association between migraine and ischaemic stroke was found with older men (odds ratio 1.4, $p=0.47$), older women (odds ratio 0.9, $p=0.80$), older men and women combined (odds ratio 1.1, $p=0.76$), and younger men (odds ratio 0.7, $p=0.33$). There was, however, a significant association between migraine and stroke in younger women (odds ratio 4.3 (95% confidence interval 1.2 to 16.3)), and this association persisted after adjustment for age and hypertension (adjusted odds ratio 4.9 (1.1 to 21.4)). Table IV shows that prevalence of migraine was the only significant difference between younger women with stroke and their controls. The younger women's risk of ischaemic stroke was higher when they had histories of both migraine and smoking: seven of the 20 women with stroke had migraine and were current smokers compared with one of the controls (odds ratio 10.2 (1.1 to 93.3)).

Discussion

We found that the prevalence of migraine in the whole group of patients with ischaemic stroke was not different from that in the matched controls, so that migraine was not a risk factor for stroke. This result differs from the results of the few other epidemiological studies of this issue. The Collaborative Group for the Study of Stroke in Young Women found that migraine was a moderate risk factor for stroke (odds ratio 1.7 (95% confidence interval 1.2 to 2.6)) when patients with stroke were compared with controls in the community but not when they were compared with controls in hospital.⁴ The results are difficult to interpret because of methodological deficiencies: a high level of non-participation, lack of adequate

TABLE I—Comparison of characteristics of 212 patients with ischaemic stroke (137 men and 75 women) and 212 controls matched for sex, age, and history of hypertension. Values are numbers of subjects unless stated otherwise

	Patients with stroke	Controls	Odds ratio (95% confidence interval)	p Value
Men:				
Mean (SD) age (years)	55.5 (13.6)	56.4 (13.4)		
History of hypertension	54	54		
Cigarette smoking	60	37	2.1 (1.3 to 3.5)	0.004
History of hypercholesterolaemia	40	28	1.6 (0.9 to 2.7)	0.08
History of diabetes mellitus	22	12	2.1 (1.0 to 4.5)	0.05
Alcoholism (intake > 500 g/week)	25	20	1.1 (0.6 to 2.1)	0.7
Women:				
Mean (SD) age (years)	56.6 (16.1)	56.4 (16.0)		
History of hypertension	36	36		
Cigarette smoking	20	11	2.8 (1.0 to 7.8)	0.04
History of hypercholesterolaemia	31	17	3.2 (1.3 to 7.9)	0.01
History of diabetes mellitus	10	10	1.0 (0.4 to 2.6)	
Alcoholism (intake > 250 g/week)	2	0		0.5
Use of oral contraceptives	24	26	0.8 (0.3 to 2.0)	0.7

TABLE IV—Comparison of main characteristics of 20 women aged <45 with ischaemic stroke and 20 matched controls. Values are numbers of subjects unless stated otherwise

	Patients with stroke	Controls	Odds ratio (95% confidence interval)	p Value
Mean (SD) age (years)	36.1 (7.1)	36.4 (6.3)		0.7
History of hypertension	2	2	1.0 (0.1 to 7.9)	0.9
Cigarette smoking	10	8	1.5 (0.4 to 5.2)	0.5
Use of oral contraceptives	15	13	1.6 (0.4 to 6.4)	0.5
History of migraine	13	6	4.3 (1.2 to 16.3)	0.03

imaging of the brain, diagnosis of migraine based on self reported symptoms, and no indication of the comparability of the patients with ischaemic stroke and the controls. Henrich and Horwitz compared 89 patients with ischaemic stroke aged 15–65 with 178 controls.⁷ They found that “classic” migraine was more common in the patients with stroke (odds ratio 2.6 (1.1 to 6.6)), but this relation did not persist after adjustment for other risk factors. In the subgroup of patients without vascular risk factors a high risk of ischaemic stroke was found in association with classic migraine (odds ratio 31.3 (4.5 to 216.7)), but the number of subjects was small, the groups were unbalanced (five patients with stroke and 48 controls), and the authors did not check if the groups were of similar ages and sex ratios (two potentially major confounding variables).

Our study had three original features. Firstly, we used the International Headache Society’s criteria for migraine, which are now the reference criteria.⁶ The prevalence of migraine in the whole control group was 16% (34/212) and in young control women was 30% (6/20), results similar to those obtained in other studies using the same criteria.¹¹ Secondly, in order to limit selection bias, all the patients with stroke were successively enrolled in two different departments of neurology. Thirdly, patients with stroke and controls were matched not only for age and sex but also for hypertension, which is a major risk factor for stroke. The existence of a link between migraine and hypertension is unlikely^{12–14} but has been debated.^{15,16} The aim of matching was to obtain comparable groups and to avoid an unbalanced pattern that could not be easily overcome by adjustment. The prevalence of other risk factors was similar to that in other studies^{7,17} and was balanced between the two groups.

When we split our subjects according to type of migraine we found that migrainous aura without headache was significantly more common among patients with stroke, and when we split subjects according to age we found an association between migraine and stroke in younger women. The results for migrainous aura without headache are, however, difficult to interpret because transient ischaemic attacks can have identical symptoms.

Although smoking was not a significant risk factor in younger women in our study, when current smoking and migraine were both present the risk of stroke was particularly high. Chen *et al* suggested that people with migraine might have a higher risk than others of

developing diseases in response to cigarette smoking, but they did not specifically study stroke because the number of events in their sample was too small.¹⁴ The Collaborative Group for the Study of Stroke in Young Women did not assess the risk of the association between migraine and tobacco.⁴

Like others, we did not find any link between migraine and oral contraceptives in younger women.¹⁵ In another study the use of oral contraceptives was associated with an increased risk of stroke,⁴ but only 13%–15% of the study’s controls used oral contraceptives compared with 65% in our study. The use of oral contraceptives was so widespread in our study that it was not possible to individualise their effects.

The number of patients in each of our groups (212) did not quite reach the calculated goal of 220. Since the prevalence of migraine was higher than expected, however, the final power was satisfactory (91%). The number of subjects in each subgroup of young women was relatively small (20). Results for this subgroup must therefore be treated cautiously even though they were significant, and they need to be confirmed by larger studies before firm conclusions can be drawn.

Bias could have resulted from the observers not having been blind to the clinical status of the subjects and therefore looking for migraine more actively in patients with stroke. To control for this the interviews were highly structured with 30 different questions on headache. The fact that a significant link between migraine and stroke was only found in one subgroup of patients makes this bias unlikely. Another potential bias was recall: the patients with stroke suffered from a brain disease and so may have been more prone to recall their headache than the controls. We think this is very unlikely in a chronic and recurrent condition such as migraine. We also included a question about head traumatism to see if the patients with stroke were likely to pay more attention to head diseases than the controls: head traumatism was reported by fewer of the patients with stroke than by the controls (17 v 28, $p=0.12$). We therefore do not think that our results can be explained by recall bias.

In conclusion, we found that migraine was not a significant risk factor for ischaemic stroke in the whole sample. There was, however, a significant association between ischaemic stroke and migraine in younger women. This result, if confirmed, would justify active detection and, if possible, correction of other cerebrovascular risk factors—particularly smoking—in young women with migraine.

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Public health implications

- Migraine has been suggested as a risk factor for ischaemic stroke
- Overall, we found no association between migraine and ischaemic stroke
- Among women aged <45, however, migraine and stroke were significantly associated, especially among young women who smoked
- Ischaemic stroke is not associated with migraine except possibly among young women

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Muslims with non-insulin dependent diabetes fasting during Ramadan: treatment with glibenclamide

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Abstract

Objective—To compare the efficacy of two glibenclamide regimens in patients with non-insulin dependent diabetes who were fasting during Ramadan and regular glibenclamide treatment in the non-fasting group.

Design—Non-randomised control group of patients who did not fast during Ramadan and two groups of patients who fasted randomised equally to one of two regimens: to take their usual morning dose of glibenclamide in the evening and their usual evening dose before dawn; or to follow this pattern but to reduce the total dose by a quarter.

Setting—Two university hospitals, one private hospital, and two private clinics in Casablanca and Rabat, Morocco.

Subjects—591 diabetic patients (198 men, 391 women, two unspecified) with similar duration of diabetes and length and amount of glibenclamide treatment, of whom 542 completed the study.

Main outcome measures—Serum fructosamine and total glycated haemoglobin concentrations and number of hypoglycaemic events.

Results—At the end of Ramadan there were no significant differences between the groups in fructosamine concentration (400 $\mu\text{mol/l}$ in controls and 381 $\mu\text{mol/l}$ and 376 $\mu\text{mol/l}$ in the fasting groups); percentage of glycated haemoglobin (14.7%, 14.0%, and 13.6%); or number of hypoglycaemic events during Ramadan (11, 14, and 10).

Conclusion—Glibenclamide is effective and safe for patients with non-insulin dependent diabetes who fast during Ramadan. The easiest regimen is to take the normal morning dose (together with any midday dose) at sunset and any evening dose before dawn.

Introduction

About one billion people worldwide follow Islam, a basic principle of which is fasting from sunrise to sunset for one lunar month during Ramadan. This poses obvious problems for patients with diabetes,^{1,2} who mostly prefer not to accept the exemptions allowed for patients with certain illnesses.³ Although the prevalence of diabetes may be 3-5% in Islamic countries,⁴ the only studies of the problems experienced by diabetic patients during Ramadan have been on small groups (fewer than 60 patients) treated with several drugs.⁵⁻⁸ At least one of the studies examined only men.⁶ Two studies of fasting among healthy subjects also examined only men.^{9,10} We have therefore conducted a randomised controlled trial of different treatment regimens in a group of patients with non-insulin dependent diabetes living in two Moroccan cities who were being treated with glibenclamide.

Patients and methods

The study was performed at one university hospital, one private hospital, and two private clinics in Casablanca and one university hospital in Rabat. These sites were chosen to guarantee the inclusion of all social classes. The study lasted from 27 January to 8 May 1992 to include a run in and follow up of about four weeks each as well as the month of Ramadan (6 March to 5 April). During this time patients were asked to visit a study centre four times in predefined time windows of about one week each: at the start of run in (27 January to 7 February), at the start of Ramadan (24 February to 5 March), at the end of Ramadan (26 March to 4 April), and at the end of follow up (22 April to 8 May). Altogether 591 patients of both sexes were recruited. They were aged 33-80 (mean 55.5) years, had established non-insulin dependent diabetes (mean duration 7.6 years), and had been treated with glibenclamide 7.5-20 mg (mean 11 mg) for at least six months. Thus newly diagnosed diabetic patients and those whose response to glibenclamide was not yet known were excluded. The study centres were asked to recruit twice as many patients who planned to fast during Ramadan as those who planned not to fast.

All the selected patients gave their informed consent to the study. They were divided into three groups. Those who had elected not to fast during Ramadan acted as a substitute for a randomised control group, which would have created some ethical problems. The remaining patients, who had decided to fast, were randomised consecutively with sealed envelopes to one of two regimens. In one group patients took their normal daily doses of glibenclamide but reversed the pattern of doses so that they took their usual morning dose at 7 pm, after the break of fasting, and their usual evening dose at 4 am, with the last meal before fasting. The 126 patients in this group who had been taking another dose at midday, a common practice in the Mediterranean and tropical countries, added this to the dose taken in the evening. The patients in the other group also reversed their normal pattern of doses but took only 75% of their normal total daily dose of glibenclamide by reducing the amount taken in the morning. The 122 patients in this group who had been taking a dose at midday divided this dose equally between the morning and evening doses.

At each visit to a study centre the patients' weight, blood pressure, and pulse rate were measured, and blood samples were taken for laboratory analysis. Patients' hypoglycaemic events were assessed retrospectively and rated on a six point scale. As far as possible the patients were asked to monitor glucose concentrations in their urine and were supplied with test strips. They were asked to monitor the first spontaneous release of urine after the start of fasting and after breaking their fast, to record the values in a booklet, and to discuss the results at the next visit. This

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