

## SHORT REPORT

# Duration, frequency, recency, and type of migraine and the risk of ischaemic stroke in women of childbearing age

M Donaghy, C L Chang, N Poulter, on behalf of the European Collaborators of The World Health Organisation Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception

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**Background:** Migraine is recognised increasingly as a risk factor for ischaemic stroke in women of childbearing age. Migraine with aura poses a higher risk than migraine without aura.

**Objective:** To investigate further the effect of duration, frequency, recency, and type of migraine on the risk of ischaemic stroke.

**Methods:** Additional analyses of a previously reported multicentre case-control study of the relation between stroke and migraine in women aged 20–44 years.

**Results:** Among 86 cases of ischaemic stroke and 214 controls, the adjusted risk of ischaemic stroke was significantly associated with: (1) migraine of more than 12 years duration, odds ratio (OR) 4.61 (1.27–16.8); (2) initial migraine with aura, OR 8.37 (2.33–30.1); (3) particularly if attacks were more frequent than 12 times per year, OR 10.4 (2.18–49.4). In no case did correction for oral contraception usage significantly alter these odds ratios. Increasing risk of ischaemic stroke was related to a change to increased frequency of headaches (trend  $p \leq 0.03$ ).

**Conclusions:** These data support earlier reports of a relation between ischaemic stroke and migraine with aura. The risk seems particularly high in those whose initial migraine type involved aura occurring more than 12 times per year.

recency of onset, attack frequency, or recency of conversion from migraine without, to with, aura. Data to address some of these questions were available from the data collected in questionnaires used in a previously reported study.<sup>6</sup>

## SUBJECTS AND METHODS

The WHO Collaborative Study of Cardiovascular Disease (CVD) and Steroid Hormone Contraception (SHC) was a hospital based case-control study designed to evaluate the association between current use of SHC and risk of CVD.<sup>12</sup> This report is based on the data collected on a subsample of those women recruited in the five European countries collaborating in the WHO Collaborative Study. Cases were women aged 20–44 years admitted to hospital with first time diagnosis of stroke between June 1990 and January 1993. Table 1 shows the characteristics of the European ischaemic stroke cases and their controls recruited in the WHO collaborative study and the subsample presented in this report. For each case, up to three controls matched by five year age band, hospital, and date of admission were identified and interviewed in hospital in a standard way with the same questionnaire. Women were excluded if they had: a transient ischaemic attack; died within 24 hours of admission; a history of stroke, natural or surgical menopause, pregnancy in the previous six weeks; or a recent history of surgery, trauma, or prolonged bed rest. Full details of the study procedures and methods have been published elsewhere.<sup>7 8 12 13</sup>

## Definition of migraine

Information on the nature and frequency of past and current headaches, accompanying aura, family history of migraine, changes in the frequency and characteristics of headache associated with use of oral contraceptives (OC), and whether headache with migrainous features had occurred within three days prior to stroke were recorded.

The classification of migraine was derived from the International Headache Society's criteria.<sup>11</sup> Migraine without aura was defined as a self reported history of severe headache lasting for more than four hours but less than three days, which occurred on one or both sides of the head, and was associated with feeling sick, finding loud noises or bright lights unpleasant, or both. Migraine symptoms which had ever been accompanied by visual disturbance, abnormalities of speech, skin sensation, or muscle power were defined as migraine with aura. Migrainous stroke was defined as those

Women of childbearing age with migraine appear to be at higher risk of ischaemic stroke than non-migraineurs. This risk appears to be further increased by the coexistence of other established risk factors including hypertension, smoking, and oral contraception.<sup>1–6</sup> Based on an estimated overall incidence of first time strokes of 5.5 per 100 000 women years<sup>7 8</sup> and an adjusted odds ratio for ischaemic stroke associated with migraine in the same population of 3.54 (95% confidence interval 1.30 to 9.61) a first stroke incidence in excess of 15 per 100 000 woman years would be expected among migraineurs.<sup>6</sup> The lifetime prevalence of migraine is estimated at 25–33%.<sup>9 10</sup>

Compared with non-migraineurs, odds ratios for migraine with aura<sup>11</sup> have been reportedly greater than for migraine without aura in all three studies which have differentiated these two migraine types: 6.2 v 3.0,<sup>3</sup> 5.2 v 1.5,<sup>4</sup> 3.81 v 2.97<sup>6</sup> respectively. The different risks associated with migraine types reported in these studies may reflect variations in the criteria used to define migraine with aura, for instance whether aura was required to be present in some, a majority, or all attacks. It is unknown whether the risk estimates are affected by age or

**Abbreviations:** CI, confidence interval; CVD, cardiovascular disease; OC, oral contraception; OR, odds ratio; SHC, steroid hormone contraception; WHO, World Health Organisation

**Table 1** Characteristics of ischaemic stroke cases and controls (European centres)

	Ischaemic stroke study <sup>7</sup>		Migraine study*	
	Cases (n=141)	Controls (n=373)	Cases (n=86)	Controls (n=214)
Mean (SD) age (y)	35.8 (5.8)	35.5 (5.9)	36.1 (6.3)	35.9 (6.3)
Mean (SD) body mass index (kg/m <sup>2</sup> )	25.0 (4.6)	24.4 (4.3)	25.0 (4.8)	24.6 (5.0)
Number of live births (%)				
0	11.4	13.1	16.3	15.0
1–2	66.7	76.1	57.0	74.3
3	22.0	10.7	26.7	10.8
Married/stable union (%)	84.4	81.5	80.2	81.3
Current OC use (%)	36.9	23.3	33.7	21.0
Education beyond secondary level (%)	13.5	27.1	14.0	25.2
Current smokers† (%)	51.1	38.3	53.5	39.3
Weekly alcohol consumption = 1 unit (%)	23.6	25.9	25.6	17.3
Self reported history (%)				
Hypertension‡	22.0	8.3	24.4	7.5
Hypertension during pregnancy§	22.0	14.8	20.9	12.6
Diabetes mellitus	3.6	1.3	4.7	0.9
Rheumatic heart disease	2.1	0.8	2.3	1.4
Family history (%)				
Stroke	3.6	1.3	4.7	1.4
Migraine	–	–	26.7	12.2

\*Those included in the current report. No significant differences from all the European cases and controls are noted. The smaller numbers relate to the delayed start of this substudy.

†Smoked at least one cigarette in the three months before event that caused hospital admission (cases) or before admission (controls).

‡Excluding hypertension during pregnancy.

§Blood pressure disorders during pregnancy, including pre-eclampsia.

stroke cases whose headache started within three days before the onset of persisting neurological deficit.

Data were collected on initial migraine headaches based on the first ever headache with migrainous features and on recent migraine headaches based on the most recent or last migraine headaches experienced.

### Statistical analysis

Interval since the first ever headache and duration of recent migraine attacks with aura were categorised into four levels: non-migraineurs,  $\leq 48$  months, 49–144 months, and  $>144$  months. Change in frequency was classified among migraineurs as decrease, no change, and increase. Odds ratios (ORs) for ischaemic stroke associated with duration (months), change in frequency, age of onset, and frequency of migraine attacks were estimated by conditional logistic regression and adjusted for confounding variables including and excluding current OC use. Separate analyses were performed on data from all stroke cases and on those who had suffered a migrainous stroke. Data were analysed using SAS.<sup>14</sup>

### RESULTS

The mean age of onset of migraine among all migraineurs was almost identical to that among those who suffered a migrainous stroke (23.4 and 23.6 years respectively). Compared with the 60 ischaemic stroke cases and 188 controls who were non-migraineurs, there was no consistent trend among all current migraineurs (26 cases and 26 controls) in the OR for ischaemic stroke associated with increasing interval since the initial onset of headaches (table 2). Stroke risk was highest for those with migraine onset during the preceding four years (data not shown) and for those with longstanding migraine for more than 12 years. However, among those who had recently suffered migraine attacks with aura, the OR of ischaemic stroke was markedly increased among those who noted an onset of such attacks within the preceding four years (table 2). However, the OR for ischaemic stroke was similar among those who suffered a migraine attack, including migrainous stroke within the past three months (18 cases and 19 controls: OR = 3.32, 95% CI: 1.11 to 9.91) and those migraineurs who had not (eight cases and seven controls: OR = 4.11, 95% CI: 0.97 to 17.4). A

**Table 2** Adjusted\* ORs (95% CI) for ischaemic stroke in relation to interval since the first ever headache (all migraineurs) or since onset of migraine with aura (recent migraineurs with aura)

Interval	Adjustment excluding OCs	Adjustment including OCs
<i>All migraineurs†</i>		
$\leq 48$ months	5.59 (0.74 to 42.0) [5/2]	2.83 (0.28 to 28.7)
49–144 months	2.03 (0.52 to 7.91) [8/12]	1.90 (0.48 to 7.43)
$>144$ months	4.61 (1.27 to 16.8) [12/12]	4.65 (1.22 to 17.5)
<i>Recent migraineurs with aura</i>		
$\leq 48$ months	12.3 (0.89 to 168.4) [5/1]	13.3 (0.50 to 357.2)
49–144	1.13 (0.23 to 5.75) [5/10]	1.03 (0.20 to 5.28)
$>144$ months	6.42 (1.31 to 31.5) [9/6]	5.15 (1.00 to 26.5)

Relative to non-migraine sufferers (60/188).

Values in square brackets represent number of cases/number of controls.

\*Adjusted for age, high blood pressure, smoking categories, family history of migraine, alcohol consumption, social class, and education: since onset of headache in all migraineurs, and since onset of migraine with aura in recent migraineurs with aura.

†One case with unknown value of the interval.

**Table 3** Adjusted\* ORs (95% CI) for ischaemic stroke in relation to change in frequency of headache

Change in frequency	Adjustment excluding OCs	Adjustment including OCs
<i>All headaches among migrainous stroke cases† and controls</i>		
Decrease	0.20 (0.001 to 34.0) [2/5]	0.21 (0.001 to 60.9)
No change	10.3 (2.14 to 49.5) [14/6]	11.0 (1.75 to 68.9)
Increase	26.9 (1.33 to 541.6) [2/4]	39.5 (1.66 to 940.7)
Trend	p=0.03	p=0.02
<i>Migrainous attacks among migraineurs with aura</i>		
Decrease	2.28 (0.10 to 52.63) [3/3]	1.85 (0.07 to 48.2)
No change	3.69 (1.20 to 11.36)[15/13]	2.77 (0.84 to 9.14)
Increase	17.6 (0.12 to 2566) [1/1]	17.6 (0.12 to 2702)
Trend	p=0.01	p=0.05

Relative to non-migraine sufferers (60/188).

Values in square brackets represent number of cases/number of controls.

\*Adjusted for high blood pressure, smoking categories, family history of migraine, alcohol consumption, social class, and education.

†One case with unknown value.

similar lack of effect of recency of attack was seen among migraineurs with aura (data not shown). Compared with non-migraineurs, the OR for ischaemic stroke among migraineurs was unaffected by the age of onset among all migraineurs (data not shown).

Of the 19 women who had suffered a migrainous stroke, compared to non-migraineurs, increasing ORs for ischaemic stroke were significantly associated ( $p = 0.03$ ) with a change to increased frequency of headaches (table 3). This change occurred on average nine months previously for cases and 51 months for controls. A similar pattern was apparent for migraineurs with aura (table 3).

Among current migraineurs the OR for ischaemic stroke associated with the type of migraine initially suffered was smaller among those who initially suffered migraine without aura (2.21, 95% CI: 0.49 to 10.1) compared with those who initially suffered migraine with aura (8.37, 95% CI: 2.33 to 30.1), although this difference did not reach statistical significance. The frequency of recent migraine attacks among migraineurs with aura was not associated with increased ORs of an ischaemic stroke (data not shown). However, ORs among those who had initially suffered migraine with aura less frequently than 13 episodes per year was less (3.58, 95% CI: 0.86 to 14.8) than among those whose initial migraine with aura occurred at  $\geq 13$  episodes per year (10.4, 95% CI: 2.18 to 49.4;  $p = 0.003$ ).

## DISCUSSION

These data suggest that risk of ischaemic stroke is influenced by frequency, type, and pattern of migraine. Previous reports suggested that stroke risk was particularly increased by migraine with aura,<sup>3,4</sup> as did our main study,<sup>6</sup> from which the present analyses were derived. These further analyses strengthen the likelihood of a greater risk associated with migraine with aura by showing an increased risk among those whose initial migraine type was with aura and during the first four years of aura attacks. It remains unknown whether, despite conventional medical opinion,<sup>15,16</sup> migraine with aura has a different biological basis to migraine without aura. Furthermore, it is not established whether factors which might convert an individual's migraine type from without aura to with aura produce an increased risk of stroke. Population based Danish studies of 40 year old migraineurs classified 38% of migraineurs as having aura, and found only 4% had attacks without aura; on this basis the two types of migraine were regarded as distinct clinical entities.<sup>17</sup> A detailed Dutch population based study of migraine prevalence reported aura in 31% of female migraineurs, but it is unclear whether this represented a one year

or lifetime prevalence of aura.<sup>10</sup> In our previously reported case-control study, 70% of migraineurs, diagnosed on the basis of a headache questionnaire, reported at least one attack accompanied by aura.<sup>6</sup> By contrast, in a population based study in which diagnosis of migraine was based on structured diagnostic interview and examination, 40% of migraineurs reported at least one attack accompanied by aura.<sup>18</sup>

Our analyses have addressed a number of factors concerning the temporal relation between migraine and ischaemic stroke. Neither the age of onset of migraine, nor the presence of a migraine attack in the preceding three months, were independent predictors of stroke. Increased frequency of headaches, for the preceding nine months on average, was associated with increased stroke. However, onset of migraine during the preceding four years was associated with an increased risk of stroke, as was a migraine history lasting more than 12 years. These effects were more marked for migraine with aura than without aura, whether or not corrected for oral contraception usage.

Overall, those who reported that their initial migraine type was with aura, were approximately three times as likely to develop subsequent ischaemic stroke. Concern has been raised that an increased risk of stroke ensues when the use of oral contraception is associated with a change of migraine type to aura.<sup>15</sup> Previously we noted that introduction of oral contraception was six times as likely to convert migraine without aura into migraine with aura, than vice versa, an effect which was similar for stroke cases and their controls.<sup>6</sup> Hence no increase in stroke risk was apparent in association with oral contraceptive induced conversion to migraine with aura. In the current analyses, we observe a relation between increased frequency of migraine with aura during the months preceding ischaemic stroke, which was not substantially altered by adjustment for OC usage. However any conclusions must be tempered by the limitations imposed by the relatively small numbers included in these and contradictory analyses.<sup>15</sup> Nevertheless, considered overall, these data suggest that the biological determinants of initial migraine type may be as important in determining risk of an ischaemic stroke as any change in migraine type induced by oral contraception.

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**Authors' affiliations**

**M Donaghy**, Department of Clinical Neurology, Radcliffe Infirmary, Oxford, UK

**C L Chang, N Poulter**, Cardiovascular Studies Unit, Imperial College of Science, Technology & Medicine, London, UK

Correspondence to: Dr M Donaghy, Department of Clinical Neurology, Radcliffe Infirmary, Woodstock Road, Oxford OX2 6HE, UK

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