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BRIEF REPORT

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Clinic-based study of family history of vascular risk factors and migraine

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Abstract The objective was to evaluate the presence of a positive family history (FH) of vascular risk factors between patients with migraine with aura (MA) and migraine without aura (MO), and in chronic migraine (CM) compared to other headache types. As migraine patients are typically too young to have developed vascular events, studying older relatives of migraine patients may be a practical means of evaluating associations between vascular risk factors and migraine. A cross-sectional study of a clinic-based sample of adults with migraine headache was carried out at the University of Utah. Predictor variables comprised first or second degree relatives with stroke, hypertension, diabetes or hypercholesterolaemia. Outcome measures comprised diagnosis of MA, MO or CM according to the revised International Headache Society criteria. There was no significant difference in FH of vascular risk factors in MA compared to MO (adjusted OR 1.04, 95% CI 0.61–1.78). CM was associated with a decreased risk of FH of stroke (OR=0.11, 95% CI 0.02–0.87, p=0.036). There was no significant difference in FH of vascular risk factors in MA patients compared to MO. CM patients were more likely to have a negative FH of stroke compared to other headache types, suggesting that CM is likely a neuronal disease rather than a vascular one.

Key words Vascular risk factors • Stroke • Migraine

Introduction

The relationship between migraine and stroke has been the subject of repeated study [1]. There appears to be a clear correlation between migraine and stroke or other cardiovascular events in rare genetic conditions such as cerebral autosomal dominant arteriopathy with subcortical infarctions and leukoencephalopathy (CADASIL), mitochondrial encephalopathy with lactic acidosis and stroke-like episodes (MELAS) and the familial dyslipoproteinaemias [2]. Association between the common forms of migraine, stroke and other vascular risk factors has been shown in several large population-based studies [3, 4]. An increase in vascular events in parents and grandparents of children with migraine compared to control subjects has been documented previously [5]. One goal of this study was to compare family history of vascular risk factors between patients with migraine with aura (MA) and migraine without aura (MO).

The potential relationship between vascular risk factors and chronic headache deserves attention, given the long-term consequences of both conditions for patients. A subset of patients with episodic MO undergo malignant transformation to a debilitating chronic form of the disorder, also known as chronic or transformed migraine [6]. Previous investigations on the aetiology, modifying factors and treatment of chronic headaches have been difficult to evaluate, as this heterogeneous group of disorders was usually classified as "chronic daily headache" and not as separate clinical entities [7]. The newly revised International Headache Society (IHS) criteria address this issue and provide specific diagnostic criteria for chronic migraine (CM), which allow standardisation of patient classification [8]. We assessed the prevalence of positive family history (FH) of vascular risk factors in patients with CM.

Methods

Study design

We conducted a cross-sectional study using the University of Utah Headache Clinic Database. The database was originally created to collect clinical/genetic data for patients in order to identify headache predisposition genes and the family history data are extremely detailed and complete. Data collected include age of onset of headache pain, headache diagnoses, frequency, duration, change in headache symptoms, medications, investigations, co-morbidities and detailed family history.

Subjects

Study subjects were adult patients who attended the University of Utah Headache Clinic and who gave informed consent to participate in the study between 1999 and 2003. Subjects for whom complete data are not available or with a primary diagnosis other than migraine were excluded from the study. All subjects were initially classified according to the 1988 IHS criteria. Medical records of subjects with a diagnosis of chronic daily headache, transformed migraine or CM were reviewed and re-classified according to the newly revised IHS criteria [8]. Only subjects who met the IHS diagnostic criteria for CM were evaluated. Predictor variables comprised first or second degree relative with: (1) stroke, (2) hypertension, (3) diabetes and (4) hypercholesterolaemia. Discrepancies in data were manually verified as all clinical records were available.

Statistical analysis

Fisher's exact test was the primary univariate statistical analysis used, as most of the variables were categorical. Comparison of means of continuous variables was carried out using Student's *t*-test. Multivariate logistic regression was used to adjust for potential confounding factors and provide estimates of odds ratios for MA/MO/CM status. The STATA 8.0 statistical software package (Stata Corporation, College Station, TX) was used for all analyses.

Results

A total of 303 subjects with a primary diagnosis of migraine were enrolled in the study. Six subjects were excluded (two had familial hemiplegic migraine, two had post-traumatic headache as the primary diagnosis and two subjects had incomplete medical records) yielding 297 eligible subjects. Of these, 126 had a diagnosis of MA and 171 had MO. Subjects who carried a diagnosis of both MA and MO were classified as having MA as the primary diagnosis. Baseline demographic characteristics appeared similar between the two groups. Univariate analyses revealed no statistically significant difference in MA *vs*. MO status compared by overall family history of vascular risk factors. The differences in family history of individual vascular risk factors (diabetes, hypertension, hypercholesterolaemia, stroke) between the two groups also appeared to be small and were not statistically significant (Table 1).

The unadjusted odds ratio (OR) of MA compared to MO was 1.05 (95% CI 0.64–1.7) for patients with a FH of vascular risk factors. The OR adjusted for potential confounding factors (age, race, headache frequency, gender) was 1.04 (95% CI 0.61–1.8). The ORs for individual cardiovascular risk factors also appeared too small to be of clinical significance (diabetes 0.91, 95% CI 0.55–1.5, hypertension 1.06, 95% CI 0.66–1.7, hypercholesterolaemia 1.21, 95% CI 0.70–2.1, stroke 1.15, 95% CI 0.67–1.9).

Table 1 Characteristics of patients with MO compared to MA

	MO (*n*=171)		MA (*n*=126)		*p*-value*
	Patients, *n*	%	Patients, *n*	%	
Gender					0.34
Male	30	17.5	17	13.5	
Female	141	82.5	109	86.5	
Race/ethnicity					0.36
Caucasian	169	98.8	121	96	
Hispanic	1	0.6	3	2.4	
Native American	1	0.6	1	0.8	
Other	0	0.0	1	0.8	
Mean age, years	40		42		0.22
Headaches/month, *n*					0.49
0–1	26	16.8	24	20.3	
2–4	45	29.0	41	34.8	
5–7	26	16.8	18	15.3	
>8	58	37.4	35	29.7	
FH vascular risk factors	119	69.6	89	70.6	0.85
FH diabetes	65	38.0	47	37.3	0.91
FH hypertension	73	42.7	57	45.2	0.66
FH hypercholesterolaemia	44	25.7	38	30.2	0.39
FH stroke	48	28.1	40	29.6	0.49

FH, positive family history
*Fisher's exact test

Table 2 Characteristics of patients with CM compared to other migraine[1]

	Other migraine (*n*=277)		CM (*n*=20)		*p*-value*
	Patients, *n*	%	Patients, *n*	%	
Gender					0.46
Male	45	16.3	2	10.0	
Female	232	83.8	18	90.0	
Race/ethnicity					<0.001
Caucasian	272	98.2	18	90.0	
Hispanic	4	1.44	0	0.00	
Native American	0	0.00	2	10.0	
Other	1	0.36	0	0.00	
Mean age, years	41.1		42.1		0.75
Headaches/month, *n*					<0.001
0–1	49	19.2	0	0.00	
2–4	84	32.9	0	0.00	
5–7	40	15.7	0	0.00	
>8	82	32.2	20	100[1]	
FH vascular risk factors	191	69.0	17	85.0	0.13
FH diabetes	102	36.8	10	50.0	0.24
FH hypertension	118	42.6	12	60.0	0.13
FH hypercholesterolaemia	75	27.1	7	35.0	0.44
FH stroke	87	31.4	1	5.00	0.010

FH, positive family history
*Fisher's exact test
[1]All patients with CM had at least 15 days of headache per month

Of the 297 subjects, 112 had a diagnosis of chronic daily headache, transformed migraine or CM. These patients were reclassified according to the revised IHS guidelines following review of medical records. Re-classification occurred as follows: CM (20 patients), headache due to overuse of analgesics (8 patients), ergotamines (2 patients) or rebound/combination medication overuse (82 patients). Baseline characteristics appeared similar in patients with CM compared to other types of headache, with the exception of race/ethnicity and headache frequency (Table 2).

Univariate analyses revealed a significant decrease in CM among patients with a FH of stroke (5%) compared to a negative family history (31.4%), p=0.010. The unadjusted OR of CM was 2.6 (95% CI 0.73–8.9) for patients with a FH of vascular risk factors. The OR adjusted for potential confounding factors was 2.4 (95% CI 0.67–8.8). The measures of association for individual cardiovascular risk factors were as follows: family history of diabetes OR=1.7 (95% CI 0.69–4.3), family history of hypertension OR=2.0 (95% CI 0.80–5.1) and family history of hypercholesterolaemia OR=1.4 (95% CI 0.55–3.8). CM was associated with a decreased family history of stroke (OR=0.11, 95% CI 0.02–0.87, p=0.036). The ORs and confidence intervals adjusted for potential confounding factors were essentially unchanged (data not shown).

Discussion

The relationship between the common forms of migraine and stroke remains an area of investigation. Data from several studies suggest that migraine may be a risk factor for the development of stroke [3, 4, 9–12] and MA may be an important risk factor for stroke in women [12, 13]. The mechanisms that underlie these observations are unclear but a reasonable hypothesis could include the presence of shared risk factors as a possible cause. As both migraine and vascular disease have a demonstrated component of heritability, it is possible that risk factors that predispose to both conditions may be inherited traits. Migraine patients are typically too young to have developed vascular events, and so we studied older relatives of migraine patients as a means of evaluating the association between vascular risk factors and migraine.

A recent population-based study found greater prevalence of white matter lesions in patients with MA and MO compared to controls, suggesting a vascular basis for the association between migraine and stroke [14]. Several lines of evidence suggest MA is more strongly associated with stroke than MO [3, 4, 12]. For our study, analysis of associations between family history of vascular risk factors and MA compared to MO found only modest positive associations, with confidence intervals that included no associations at all. This is compatible with previously reported findings [5], and very large population-based studies may be required to fully elucidate this issue.

Chronic headache has been found to be an independent predictor of stroke among men in one study [15]. We found a large, statistically significant negative association between family history of stroke and development of CM, compared to non-CM migraine (OR=0.11, 95% CI 0.02–0.87, p=0.036). This suggests that stroke susceptibility factors may not promote development of CM, compared to other migraine types. Family history of diabetes, hypertension and hypercholesterolaemia tended toward positive association with CM, but were smaller and not statistically significant. In addition, these conditions may not be as accurately reported by patients as stroke. It is possible that the pathophysiology of CM involves factors completely unrelated to those traditionally associated with vascular pathology, such as disruption of calcium homeostasis causing neuronal hyperexcitability [16], and that CM may be considered a neuronal disease rather than a vascular one. This finding merits further investigation using a larger, prospective cohort or case-control study.

The strengths of the study include a well defined, homogeneous population, for which complete medical records were available, and outcome ascertainment by a single physician (KBD) with expertise in headache diagnosis and treatment. Population stratification and confounding factors such as alcoholism and smoking are greatly reduced given the unique characteristics of this patient population.

The main limitations of this study are its retrospective nature and small sample size. There is also the potential for selection/ascertainment bias as these patients are most likely to have disabling illness and to present to a specialty clinic for care. However this is unlikely to influence family history of vascular risk factors between the comparison groups. As our interest is in evaluation of stroke risk factors and patients with severe, disabling migraine, a clinic-based study is appropriate.

The observed differences in family history of vascular risk factors among patients with different types of migraine may potentially yield clues to understanding migraine biology and pathogenesis. In addition, these findings may have implications for treatment of patients with different migraine types. In the case of CM, our study suggests that traditional vascular risk factors may not be important in its development, in contrast to previous studies [15]. This highlights the importance of further research in determining risk factors for the development of this debilitating condition.

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