Migrainous cerebral infarction in the Sagrat Cor Hospital of Barcelona stroke registry

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Nine of 2000 consecutive stroke patients included in the Sagrat Cor Hospital of Barcelona Stroke Registry over a 10-year period fulfilled the strictly defined International Headache Society criteria for migrainous stroke and in whom other causes of stroke were ruled out. They accounted for 13% of all first-ever ischaemic stroke of unusual cause. Migrainous stroke was more common in women (67%) and in patients aged ≤ 45 years (78%) compared to the remaining ischaemic strokes of unusual cause. No patient died during hospital stay and 67% were symptom-free at discharge. In the multivariate analysis, nausea or vomiting (odds ratio (OR) 8.40, 95% confidence interval (CI) 1.49–47.21) and age (OR 0.95, 95% CI 0.91–0.99) were predictors of migrainous stroke. Migrainous stroke is a rare entity. Vascular risk factors are uncommon and the prognosis is generally good. Patients with migrainous stroke present some different clinical features from other ischaemic strokes of unusual aetiology. □*Migraine, ischaemic stroke, migrainous stroke, unusual cause*

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Introduction

Cerebral infarction of unusual cause is a recently individualized and uncommon subtype of ischaemic stroke (about 6% of all cerebral infarctions) with numerous causative conditions (1). Migraine is a rare aetiology of ischaemic stroke of unusual cause. Migrainous cerebral infarction has recently re-defined with the use of International Headache Society (IHS) criteria (2). Because no common definition of migrainous stroke has been used in the past (up 17% of stroke cases in patients under 50 years of age in hospital-based studies conducted before 1989 were attributed to migraine) (3, 4), evidence that previously reported cases are true migraine-induced stroke is uncertain. On the other hand, migrainous stroke is infrequently individualized in the different prospective stroke registries and there are a few studies analysing cases of migrainous infarction fully meeting IHS criteria.

To improve our knowledge of migrainous cerebral infarction, we carried out a descriptive epidemiological study of nine patients with migrainous stroke collected from the hospital-based Sagrat Cor Hospital of Barcelona Stroke Registry, with the following three objectives: firstly to determine the incidence of migrainous stroke with regard to all patients with first-ever stroke, cerebral infarction, cerebral infarction of unusual aetiology, and cerebral infarction in young adults (≤45 years of age); secondly to assesss demographic data, clinical variables, and prognostic features of migrainous stroke; and finally to compare the characteristics of the nine patients with migrainous stroke with the remaining group of 61 patients with ischaemic stroke of unusual cause.

Patients and methods

Between January 1986 and December 1995, data of 2000 acute stroke patients admitted consecutively to the Department of Neurology of Sagrat Cor Hospital (an acute-care 350-bed teaching hospital in the city of Barcelona serving a population of approximately 250 000) were collected prospectively in a stroke reg-

istry. The characteristics of this database have been previously described (5). Briefly, a total of 167 items including type/subtype of stroke and cause of stroke have to be fulfilled for each patient. Therefore, data is collected prospectively and diagnosis is made according to cerebrovascular risk factors, clinical findings, topography, and diagnostic studies during the patient's admission to the hospital.

Patients with previous ischaemic or haemorrhagic stroke ($n = 383$) were excluded. The medical records of 1617 patients with first-ever stroke ($n = 1614$) or transient ischaemic attack ($n = 201$) were collected prospectively in our stroke registry. Subtypes of stroke were classified according to the Cerebrovascular Study Group of the Spanish Neurological Society (6), which is similar to the National Institute of Neurological Disorders and Stroke Classification (7) and has been used by our group in previous studies (1, 5). Subtypes of stroke included transient ischaemic attack (TIA) ($n = 201$), atherothrombotic stroke ($n = 339$), lacunar stroke ($n = 285$), cardioembolic infarction ($n = 274$), infarction of undetermined origin ($n = 196$), infarction of unusual cause ($n = 70$), intracerebral haemorrhage ($n = 201$), subarachnoid haemorrhage ($n = 31$), spontaneous subdural haematoma ($n = 19$) and spontaneous epidural haematoma ($n = 1$).

Ischaemic stroke of unusual aetiology was defined (1) as small, medium-sized or large infarction; cortical, subcortical, carotid or vertebrobasilar in location; and occurring in a patient in whom an ischaemic stroke fulfilling the diagnostic criteria for lacunar, cardioembolic, atherothrombotic infarction or infarction of undetermined origin, has been excluded. The acute cerebrovascular event may occur as a presenting sign or in the course of the underlying disease.

Migrainous cerebral infarction was defined according the strict criteria fulfilling the proposal of the IHS (2) in which: (a) the patient has previously fulfilled criteria for migraine with aura; (b) the neurological deficit is manifested in the exactly vascular distribution as the aura but that is not completely reversible within 7 days and/or neuroimaging studies demonstrate an ischaemic infarction in relevant area; (c) all other potential causes of ischaemic stroke are ruled out by appropriate investigations although stroke risk factors may be present. Ischaemic cerebrovascular event accompanied by headache, coexisting stroke and migraine, stroke with clinical features of migraine, and migraine that mimics stroke were excluded (2, 8). Migraine patients were also identified according to criteria of the International Headache Society (4). Active migraine was diagnosed when the patient presented with at least two migraine attacks in the previous 2 months before the acute stroke onset (9).

For the purpose of this study, the group of 70 patients with ischaemic stroke of unusual cause was selected. There were 9 patients with migrainous stroke and 61 patients cerebral infarction of other unusual aetiologies, including haematological disorders (17 patients), infection (11 patients), cerebral infarction secondary to venous thrombosis (9 patients), primary inflamatory arteritis (6 patients) and miscellaneous disorders (18 patients).

All patients were admitted to the hospital within 48 h of the onset of symptoms. On admission, demographic characteristics, salient features of clinical and neurological examination and results of laboratory tests (blood cell count, biochemical profile, serum electrolytes, urinalysis), chest radiography and 12-lead electrocardiography were recorded. Neurological examination was performed on a daily basis. In all patients, brain computed tomography (CT) scan were performed within this first week of hospital admission. Overall, 67% of patients were studied by magnetic resonance imaging (MRI), 53% by B-mode transthoracic or transoesophagic echocardiography, 50% by arterial digital subtraction angiography, 90% by Doppler ultrasonography of the of supra-aortic trunks and 13% by immunological studies.

For each patient, demographic data, vascular risk factors, clinical features, neuroimaging findings, and outcome were recorded. Demographic variables included age and sex. Anamnestic findings consisted of history of hypertension, diabetes mellitus, myocardial infarction or angina, rheumatic heart disease, congestive heart failure, atrial fibrillation, smoking (>20 cigarettes/day), alcohol abuse (>80 g/day), intermittent claudication, transient ischaemic attack (TIA), previous cerebral infarction, hyperlipidaemia, renal dysfunction, cirrhosis or chronic liver disease, chronic obstructive pulmonary disease (COPD) and age >85 years. Clinical variables included sudden onset of symptoms (minutes); headache; dizziness; seizures; nausea or vomiting; altered consciousness (drowsy, stuporous, comatose); limb weakness (hemiparesis or hemiplegia, Babinski's sign not mandatory); sensory symptoms; aphasia or dysarthria; ataxia; cranial nerve palsy; presence of lacunar syndrome (pure motor hemiparesis, pure sensory stroke, sensorimotor stroke, ataxic hemiparesis, and dysarthria-clumsy hand) (10). Outcome variables included absence of limitation at discharge, mean length of hospital stay, and in-hospital mortality.

Statistical analysis

Univariate analysis for each variable in relation to the diagnosis of migrainous stroke ($n = 9$) vs. other ischaemic stroke of unusual aetiology ($n = 61$) as well as differences in the frequency of demographic characteristics, vascular risk factors, clinical events, neuroimaging data, and outcome were assessed with the Student's t-test for continous variables and the chi-square test (χ^2) (with Yate's correction when necessary) for categorical variables. Statistical significance was set at $P < 0.05$. Variables related to migrainous stroke plus sex were subjected to multivariate analysis with a logistic regression procedure and forward stepwise selection if $P < 0.10$. The predictive model was based on demographic, anamnestic, and clinical variables (total 7 variables). Migrainous cerebral infarction, coded as presence = 0, absence = 1 was the dependent variable. The level of significance to remain in the model was 0.15. The maximum likelihood approach was used to estimate weights of the logistic parameters (11). Odds ratio (OR) and 95% confidence intervals (CI) were calculated from the beta coefficients and standard errors. The hypotehesis that the logistic model adequately fits the data was tested by means of the goodnes-of-fit χ^2 test.The SPSS-PC + (12) and BMDP (13) computer programs were used for statistical analysis.

Results

Six women and three men fully met IHS criteria (2) for migrainous cerebral infarction. The mean (SD) age of the patients was 35.7 ± 12 years. Seven patients (77.8%) were under the age of 45 years. This group of patients with migrainous stroke accounted for 0.6% (9/1617) of all first-ever acute strokes, 0.8% (9/1164) of ischaemic strokes, 12.8% (9/70) of ischaemic strokes of unusual aetiology and 13.7% (7/51) of ischaemic strokes in young adults (≤ 45 years of age).

Demographic features, vascular risk factors, clinical manifestations, and neuroimaging findings of migrainous cerebral infarction are shown in Table 1, with a copule of case examples in the footnote. Hypertension, diabetes mellitus, or atrial fibrillation – the most common vascular risk factors for ischaemic stroke – were not recorded. Active migraine was present in 8 (88.9%) patients and 2 (22.2%) patients were taken oral contraceptives. All patients suffered from headache at the onset of neurological deficit. The stroke manifested as limb weaknes in 5 patients, sensory symptoms in 5, hemianopia in 4, nausea and vomiting in 4, and aphasia in 1. Six patients had a cerebral infarct visible on neuroimaging studies (middle cerebral artery 3, posterior cerebral artery 2, superior cerebellar artery 1).

Table 1 Features of migrainous cerebral infarction

Case	Sex	Age	Risk factors	Symptoms	Infarction topography on neuroimaging studies
1	M	39	None	Nausea, vomiting + visual + motor	Middle cerebral artery
2	M	30	None	Nausea, vomiting + visual + motor + sensory	Undetermined
3	M	49	Hyperlipidaemia	Sensory	Superior cerebellar artery
4*	F	35	None	Visual + nausea, vomiting	Posterior cerebral artery
5	F	32	None	Sensory	Middle cerebral artery
6†	F	25	Oral contraceptives Smoking	Motor + sensory + visual + aphasia	Middle cerebral artery
7	F	27	None	Sensory + visual	Undetermined
8	F	24	Contraceptives	Motor	Undetermined
9	F	60	None	Nausea, vomiting + sensory + visual	Posterior cerebral artery

*Case 4. A 35-year-old woman had suffered from attacks of migraine with visual aura. In November 1992, during a typical migraine attack, she had a persistent right hemianopia accompanied by nausea and vomiting. The CT scan and MRI studies revealed an ischaemic lesion in the left occipital lobe in the distribution of the posterior cerebral artery. Other investigations were unrevealing.

†Case 6. A 25-year-old woman had a long history of attacks of migraine with and without typical aura consisting of speech difficulty and right hemiparesthesia and weakness lasting about 10 min She was a heavy smoker (> 20 cigarettes/day) and currently taking oral contraceptives. In 1994, during a typical migraine attack, she developed mental confusion, aphasia, right homonymous hemianopia and persistent right hemiparesis and hemihypoesthesia. The CT and MRI studies showed an ischaemic lesion in the left temporoparietal lobe in the distribution of the middle cerebral artery. Other investigations were unrevealing.

In the remaining three patients with negative neuroimaging findings, neurological deficit lasted at least 7 days. In the case of migrainous stroke in which infarction occurred in the superior cerebellar artery territory, the aura was sensitive (hemiparesthesia), whereas in the three cases of undetermined topography, the aura was visual (hemianopia) in two and motor (weakness) in one. The mean length of hospital stay was 9.75 ± 6.2 days. No patient died during hospital stay and 67% were symptom-free at discharge.

Patients with migrainous stroke compared with the remaining 61 patients with ischaemic stroke of unusual cause were significantly younger. These patients also had a significantly higher ocurrence of active migraine, headache at stroke onset, and presence of nausea or vomiting (Table 2). On the other hand, the following clinical profiles were also significantly more frequent in patients with migraine-induced stroke than in patients with ischaemic stroke of unusual aetiology: female sex and ≤ 45 years of age (55.6% vs. 16.4%, $P < 0.02$); female sex and active migraine (55.6% vs. 1.6%, $P < 0.001$); female sex, ≤ 45 years of age, and active migraine (44.4% vs. 0%, $P < 0.001$); and female sex, ≤ 45 years of age, active migraine, and headache at the onset of neurological deficit (44.4% vs. 0%, $P < 0.001$).

After multivariate analysis, nausea or vomiting (OR = 8.40) and age (OR = 0.95) were selected as independent predictors in a logistic regression model based on demographic, risk factors, and clinical variables (Table 3). Taking a cut-off point of 0.50

Table 2 Comparison of migraine-induced stroke and other cerebral infarction of unusual cause

Data	Migraine-induced stroke (*n* = 9)	Ischaemic stroke unusual aetiology (*n* = 61)	*P*-value
Demographic features			
Female, sex	6 (66.7)	32 (52.5)	NS
Age, years, mean (SD)	35.7 (12)	54.3 (22.6)	<0.001
Age, ≤ 45 years	7 (77.8)	24 (39.3)	<0.07
Vascular risk factors			
Hypertension	0	11 (18)	NS
Diabetes	0	1 (1.6)	NS
Rheumatic heart disease	0	3 (4.9)	NS
Atrial fibrillation	0	3 (4.9)	NS
Heart failure	0	1 (1.6)	NS
Oral contraceptives	2 (22.2)	4 (6.6)	NS
Smoking (>20 cigarettes/day)	1 (11.1)	12 (19.7)	NS
Alcohol abuse (>80 g/day)	0	3 (4.9)	NS
Previous transient ischaemic attack	1 (11.1)	5 (8.2)	NS
Hyperlipidemia	1 (11.1)	4 (6.6)	NS
Active migraine	8 (88.9)	2 (3.3)	<0.001
Chronic obstructive pulmonary disease	0	1 (1.6)	NS
Clinical findings			
Sudden onset	6 (66.7)	24 (39.3)	NS
Headache	9 (100)	24 (39.3)	<0.01
Seizures	0	7 (11.5)	NS
Nausea, vomiting	4 (44.4)	7 (11.5)	<0.05
Altered consciousness	0	10 (16.4)	NS
Aphasia, dysarthria	1 (11.1)	23 (37.7)	NS
Limb weakness	5 (55.6)	39 (64.0)	NS
Sensory symptoms	5 (55.6)	26 (42.6)	NS
Hemianopia	4 (44.4)	22 (36.1)	NS
Cranial nerve palsy	0	3 (4.9)	NS
Ataxia	0	4 (6.6)	NS
Lacunar syndrome	0	2 (3.3)	NS
Outcome			
Absence of limitation at discharge	6 (66.7)	19 (31.1)	<0.08
Length of stay, days, mean (SD)	9.75 (6.2)	25.7 (24.5)	<0.07
In-hospital mortality	0	5 (8.2)	NS

Table 3 Independent predictive value of different variables associated with migrainous cerebral infarction

Variable	β	SE (β)	Odds ratio (95% CI)
Nausea, vomiting	2.1279	0.8810	8.40 (1.49 to 47.21)
Age	–0.0512	0.0230	0.95 (0.91to 0.99)

β = –0.2253; SE (β) = 0.9162; goodness-of-fit $\chi^2 = 3.7877$; d.f. = 8; $P = 0.8757$.

Area under the ROC curve 0.837, sensitivity 0.88, specificity 0.67, positive predictive value 0.29, negative predictive value 0.98, accuracy 0.70.

for predicting migrainous cerebral infarction, resulted in a sensitivity of 88%, a specificity of 67%, and total correct classitfication of 70%. These percentages were not significantly improved by using an optimal cut-off value, as indicated by receiver operating characteristics (ROC) curves.

Discussion

Clinical data of migraine-induced stroke collected from stroke registries in which cases fully meet IHC criteria (2) are limited. In the present study, migrainous cerebral accounted for 0.55% of first-ever strokes, 0.77% of first-ever brain infarcts, 12.8% of infarctions of unusual aetiology, and 13.7% of infarcts in young adults. In the Baltimore-Washington Cooperative Young Stroke Study (14), migraine was the aetiology assigned to 1.4% of 428 first strokes, whereas in the Dijon Stroke Registry (15), migraine-induced stroke accounted for 0.50% of all first-ever strokes. The incidence of migraine-induced stroke observed in Dijon (around 0.80/100000/year) was lower than in Oxford (around 3.36/100000/year) (16), but, as in all other studies (17, 18), commoner in women. In the study by Linetsky et al. (19), migrainous stroke accounted for 0.8% of all acute strokes. Therefore, stroke can occur in migraine, but the association between migraine and stroke is infrequent (20–22). However, the following aspects should be taken into consideration: (a) headache is a common feature of stroke itself and may be mistaken for a migraine attack (23, 24); (b) thromboembolic cerebral ischaemic events may trigger an attack of migraine aura with or without headache particulary in migraineurs but also in nonmigraineurs (25); (c) the IHS criteria for migrainous stroke are very strict and do not permit the diagnosis of migrainous stroke in patients with migraine without aura (2) because it is not associated with focal blood flow reduction (2, 17), although some authors have recently considered migraine-induced stroke as a possible complication of both migraine with and without aura (26).

Migraine-induced stroke indicates that it occurs more frequently in women (66.7%) and in patients ≤ 45 years of age (77.8%). These findings are similar to those reported by others (9, 15, 17, 18). Cerebrovascular risk factors are uncommon, which is in contrast to well know vascular risk factor profile in cardioembolic and atherothrombotic stroke. History of hypertension, diabetes, atrial fibrillation, or rheumatic heart disease was not recorded in any of our nine patients. On the other hand, ischaemic strokes attributed to migraine occur in the territories of the posterior or middle cerebral arteries, which is in agreement with data of previous studies (17, 18, 27). The functional outcome is good with no case of hospital death and functional-associated disability is moderate, (66.7% of patients were symptom free at discharge). This favourable outcome is consistent with data reported by Hekstra-van Dalen et al. (28), in which 14 patients with migraine-induced stroke were independent in their daily activities and the long-term functional outcome was good.

Independent predictive factors associated with migrainous cerebral infarction in the logistic regression model included nausea and/or vomiting and age. The presence of nausea and vomiting is more common in migraine-induced stroke and this may be explained because vascular headache accompanying migrainous cerebral infract is usually associated with neurovegetative manifestations and gastrointestinal symptoms. By contrast, headache accompanying the remaining cerebral infarcts, on the one hand, is less frequent (16–40%) and, on the other, nausea and vomiting are usually absent because these manifestations are more characteristic of intracerebral haemorrhage than of ischaemic brain infarcts (23, 24, 29). On the other hand, age was the second independent variable associated with migraine-induced stroke, which is in agreement with previous of ischaemic stroke of unusual cause occurring in patients significantly younger than the remaining ischaemic stroke patients (mean age 52.8 vs. 73.5 years in a previous study by our group) (1). However, it should be noted that 77.8% of patients with migrainous cerebral infarction in the present study were 45-year-old-or younger.

Evidence from large epidemiological studies suggests that migraine with aura is a risk factor for stroke, mainly in young women with hypertension, and in women using oral contraceptives or who were heavy smokers (20 or more cigarettes per day) (21, 30). Although the absolute risk of stroke remains low, young migranious women should be firmly

advised not to smoke and if they use oral contraceptives as well as to choose pills with low oestrogen content.

We concluded that migraine may, in rare cases, cause mild ischaemic cerebrovascular deficits with a relatively benign prognosis. Patients with migraine cerebral infarction present some different clinical features from other ischaemic strokes of unusual cause.

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