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Malignant Middle Cerebral Artery Infarction: A Clinical Study of 32 Patients

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ABSTRACT

Background and Objective: Malignant middle cerebral artery infarction is a devastating type of ischemic stroke whose clinical predictors remain scarcely known. The present study aims to improve the knowledge about the prognosis factors through an analysis of a malignant middle cerebral artery infarction sample of patients from our stroke registry. **Material and Methods**: From a total of 1,396 patients with ischemic stroke in the middle cerebral artery included in the "Sagrat Cor Hospital of Barcelona Stroke Registry", we identified 32 patients with malignant middle cerebral artery infarction (2.3%). Demographic, anamnestic, clinical, and outcome variables in this subgroup of patients were compared with those of the middle cerebral artery. The independent predictive value of each variable on the development of malignant middle cerebral artery infarction was assessed with a logistic regression analysis. **Results**: The mean age was 74.7 (SD, 11.4) years and 50% were males. In-hospital death was observed in eight patients (25%) and early bad prognosis (in-hospital death or severe residual focality at discharge) was present in 16 patients (50%). Decreased consciousness (OR: 4.17; 95% CI: 2.02-8.61), presence of nausea or vomiting (OR: 3.65; 95% CI: 1.40-8.49), and heavy smoking (> 20 cigarettes/day; OR: 2.62; 95% CI: 1.03-6.64) appeared to be independent prognostic factors for malignant middle cerebral artery infarction in the multivariate analysis. **Conclusions**: Malignant middle cerebral artery infarction is an infrequent clinical condition associated with poor prognosis and high mortality rate. In our sample, decreased consciousness, nausea or vomiting, and heavy smoking are the main clinical factors associated. (REV INVEST CLIN. 2015;67:64-70)
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INTRODUCTION

Malignant middle cerebral artery (MCA) infarction is a form of hemispheric ischemic stroke that takes a severe course, being characterized by the large size of the ischemic lesion, which involves more than 50% of the area of the MCA territory and usually extends into adjacent vascular territories[1]. Malignant MCA infarction causes a mass effect on brain midline structures because of the associated cytotoxic edema, and

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usually has a devastating clinical course with a high rate of early death, which varies from 25 to 80% depending on the cohort, and a high incidence of severe neurological sequelae in patients who survive[1-4].

Malignant MCA infarction is a well-described clinical entity, but there are aspects of its natural history that remain poorly understood. Medical treatment is unsatisfactory since administration of intravenous tissue plasminogen activator is not effective and the effectiveness of intra-arterial or mechanical thrombolysis is doubtful, although the benefits of hemicraniectomy have been demonstrated and mild hypothermia is postulated to exert neuroprotective benefits[5-7].

There is widespread consensus among experts that improvements in the knowledge of clinical and neuroimaging predictors associated with malignant MCA infarction are necessary in order to identify it quickly and thus be able to offer patients an individualized treatment regimen early on.

The purpose of this study is twofold. The first is to analyze demographic, clinical, and prognostic variables associated with the natural history of malignant MCA infarction. Secondly, to identify, analyze, and assess the existence of a profile of early clinical predictors of progression to malignancy in MCA infarction. To this end, we analyzed a cohort of 32 patients with malignant MCA infarction, taken from a prospective hospital-based stroke registry, after being identified from among 1,396 patients with MCA territory infarction, who in turn were identified from a total of 3,808 stroke patients who were consecutively treated over a period of 19 years.

PATIENTS AND METHODS

We present a clinical study of the analysis of 3,808 consecutive patients admitted to the Division of Neurology at the Hospital Universitari Sagrat Cor in Barcelona over a period of 19 years from 1986 to 2004 (both inclusive) and who were included in the hospital's cerebrovascular diseases registry. This registry was recently published and validated. The database consists of 161 data sets for each patient relating to demographics, risk factors, clinical data, neuroimaging, complementary examinations, topographic diagnosis of the brain parenchyma, cerebrovascular, nosological and etiological data, information about clinical course and prognosis, and focal neurologic deficits on discharge from hospital[8].

Stroke subtypes are classified according to the guidelines of the Cerebrovascular Disease Study Group of the Spanish Society of Neurology and Cerebrovascular Disease Study Group of the Catalan Society of Neurology and have been used by our group in other studies[8,9], i.e. transient ischemic attacks (n = 612; 16%), cerebral infarction (n = 2,703; 71%), intracerebral hemorrhage (n = 407; 10.50%), subarachnoid hemorrhage (n = 47; 1.25%), spontaneous subdural hematoma (n = 38; 1.20%), and spontaneous epidural hematoma (n = 1; 0.05%). Subtypes of cerebral infarction include: atherothrombotic strokes (n = 770; 28.20%), cardioembolic strokes (n = 763; 28.20%), lacunar strokes (n = 733; 27.10%), essential strokes (n = 323; 12%), and strokes of unusual etiology (n = 114; 4.50%).

The definitions of cerebrovascular risk factors: abuse of alcohol (daily intake greater than 80 g/day), smoking (more than 20 cigarettes/day), clinical symptoms, and clinical course are the same as those used by our group in previous studies[8-10].

To fulfill the objectives of our study, we began by analyzing the cohort of 2,703 patients in the registry who had had a cerebral infarction. Neuroimaging techniques were used with regard to the location of the stroke in the brain to identify those patients with a MCA territory infarction (n = 1,396). Finally, 32 patients with a "malignant stroke" of the MCA (malignant MCA infarction) were selected for the study. Malignant MCA infarctions were classified according to criteria described by Hacke, et al.[1], i.e. extensive hemispheric ischemic strokes involving the entire vascular territory of the MCA (or most of it), often extending into adjacent vascular territories (anterior cerebral artery, posterior cerebral artery, or anterior choroid artery), and evidence of mass effect on neuroimaging prompted by brain edema. All of the patients were admitted within 48 hours of the onset of symptoms (18 within the first 12 hours and 30 within the first 24 hours). Demographic characteristics, cerebrovascular risk factors, medical history, and general clinical and neurological symptoms were recorded. All patients underwent the following complementary examinations: blood and biochemistry tests, basic

hemostasis test, electrocardiogram, chest x-ray, Doppler ultrasound of supra-aortic trunks and computed tomography (CT) scan or magnetic resonance imaging (MRI) of the brain. In a few cases, transthoracic echocardiography, magnetic resonance angiography, 24-hour Holter monitoring, and an electroencephalogram were performed. None of the patients in the sample received thrombolysis as this type of treatment was only approved for use in our hospital in 2006 when we participated in the SITS-MOST European clinical trial[8,9].

The in-hospital mortality rate and causes of death were analyzed. Following the criteria used in previous studies[8-10], cause of death was considered to be neurological (brain herniation or recurrent cerebral event), non-neurological (due to infectious, cardiac, vascular, urinary, or respiratory complications), or of unknown cause. The level of functional disability of all of the patients was quantified using the modified Rankin scale at the time of discharge from hospital or at 30 days of admission to hospital.

The clinical characteristics of patients with malignant MCA infarction were compared to those of patients with MCA stroke.

The study was approved by our hospital's Ethics Committee.

Statistical analysis

Univariate analysis of variables related to malignant MCA infarction was performed using Student's *t* test for continuous variables and the Chi-square test (with Yates' correction where necessary) for categorical variables. Median length of hospital stay was compared using the Mann-Whitney U test. The level of statistical significance was set at $p < 0.05$. The variables were subjected to multivariate analysis using a stepwise logistic-regression procedure when $p < 0.10$ in the univariate analysis. The predictive value of each variable for malignant MCA infarction was then analyzed using a predictive model based on demographic data, medical history, and clinical data, with a total of seven variables. Presence or absence of malignant MCA infarction was the dependent variable in the predictive model. The level of statistical significance required to remain included in the model was set at 0.15. SPSS/PC+ and BMDP software were used to perform statistical analysis.

RESULTS

The 32 patients in the study group with malignant MCA infarction made up 2.3% of the total of MCA strokes in the registry; 16 patients (50%) were male and mean age was 74.7 (SD: 11.4) years. Six patients (18.8%) were older than 85 years and one patient (3.1%) was under 50 years of age. The main risk factors for stroke were hypertension (53.1%), atrial fibrillation (40.6%), diabetes mellitus (28.1%), ischemic heart disease (21.9%), a history of cerebrovascular disease (21 9%), and smoking (18.8%). Twenty-six patients (81%) presented with hemiparesis, 17 (53.1%) with decreased levels of consciousness, 17 (53.1%) with language deficits (aphasia or dysarthria), 15 (46.9%) with sensory deficits, 11 (34.4%) with homonymous hemianopia, six (18.8%) with nausea or vomiting (18.8%), and three (9.4%) with early seizures (within the first 48 hours after onset of symptoms). Median NIHSS (National Institutes of Health Stroke Scale) score[8-10] on admission for the last 12 patients in the sample was 21. The main etiological subtypes were cardioembolism (43.8%) and atherothrombosis (37.5%).

None of the patients received intravenous or intra-arterial reperfusion therapy. Six patients (19%) received anticoagulation therapy at therapeutic doses and 24 (75%) patients received antiplatelet therapy. Anticoagulation with heparin in prophylactic doses was prescribed for 26 patients (81%). Decompressive craniectomy was performed in one patient (3.1%).

Eight patients died during hospitalization (25%). The causes of death were brain herniation in six patients and sudden death in one patient. In one case the cause of death was unknown.

Eight patients (25%) had a modified Rankin scale score of 5, which indicates severe functional disability, and the remaining 16 patients (50%) had a score of 4, indicative of moderately severe functional disability. Hence, half of the patients in the sample (n = 16) had poor early clinical outcomes (death or severe functional disability on discharge from hospital).

At the time of discharge, when patients in the group with malignant MCA infarction (n = 32) were compared to patients with MCA stroke (n = 1,364), those with malignant MCA infarction presented with higher rates of smoking, early seizures, nausea or vomiting,

decreased levels of consciousness, and homonymous hemianopia, in addition to a significantly higher presence of neurological complications and poor clinical outcome in comparison to patients with MCA stroke (Table 1). In-hospital mortality in the malignant MCA infarction group (25%) was also significantly higher than mortality among the 51 patients with anterior cerebral artery stroke (7.8%; p = 0.034) and the 232 patients with posterior cerebral artery stroke (3.9%; p = 0.01) in the hospital's stroke registry.

In the multivariate analysis, three significant variables were identified as independent predictive markers associated with malignant MCA infarction (Table 2). These were: decreased levels of consciousness (OR: 4.17; 95% CI: 2.02-8.61), presence of nausea or vomiting (OR: 3.65; 95% CI: 1.40-8.49) and smoking (OR: 2.63; 95% CI: 1.03-6.64).

DISCUSSION

Stroke is a common and serious disease in our community, with a sex-specific cumulative incidence rate per 100,000 population per year in adults over the age of 24 of 218 in men and 127 in women[11]. Our study population suffers from selection bias due to the characteristics of the hospital itself, as it is predominantly made up of stroke patients who are elderly[12].

Malignant MCA infarctions are not frequent in our patient population, constituting only 2.3% of all MCA strokes. This coincides with what has been reported by other authors[13] who consider that this type of stroke represents less than 10% of supratentorial ischemic strokes.

The poor prognosis of malignant MCA infarction is reflected in the high in-hospital mortality rate, which was 25% in our cohort, similar to the 28% mortality rate in a recent case series reported by Walcott, et al.[14], and the poor prognostic outcomes since 50% of patients die or present with severe functional disability. The MCA infarctions are usually caused by thrombotic or embolic occlusion of a large artery, generally involving the distal portion of the internal carotid artery or the sphenoidal segment of the MCA (M1), locations where recanalization is rarely achieved, whether spontaneously or after administration of intravenous tissue plasminogen activator within the therapeutic window of 4.5 hours from the onset of the symptoms[1]. Likewise, the distinctive pathophysiological substrate associated with malignant MCA infarction is cerebral edema causing mass effect, compression, distortion, and herniation of brain structures that lead to neurological deterioration and death due to the compression of vital centers in the brainstem, as was observed in 75% of the deceased patients in our cohort, similar to the 78% death rate that was observed by Hacke, et al[1]. This is why this type of stroke is referred to by the term "malignant", as it has a high rate of morbidity and mortality despite following recommendations for best medical treatment[1,5].

Because of this poor prognosis, an effort has been made recently to help identify clinical parameters that may predict progression to malignant infarction of the MCA. However, there is still little experience in this regard.

In our cohort, early impairment of consciousness (OR: 4.17) may be the clinical parameter that was found to have the greatest predictive power, similar to observations made by Wartenberg[15], who also associated it with significant early focal neurologic deficits quantified by a high score on the NIHSS scale in the first six hours from the onset of clinical symptoms, with scores equal to or greater than 20 if the dominant cerebral hemisphere was involved, and equal to or greater than 15 if the non-dominant cerebral hemisphere was affected. Involvement of the reticular activating system that is located in the brainstem tegmentum and that would be affected by the compression caused by cerebral edema may be the reason for the depressed level of awareness.

The presence of early nausea or vomiting (OR: 3.65) is another clinical predictor of malignant brain edema, similar to that observed by Treadwell, et al.[16] The vomiting center in the brain is a structure that is located in the medulla oblongata and in the event of brain herniation, its involvement would activate the neurovegetative symptoms that characterize autonomic dysfunction.

Although other clinical factors associated with malignant MCA infarction, such as pupil asymmetry, fever, heart failure, hypertension, and age, have been described in the literature[14-17], smoking status (OR: 2.62) has not been identified as one previously and, as we found in our study, may be a new predictor of malignant brain edema.

Table 1. Results of the univariate comparative analysis between patients with malignant middle cerebral artery infarction and patients with middle cerebral artery stroke

Variable, number (%)	Malignant MCA infarction (n = 32)	MCA stroke (n = 1,364)	p value
Demographic and clinical data			
– Gender, male	16 (50)	639 (46.8)	0.430
– Mean age, (years, SD)	74.7 (DE =11.4)	75.9 (DE = 11.5)	0.543
– Age ≥ 85 years	6 (18.8)	303 (22.2)	0.415
– Hypertension	17 (53.1)	775 (56.8)	0.404
– Diabetes	9 (28.1)	303 (22.2)	0.273
– Valvular heart disease	3 (9.4)	95 (7.0)	0.393
– Ischemic heart disease	7 (21.9)	224 (16.4)	0.270
– Atrial fibrillation	13 (40.6)	462 (33.9)	0.268
– Heart failure	2 (6.3)	89 (6.5)	0.653
– TIA	4 (12.5)	153 (11.2)	0.493
– Prior CVD	7 (21.9)	289 (21.2)	0.925
– COPD	2 (6.3)	115 (8.4)	0.489
– Intermittent claudication	3 (9.4)	103 (7.6)	0,444
– Alcohol abuse (> 80 gr/day)	1 (3.1)	39 (2.9)	0.610
– Anticoagulants	2 (6.3)	41 (3.0)	0.259
– Smoking (> 20 cig/day)	6 (18.8)	134 (9.8)	0.093
– Dyslipidemia	5 (15.6)	228 (16.7)	0.551
– Sudden onset	16 (50.0)	727 (53.3)	0.423
– Headache	3 (9.4)	123 (9.0)	0.563
– Early seizures	3 (9.4)	26 (1.9)	0.027
– Nausea. vomiting	6 (18.8)	63 (4.6)	0.004
– Decrease in consciousness	17 (53.1)	280 (20.5)	0.000
– Hemiparesis	26 (81.3)	1,153 (84.5)	0.378
– Sensory deficits	15 (46.9)	559 (41.0)	0.310
– Hemianopia	11 (34.4)	266 (19.5)	0.037
– Language deficits	17 (53.1)	820 (60.1)	0.267
– Ataxia	0	34 (2.5)	0.450
– Cranial nerve palsies	1 (3.1)	24 (1.8)	0.443
Subtypes of cerebral infarction†		0.230	
– Cardioembolic	14 (43.8)	483 (35.4)	
– Atherothrombotic	12 (37.5)	401 (29.4)	
– Essential	4 (12.5)	426 (31.3)	
– Unusual	2 (6.3)	54 (4.0)	
Prognosis			
– Neurological complications	10 (31.3)	158 (11.6)	0.003
– Respiratory complications	5 (15.6)	176 (12.9)	0.402
– Urinary tract infections	2 (6.3)	158 (11.6)	0.270
– Cardiac complications	1 (3.1)	79 (5.8)	0.443
– Vascular complications	0	26 (1.9)	0.544
– Infectious complications	4 (12.5)	238 (17.4)	0.325
– Rankin 5 (severe disability)	8 (25.0)	201 (14.7)	0.108
– In-hospital mortality	8 (25.0)	236 (17.3)	0.257
– Poor outcome#	16 (50.0)	437 (32%)	0.032
– Hospital stay, median* (interquartile range)	14 (8-23)	13 (9-23)	0.637

*Mann-Whitney U test; †Chi-square with Bonferroni correction; #Death or severe disability.
MCA: middle cerebral artery; SD: standard deviation; TIA: transient ischemic attack; CVD: cerebrovascular disease; COPD: chronic obstructive pulmonary arteries disease.

Table 2. Clinical variables associated with malignant hemispheric infarction of the middle cerebral artery

Variables*	β	SE (β)	Odds ratio (95% CI)	p
Alteration in level of consciousness	1.428	0.370	4.17 (2.02-8.61)	0.000
Nausea/vomiting	1.295	0.487	3.65 (1.40-8.49)	0.008
Smoking (> 20 cig/day)	0.962	0.475	2.62 (1.03-6-64)	0.043

*β = –4.528; SE (β) = 0.289; goodness of fit chi-square = 0.993; *df* = 1; p = 0.319.
Area under the ROC curve = 0.691. Sensitivity 62.5%, specificity 68.1%, PPV = 4.4%, NPV = 98.7% and correctly classified = 67.9%.
df = degrees of freedom; PPV: positive predictive value; NPV: negative predictive value.

It is possible that the damaging effects of smoking, which mainly affect large caliber vessels (such as the internal carotid artery or the MCA), unlike other risk factors for stroke such as hypertension or diabetes, which are more likely to involve cerebral arterioles or perforating arterial vessels[9,18], may explain this eventuality and alert the clinician to the need for further improvement of health education and awareness about the hazards of tobacco use.

Apart from the large size of the lesions in malignant MCA infarction, whose early visualization through the use of neuroimaging techniques is a predictor for the development of malignant edema[14,15], their poor prognosis may also be related to the fact that recanalization is often not effective and that use of intra-arterial thrombolysis and modern endovascular embolectomy techniques has not been definitively established in randomized controlled trials[5]. Corticosteroids are not indicated for treatment of ischemic edema[5,19]. At the moment, moderate hypothermia, which is being evaluated in ongoing clinical trials, and surgical decompression, in the form of decompressive craniectomy within 48 hours of the onset of symptoms, to increase the volume of the cranial cavity and allow for expansion of the edematous brain, thus avoiding compression of the brainstem by reducing intracranial pressure, increasing cerebral blood flow and tissue oxygenation[19-26], are being pursued as potential therapeutic options. At present, we can point out that there is a high level of evidence regarding the effectiveness of decompressive craniectomy, which should be recommended at an early stage for patients with malignant MCA infarction who are under the age of 65.

Finally, we may attribute the lower in-hospital mortality rate of the study sample in comparison to other cohorts to the advanced age of the patients (mean age 74.7 years). We can speculate that cerebral atrophy, which is a common biological feature in the elderly, may partially mitigate the harmful effects of increased intracranial pressure and subsequent brain herniation[27], as can be observed in the natural course of spontaneous or post-traumatic subdural hematomas when they present in elderly patients.

To conclude, malignant MCA infarctions are unusual but very serious. Smoking, a decrease in the level of consciousness, and the presence of nausea and vomiting are the main clinical data in the early stages of their onset and development.

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