Abstract

Background: To determine clinical factors of spontaneous early neurological deterioration (END) and prognosis in a cohort of 480 consecutive patients with cardioembolic stroke (CS) without thrombolytic therapy hospitalized within 24 hours of the onset of symptoms.

Methods: END was defined as a drop of ≥1 point in the Canadian Stroke Scale or ≥2 points in the Glasgow Coma Scale between admission and after 72 hours. All patients underwent computerized tomography and/or MRI examination.

Results: END is present in 8.3% of CS patients. CS patients with END (n = 40) in comparison with patients without ND (n = 440) showed a worse early prognosis with statistically significant differences in absence of neurological deficit at hospital discharge (5% versus 17.3%), length of hospitalization (30.8 versus 18.5 days) and in-hospital mortality (47.5% versus 8.4%). In the multivariate analysis, early seizures, severe headache and hypertension were independent clinical predictors of END.

Conclusions: In patients with CS, early seizures, severe headache and hypertension are clinical variables associated with END. CS with END constitutes a subgroup of patients with severe prognosis. Because most causes of worsening can be treated effectively, the deteriorating cardioembolic stroke patient merits a swift and incisive diagnostic and therapeutic approach.

Keywords: Cerebrovascular disease; Headache; Cardioembolic stroke; Early neurological deterioration; Early seizures; Hypertension; Prognosis

Introduction

Cardioembolic ischemic stroke accounts for one quarter of all cerebral infarcts [1]. Cardioembolic ischemic stroke is the most severe ischemic stroke subtype, with a low frequency of absence of neurological dysfunction at hospital discharge and a non-negligible risk of early embolic recurrence (1-10%) [1-4]. Cardioembolic stroke is also the stroke subtype with the highest in-hospital mortality (6-27%) [1, 2-4]. Cardioembolic stroke is a homogeneous subtype of ischaemic stroke characterized by sudden onset of neurological deficit [1]. Patients with acute ischemic stroke of cardioembolic origin show maximal neurological at stroke onset or within a few minutes after the onset of symptoms, which is contrast with patients suffering from atherothrombotic stroke or lacunar infarction (LI) in which neurological dysfunction is progressively established in the course of several hours. Progression was most frequent in patients with LI (37%) and large-artery occlusive disease (33%) and least frequent in patients with embolism (7%) [5].

Spontaneous early neurological deterioration (END) has been reported in 12 to 43% of patients with acute ischaemic stroke and is associated with an unfavourable outcome, with increased morbidity and mortality [6-9]. However, there is little data on END when patients are individualized by the different subtypes of ischaemic stroke. Therefore, progressing or deteriorating stroke is uncommon in cardioembolic stroke and clinical factors and prognosis associated with early neurological deterioration in this stroke subtype have been scarcely assessed. The objective of this study was to identify prognosis and clinical variables associated with cardioembolic stroke patients associated with spontaneous early neurological deterioration.
Materials and Methods

Since January 1986 an ongoing hospital-based stroke registry has been established at the Hospital of Sagrat Cor (an acute-care 350-bed teaching hospital in the city of Barcelona), so that data of all first-ever stroke patients admitted consecutively to the Department of Neurology of the hospital are collected prospectively in the stroke registry [10]. Data from all patients are entered following a standardized protocol with 186 items regarding demographic features, risk factors, clinical findings, laboratory and neuroimaging data, complications, and outcome. The use of the same protocol for all patients ensures completeness of the information in the database. Subtypes of stroke were classified according to the Cerebrovascular Study Group of the Spanish Society of Neurology [11], which is similar to the National Institute of Neurological Disorders and Stroke Classification [12]. Definitions of cardiovascular risk factors and stroke subtype were those used by our group in previous studies [10, 11, 13].

For the purpose of this hospital-based prospective study, the cohort of 669 patients with cardioembolic infarction included in the stroke registry up to December 2002, the particular time at which data of 3420 patients had been entered in the database was selected. The remaining patients with transient ischaemic attack (TIA), ischaemic stroke (atherothrombotic infarction, lacunar infarction, infarction of unusual cause, infarction of undetermined cause), intracerebral haemorrhage, subarachnoid haemorrhage, and spontaneous subdural hematoma were excluded.

As in previous studies, to classify a patient as having cardioembolic infarction [10, 13, 14] the following was required: presence of a medium-sized (maximal diameter of the lesion, 1.5 to 3 cm) or large (> 3 cm) cerebral infarction; stroke onset of non-lacunar syndrome during ordinary daily activities; duration of neurological deficit > 24 hours; and identification of a commonly accepted cardiac source of embolus in the absence of stenosis > 50% in the ipsilateral supra-aortic trunks.

On admission, demographic characteristics, salient features of clinical history and neurologic examination, results of routine laboratory tests, chest radiography, and twelve-lead electrocardiography were recorded. In all patients, brain CT scans were performed within the first week of hospital admission. Patients with negative results had a second CT examination to exclude the concomitant presence of subarachnoid haemorrhage, arterial dissection, central venous thrombosis, or Horton’s temporal (giant cell) arteritis.

Early epileptic seizures were defined as those starting at the beginning or within 48 hours of the cerebrovascular event in a patient without history of seizures. Limb-shaking TIA, transient hemiballism/hemichorea, decerebrate fits and convulsive-like movements (in brainstem stroke) were ex-
Seizures were classified following the recommendation of the International League Against Epilepsy [19].

In the acute phase, the stroke patients were managed in accordance with recommendations of the Cerebrovascular Study Group of the Spanish Society of Neurology [20]. Main strategies were as follows: (a) maintenance of blood pressure without the use of hypotensive drugs unless the systolic blood pressure was ≥ 220 mm Hg or the diastolic blood pressure ≥ 120 mm Hg; (b) early treatment of hyperglycemia avoiding the use of glucose infusion; (c) prevention of pulmonary thromboembolism with low-dose heparin; (d) early anticoagulation therapy except when antiplatelet was recommended, and (e) physical and respiratory therapy was performed during the patient’s stay in hospital. No patient received thrombolytic therapy because such treatment was not allowed in our hospital until 2006.

Prior to conducting the study, approval was obtained from the Ethical Committee on Clinical Research of the hospital.

### Statistical analysis

Demographic characteristics, clinical events, and outcome of patients with cardioembolic infarction with END were compared with patients without END. In the univariate analyses, continuous variables were analyzed with the Student’s t-test and categorical variables with the chi-square ($\chi^2$) test (with Yate’s correction when necessary). Statistical significance was set at $P < 0.05$. Variables related to cardioembolic stroke with END in the univariate analysis plus age and sex were studied in a multiple linear regression model. Age was used as a continuous variable with a constant odds ratio (OR) for each year. The predictive model was based on demographic, vascular risk factors and clinical data. Cardioembolic infarc-
tion with END, coded as absence = 0, presence = 1, was the dependent variable. The level of significance was set as 0.15, and the tolerance level at 0.0001. The maximum likelihood approach was used to estimate weights of the logistic parameters. Odds ratio and 95% confidence interval (CI) were calculated from the beta coefficients and standard errors. The hypothesis that the logistic model adequately fitted the data was tested by means of the goodness of fit \( \chi^2 \) test. The SPSS-PC+ and the BMDP computer programmes were used for statistical analyses.

**Discussion**

Cardioembolic stroke is a subtype of cerebral infarction in which maximal neurological deficit usually occurs suddenly at the onset of stroke in contrast to atherothrombotic stroke, lacunar infarction or infarction of unknown cause where neurological deficit generally progresses over the first hours after stroke onset [2, 21]. In the present series, END was observed in 8.3% of patients. In accordance with data from patients with cerebral infarction in general showing that early neurological worsening is associated with poor prognosis, our patients with END compared with the group of patients without END showed higher in-hospital mortality rate (47.5% versus 8.4%), lower percentage of symptom-free patients at hospital discharge (5% versus 17.3%) and longer hospital stay (30.8 versus 18.5 days).

Many different causes are likely to contribute to the progressive deterioration of ischaemic stroke: 1) neurologic deterioration (gradual or stepwise progression of neurologic focal deficits while the patient usually remains alert and free of medical complications); 2) brain edema (a complication of mostly large strokes, especially hemorrhages that are accompanied by decreased consciousness); and 3) systemic medical complications, especially infection and fever which may also lead to increased brain ischemia. Other medical complications include, high serum glucose levels, changes in blood pressure, thrombus propagation, seizures, low collateral blood flow, cerebral hemodynamic reserve impairment and neuroexcitotoxicity [5-8, 22, 23].

Interestingly, the multivariate analysis showed in our study the presence of three independent clinical variables associated with END, including early seizures (OR = 5.69), severe headache (OR = 2.95) and hypertension (OR = 2.04). Early epileptiform activity has a deleterious effect on infarcted areas, perhaps by an anoxic event, and contributes to secondary brain damage, which may favour the presence of END. Early seizures occurred in the temporal window where a penumbra of potentially salvageable brain tissue is believed to exist and this may determine a greater area of definite cerebral infarction, which in turn would be associated with a poorer clinical course [24-26]. The SASS inves-

<table>
<thead>
<tr>
<th>Variable</th>
<th>( \beta )</th>
<th>SE (( \beta ))</th>
<th>Odds ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early seizures</td>
<td>1.738</td>
<td>0.741</td>
<td>5.69 (1.33-24.29)</td>
<td>0.019</td>
</tr>
<tr>
<td>Severe headache</td>
<td>1.081</td>
<td>0.463</td>
<td>2.95 (1.19-7.30)</td>
<td>0.020</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.715</td>
<td>0.356</td>
<td>2.04 (1.02-4.11)</td>
<td>0.044</td>
</tr>
</tbody>
</table>

\( \beta = -3.004, SE (\beta) = 0.297, \text{ goodness-of-fit } \chi^2 = 0.024, \text{ d.f. } = 1, P = 0.876. \text{ Area under the ROC curve } = 0.649, \text{ sensitivity 75\%, specificity 48\%, positive predictive value 12\%, negative predictive value 95\%, correct classification 50\%.} \)
tigators found higher mortality rates among stroke patients with seizures after 30 days and 1 year [27]. Those with post-ischaemic seizures also had a significantly poorer neurological score during the acute hospitalization and worse Rankin scores at follow-up (median 9 months). These data would coincide, in part, with the present findings in which the poorer outcome of patients with early seizures would be mediated by a higher probability of END.

The presence of severe headache at the onset of cardioembolic stroke occurred in 17.5% of patients with END compared with 7% in patient with non-END (P = 0.029). Moreover, severe headache was an early clinical marker significantly associated with END in the logistic regression analysis (OR = 2.95). In a previous study by our group [28], the incidence of headache in cardioembolic stroke was 39% (severe-incapacitating 11% and mild-moderate intensity in 28%), which is similar to the frequency reported in other studies [29, 30]. As far as we are aware, this is the first study showing an association between severe headache at stroke onset and END in patients with cardioembolic infarction. The association between headache and neurologic impairment may be in part the result of the effect of brain edema and/or the effect of excitatory neurotransmitters. Leira et al [30] suggested that headache at stroke onset of ischaemic stroke is an independent predictor of neurological worsening and hypothesized that headache might be a surrogate marker of the molecular mechanisms involved in neurological worsening after acute stroke. CSF concentrations of glutamate, interleukin-6 and nitric oxide metabolites were significantly greater in patients with progressive stroke and these biochemical markers were also significantly higher in patients with headache than in those without headache, as well as associated with the presence of early signs of cerebral ischaemia in brain CT studies [23, 30, 31].

On the other hand, and in agreement with other studies [8, 23], history of arterial hypertension is related to END. Severe hypertension may promote early brain edema and increased risk of haemorrhagic transformation [8, 9].

The characteristics of the patients included in the present study are not influenced by thrombolitic treatment [32] because thrombolysis was introduced as standard treatment in our hospital in 2006. Our study therefore allows a better understanding of the natural history of a subgroup of patients with cardioembolic stroke and severe early outcome.

In summary, cardioembolic stroke with END is a subgroup of patients with high early death and severe prognosis. Early seizures, severe or incapacitating headache at the onset of cardioembolic stroke and arterial hypertension adversely affects outcome in acute cardioembolic ischemic stroke and are clinical factors associated with END. Because most causes of worsening can be treated effectively, the predictive clinical factors of deteriorating cardioembolic stroke merits a swift and incisive diagnostic and therapeutic approach.

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Conflict of Interest

No conflict of interest.

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References

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