Ischemic stroke in patients with intermittent claudication: a clinical study of 142 cases

Adrià Arboix, Marc Tarruella, Lluís García-Eroles, Montserrat Oliveres, Carles Miquel, Miquel Balcells and Cecilia Targa

Abstract: The clinical features, risk factors, neuroimaging findings, and outcome of acute ischemic stroke were assessed in patients with intermittent claudication. Data from 142 patients with ischemic stroke and intermittent claudication were collected from a prospective hospital-based stroke registry in which 2500 consecutive acute stroke patients attended over a 12-year period. Ischemic stroke in patients with intermittent claudication accounted for 7.7% of all ischemic strokes (n = 1840). Ischemic stroke with and without intermittent claudication showed a similar in-hospital mortality rate (16% vs 14%) and absence of functional limitation at hospital discharge (20.5% vs 18.5%). Ischemic stroke patients with intermittent claudication showed a significantly shorter length of stay than patients without symptomatic peripheral arterial disease (14.6 vs 18.8 days, p < 0.05). Ischemic heart disease, transient ischemic attack (TIA), renal dysfunction, and watershed infarct were significant independent predictors of ischemic stroke in patients with intermittent claudication. Although cerebral infarction in patients with intermittent claudication showed a clinical profile suggestive of poor outcome, the prognosis was similar to that of ischemic stroke without intermittent claudication.

Key words: arterial occlusive diseases; brain infarction; cerebrovascular accident; intermittent claudication; ischemic stroke

Introduction

Studies assessing ischemic stroke in symptomatic atherosclerosis peripheral artery disease or intermittent claudication have been relatively small. Intermittent claudication is not only a symptom of leg artery occlusive disease, but also an indicator of generalized atherosclerosis and is associated with a greatly increased cardiovascular and cerebrovascular morbidity and mortality rate. Patients with intermittent claudication have a high risk of death from premature ischemic heart disease and stroke.

However, little is known about the clinical features, risk factor profiles, and prognosis of cerebral infarction in patients with intermittent claudication. On the other hand, it seems plausible to consider that this subset of patients may present, (a) a risk factor profile and clinical features different from those of the remaining patients with cerebral infarct and (b) a poor early outcome compared with ischemic stroke patients without symptomatic peripheral arterial disease. In order to confirm these hypotheses, we assessed clinical features, risk factors, neuroimaging findings, and outcome of acute ischemic stroke in patients with intermittent claudication collected from a prospective hospital-based stroke registry. A comparison was made with the remaining patients with ischemic stroke without symptomatic peripheral arterial disease.

Methods

Between January 1986 and December 1995, data from 2500 acute stroke patients admitted consecutively to the Department of Neurology of the Sagrat Cor Hospital (an acute-care 350-bed teaching hospital in the city of Barcelona, Spain) were collected prospectively in a stroke registry. Patients with transient ischemic attack (TIA) (n = 328), intracerebral hemorrhage (n = 270), subarachnoid hemorrhage (n = 35), and spontaneous subdural hematoma (n = 27) were excluded. The study population consisted of 1840 patients with acute ischemic stroke. Subtypes of stroke were classified according to the Cerebrovascular Study Group of the Spanish Neurological Society, which is similar to the National Institute of Neurological Disorders and Stroke Classification, and are those used by our group in previous studies. Subtypes of stroke included atherothrombotic infarct (n = 553), lacunar infarction (n = 484), cardioembolic infarction (n = 468), infarction of undetermined origin (n = 248), and infarction of unusual etiology (n = 87). Definitions of cerebrovascular risk factors were those used in previous studies.

Patients included in the study had a history of intermittent claudication as defined by the WHO classification, that is, effort-induced pain which forced the patient to stop walking, but which disappeared within 10 min of rest. The presence of leg artery occlusive disease was confirmed by an ankle–brachial pressure index $\leq 0.90$. This index was calculated by dividing the ankle pressure by the brachial pressure. Patients who had undergone reconstructive vascular surgery to relieve the symptoms of intermittent claudication, or amputation, were also eligible for inclusion in the study.
For the purpose of this hospital-based prospective study, 142 patients with ischemic stroke and intermittent claudication secondary to symptomatic atherosclerotic peripheral arterial disease were selected. 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 routine laboratory tests (blood cell count, biochemical profile, serum electrolytes, urinalysis), chest radiography, and 12 lead electrocardiography were recorded. Neurological examination was performed every day after admission to the hospital. In all patients, a brain computed tomography (CT) scan was performed within the first week of hospital admission. Other investigations included magnetic resonance imaging (MRI) or angio-MRI in 22% of patients, arterial digital subtraction angiography in 16%, B-mode echocardiography in 28%, carotid duplex scan in 59%, and immunological study in 7.7%.

As in previous studies,5,8,9 demographic variables included age and sex. Anamnestic findings were dichotomized as present versus absent and included history of hypertension, diabetes, ischemic heart disease, rheumatic heart disease, congestive heart failure, atrial fibrillation, smoking habit (>20 cigarettes/day), alcohol abuse (>80 g/day), previous TIA, previous cerebral infarction, hyperlipidemia, renal dysfunction (clinically significant impaired renal function with serum creatinine concentration ≥200 µmol/l), cirrhosis or chronic liver disease, chronic obstructive pulmonary disease (COPD), and age 85 years or older. Patients were excluded if they were already receiving dialysis for chronic renal failure. Clinical variables were also dichotomized as present versus absent and 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, hemianopia, aphasia or dysarthria, ataxia, cranial nerve palsy, presence of lacunar syndrome, and cranial nerve palsy. Neuroimaging variables, also dichotomized as present versus absent, included middle cerebral artery topography, anterior cerebral artery, posterior cerebral artery, watershed cerebral infarct, and vertebral and basilar artery topography. The presence of thrombotic arterial vascular occlusion was also analyzed. Outcome variables also dichotomized as present versus absent included in-hospital mortality, absence of functional limitation at hospital discharge, and length of hospital stay.

Statistical methods
A comparative analysis of demographic characteristics, vascular risk factors, clinical variables, topography, and outcome data between ischemic stroke in patients with and without intermittent claudication was performed using the Student's t-test for continuous variables and the chi-squared (𝜒²) test (with Yate's correction when necessary) for categorical data. Statistical significance was set at 𝑝 < 0.05. Variables related to ischemic stroke in patients with intermittent claudication were studied in the univariate analysis plus age (used as a continuous variable with a constant odds ratio for each year) were studied in two logistic regression models and forward stepwise selection if 𝑝 < 0.10. The first predictive model was based on demographic variables and cardiovascular risk factors, with a total of seven variables, and the second predictive model was based on demographic variables, cardiovascular risk factors, and neuroimaging data, with a total of 10 variables. Ischemic stroke with intermittent claudication, coded as absent = 0, present = 1, was the dependent variable. The level of significance to remain in the models was 0.15. The tolerance level was established as 0.0001. The maximum likelihood approach was used to estimate weights of the logistic parameters.12 Odds ratios (OR) and 95% confidence intervals (CI) were calculated from the beta coefficients and standard errors. The hypothesis that the logistic model adequately fit the data was tested by means of the goodness of fit 𝜒² test.13 The SPSS-PC +14 and BMDP15 computer programs were used for statistical analyses.

Results
Ischemic stroke in patients with intermittent claudication accounted for 7.7% of all ischemic stroke patients (142 out of 1840). There were 96 men and 46 women with a mean (SD) age of 74.1 (9.1) years. Main vascular risk factors included hypertension that was present in 58% of patients, ischemic heart disease in 29.6%, atrial fibrillation in 29.6%, and diabetes in 27.5%. TIA prior to ischemic stroke was recorded in 18.3% of patients. Renal dysfunction was present in 5.6% of patients. Main clinical findings included limb weakness in 80.3% of patients, speech disturbances in 50.7%, and sensory symptoms in 35.9%. In relation to subtypes of stroke, atherothrombotic infarction occurred in 48.6% of patients, lacunar infarct in 27.5%, cardioembolic infarct in 20.4%, infarct of undetermined cause in 2.1%, and infarct of unusual etiology in 1.4%. The main vascular topography was the middle cerebral artery in 48.6% of cases, basilar artery in 8.5%, and cerebral posterior artery in 5.5%. Watershed infarct was observed in 4.4% of cases. A total of 23 patients died, with an in-hospital mortality rate of 16.2%. Absence of deficit at discharge was observed in only 20.5% of the patients. The mean (SD) length of stay was 14.6 (9) days.

In the comparison of ischemic stroke that occurred in patients with and without intermittent claudication (Table 1), it was found that in the group with intermittent claudication there was a higher frequency of male gender, diabetes, ischemic heart disease, previous TIA, renal dysfunction, watershed infarct, thrombotic occlusion, and atherothrombotic infarction, as well as a lower frequency of patients aged 85 years or older, cerebral posterior topography, infarction of undetermined etiology, and mean length of hospital stay. Differences regarding other stroke subtypes, including lacunar infarct, cardioembolic infarct, and infarct of unknown cause, were not found. The overall in-hospital mortality rate, the in-hospital mortality rate in patients older than 85 years of age, and the percentage of patients with absence of functional deficit at discharge were also similar. On the other hand, the mean [SD] length of stay of patients with cerebral infarction and intermittent claudication who died was not significantly different from that of patients with cerebral infarction without intermittent claudication (15.14 [11.55] days vs 18.8 [22.75] days).
In the multivariate analysis (Table 2), ischemic heart disease (OR = 2.83), watershed infarct (OR = 2.57), renal dysfunction (OR = 2.22), and previous TIA (OR = 1.76) were the only independent predictors of ischemic stroke in patients with intermittent claudication.

**Discussion**

This study shows that 7.7% of patients with ischemic stroke had symptomatic peripheral arterial disease. This percentage is similar to a prevalence of intermittent claudication of 5.6% reported by Liu et al\(^\text{16}\) and of 6.9% reported by Gracia et al\(^\text{17}\). As expected, the number of atherothrombotic strokes was higher in patients with intermittent claudication. However, this study shows that ischemic stroke patients with intermittent claudication may also suffer from other subtypes of stroke, particularly lacunar infarction and cardioembolic stroke. The present findings confirm the first hypothesis of differences in the risk factor profiles between ischemic stroke patients with and without intermittent claudication. On the other hand, in the multivariate analysis, three clinical variables (previous TIA, ischemic heart disease, and renal dysfunction) and one neuroimaging variable (watershed infarct) were independently associated with ischemic stroke in patients with intermittent claudication.

The comparison of risk factor differences between the study of Liu et al\(^\text{16}\) and this study shows similar frequencies of hypertension (59.4% vs 57.7%), diabetes...
(23.3% vs 27.5%), and prior TIAS (17.8% vs 18.3%). However, the occurrence of hyperlipidemia is lower in our study (14.8% vs 37%), a plausible observation in accordance with the beneficial effect of the components (olive oil, fruits, vegetables) of the Mediterranean diet in our patients. Internal carotid artery disease was a risk factor in the study of Liu et al., which is consistent with atherothrombotic stroke being the most frequent stroke subtype in our study.

On the other hand, the higher occurrence of TIA in ischemic infarction with intermittent claudication may be explained by the greater occurrence of TIA in atherothrombotic stroke. In our study, the prevalence of atherothrombotic stroke in patients with intermittent claudication was significantly higher than in patients without intermittent claudication (48.6% vs 28.5%). By contrast, cerebral infarcts of undetermined etiology were more frequent in ischemic stroke patients without intermittent claudication, which is similar to that observed in the study of Liu et al. These findings are consistent with the results of a study in which the frequency of TIA associated with large ischemic infarction in the area of the middle cerebral artery (mainly due to atherothrombotic infarcts) was significantly higher than that of TIA associated with lacunar infarcts (38% vs 17.5%). Moreover, in a recent study, TIA was an independent predictor only for atherothrombotic infarction, which is in agreement with the study of Whisnant et al. in which TIA was mostly a marker of large artery disease. On the other hand, the higher frequency of ischemic heart disease in cerebral infarcts with intermittent claudication is consistent with previous observations of an increased occurrence of coronary events in claudicants. In the study of Liu et al., cardiac ischemia was significantly more frequent in stroke with intermittent claudication than in stroke without intermittent claudication.

Renal dysfunction was observed in 2.7% of our patients, which is similar to 3.2% in the study of MacWalter et al. However, the frequency of renal dysfunction in claudicants (5.6%) was significantly higher than in nonclaudicants (2.5%). Serum creatinine acts as a marker for generalized vascular disease. Renal dysfunction may represent the influence of generalized vascular disease on the kidney or seems more likely to be a marker for the severity or duration of hypertension.

The higher frequency of watershed infarcts may be explained because watershed infarcts are more common in severe stenosis or occlusion of large extracranial arteries, a fact that is more frequent in ischemic stroke in patients with intermittent claudication.

By contrast, the second hypothesis regarding a poor early outcome with ischemic stroke patients without symptomatic peripheral arterial disease was not confirmed given that the immediate prognosis of ischemic stroke patients with intermittent claudication is not worse than the outcome of patients without intermittent claudication, without statistically significant differences between both groups. Although peripheral arterial disease is rarely fatal, coronary heart disease and symptomatic peripheral arterial disease tend to be associated. The general prognosis for patients with symptomatic peripheral arterial disease is particularly negative. In the general population, symptomatic peripheral atherosclerosis is a strong predictor of cardiovascular disease and death. Survival following onset of intermittent claudication is only two-thirds of that of the general population: after 10 years, 60% died. In addition, in the study of Bowling et al., intermittent claudication, angina pectoris, advancing age, male gender, and computed tomographic evidence of any cerebral infarct especially a watershed infarct or white matter hypodensity factors that were all present and associated with ischemic stroke in patients with intermittent claudication in our study were independent risk factors for major vascular events (stroke, myocardial infarction, or vascular death) in patients with a recent TIA or minor stroke. In another study, renal dysfunction was a significant predictor of increased mortality in acute stroke patients in both the short- and long-term. In the present study, the early prognosis of patients with ischemic stroke with and without claudication was similar, with no differences in the percentages of in-hospital mortality (16% vs 14%) and absence of functional limitation at hospital discharge (20.5% vs 18.5%). In addition, patients with intermittent claudication showed a significantly shorter length of stay than those without intermittent claudication (14.6 vs 18.8 days).

It has been shown that the short duration of ischemic episodes reduces cerebral damage originating from a later persistent ischemia in experimental studies and clinical studies. In animal models of focal cerebral ischemia, a brief sublethal ischemic event (a process called ischemic preconditioning) protects tissue from subsequent more severe ischemic injury (ischemic tolerance). There is already clinical evidence to support the phenomenon of

---

**Table 2** Independent predictive value of different variables on ischemic stroke in patients with intermittent claudication.

<table>
<thead>
<tr>
<th>Logistic regression models</th>
<th>$\beta$</th>
<th>SE ($\beta$)</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic and vascular risk factors$^a$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>1.0411</td>
<td>0.1983</td>
<td>2.83 (1.92 to 4.18)</td>
</tr>
<tr>
<td>Transient ischemic attack</td>
<td>0.5643</td>
<td>0.2323</td>
<td>1.76 (1.12 to 2.77)</td>
</tr>
<tr>
<td>Demographic, vascular risk factors, and neuroimaging data$^b$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>1.1071</td>
<td>0.1995</td>
<td>2.75 (1.86 to 4.06)</td>
</tr>
<tr>
<td>Watershed infarct</td>
<td>0.9454</td>
<td>0.4707</td>
<td>2.57 (1.02 to 6.47)</td>
</tr>
<tr>
<td>Renal dysfunction</td>
<td>0.7974</td>
<td>0.4037</td>
<td>2.22 (1.01 to 4.90)</td>
</tr>
<tr>
<td>Transient ischemic attack</td>
<td>0.5629</td>
<td>0.2330</td>
<td>1.76 (1.11 to 2.77)</td>
</tr>
</tbody>
</table>

$^a\beta = -2.7801$, SE ($\beta$) = 0.1127, goodness of fit $\chi^2 = 0.0013$, df = 1, $p = 0.9715$. Area under the ROC curve = 0.606, sensitivity 76%, specificity 43.6%, correct classification 73.6%.

$^b\beta = -2.8296$, SE ($\beta$) = 0.1155, goodness of fit $\chi^2 = 0.0825$, df = 1, $p = 0.7740$. Area under the ROC curve = 0.623, sensitivity 73.3%, specificity 49.3%, correct classification 71.5%.
ischemic tolerance in the human heart. In a recent study, Moncayo et al. analysed the outcome of 2490 patients with cerebral infarction and showed that patients with previous TIAs (n = 293) had a significantly more favourable outcome than those without TIAs. In that study, after adjustment for confounding variables, TIAs lasting 10–20 min were still significantly associated with a favourable outcome. The authors conclude that ischemic tolerance may play a role in patients with TIAs before cerebral infarction, allowing a better recovery from a subsequent ischemic stroke.

In summary, although cerebral infarction in patients with intermittent claudication showed a clinical profile suggestive of poor outcome, including history of TIA, ischemic heart disease, renal dysfunction, and watershed infarction, the prognosis was similar to that of ischemic stroke without intermittent claudication.

Acknowledgements

We thank Dr O Aguado from the Department of Internal Medicine and Dr J Massons and Dr E Comes from the Department of Neurology for their valuable scientific contribution, and Marta Pulido for editing the manuscript and editorial assistance.

References