Introduction: Acute lacunar stroke in subjects under 55 years of age has been poorly characterized. Methods: We assessed the clinical features of lacunar stroke in 51 patients aged ≤55 years (84.5% men, mean standard deviation [SD] age 49.8 [5.2] years) collected from a prospective hospital-based stroke registry in Barcelona, Catalonia, Spain. Results: This subset of young lacunar stroke patients accounted for only 5.2% of all lacunar strokes, 1.2% of all ischemic strokes, and 1.1% of all acute strokes included in the registry over a 24-year period. In the multivariate analysis, factors independently associated with acute lacunar stroke in patients aged ≤55 years were alcohol consumption (>60 g/day) (odds ratio [OR] = 6.67), heavy smoking (>20 cigarettes/day) (OR = 3.02), obesity (OR = 2.81), essential etiology (OR = 2.73), and headache at stroke onset (OR = 2.45). Conclusion: Characterization of the clinical profile of acute lacunar stroke in younger patients contributes to a better knowledge of the full clinical expression of this ischemic stroke subtype.

KEYWORDS: acute cerebrovascular event • ischemic stroke • lacunar infarction • lacunar stroke • stroke registry • young adults

Acute stroke occurring in young adults is uncommon, and its etiology, risk factors and prognosis are different from stroke usually observed in elderly patients [1–3]. Lacunar stroke is an ischemic stroke subtype, which comprises around 25% of all cerebral infarctions and is a well-recognized cause of dementia of vascular origin [4–6]. Majority of patients with lacunar stroke are between the sixth and seventh decades of life [7]. There has been an increase in the ages of patients with lacunar stroke and a steady rise in the frequency of lacunar stroke in patients aged 85 years and more (very old patients) [8,9]. Also, a number of studies have assessed the influence of age in patients with acute stroke [10,11], as well as different epidemiological and clinical aspects of stroke in very old people, including poor outcome, restricted access to resources or contribution to healthcare utilization [12–16]. However, clinical features in the subset of younger patients with lacunar stroke have been poorly characterized.

Therefore, a clinical study was designed with two aims: to describe the clinical profile (including risk factors, clinical features and presentation, diagnostic workup and early outcome) of patients with acute lacunar stroke aged 55 years or younger; and to assess differences in patients with lacunar stroke according to age (≤55 vs >55 years). Data of these two cohorts of patients were collected from a hospital-based prospective stroke registry over a 24-year period.

Methods
This study included 4597 patients with acute stroke admitted consecutively to the Department of Neurology of Sagrat-Cor Hospital of Barcelona, Catalonia (Spain) between January 1986 and December 2009. Data of these patients were collected prospectively in a stroke registry, the details of which have been previously reported [17]. Criteria of the Cerebrovascular Study Group of the Spanish Society of Neurology [18] and Guidelines of the Catalan Society of Neurology [19], which are similar to the National Institute of Neurological Disorders and Stroke Classification [20], were used for the classification of stroke subtypes.

For the purpose of the present study, lacunar stroke in patients aged 18–55 years (younger patients) and in patients aged >55 years (older patients) were selected. Prior to
conducting the study, approval was obtained from the Ethical Committee of Clinical Research of the hospital.

Acute lacunar stroke was defined according to clinical and neuroimaging criteria as follows [7,9]: sudden or gradual onset of a focal neurological deficit lasting >24 h of the type described in the common lacunar syndromes (pure motor hemiparesis, pure sensory stroke, sensorimotor stroke, ataxic hemiparesis, dysarthria–clumsy hand and atypical lacunar syndromes); brain CT scans or MRI studies were either normal or demonstrated only small, localized brain lesions with diameter smaller than 20 mm, which seemed appropriate for the neurological deficits, and absence of cortical ischemia, cerebral carotid stenosis (>50% diameter) or major source for cardioembolic stroke. In cases in which the initial CT scan was unrevealing, a second CT scan was performed before the patient’s discharge from the hospital to exclude nonlacunar ischemic lesions that could have passed unnoticed on the first evaluation. Nonlacunar syndromes in patients with acute lacunar stroke were classified as atypical lacunar syndrome. Involvement of two of the following motor areas: facial, brachial or crural was needed for a diagnosis of pure motor hemiparesis.

All patients were admitted to the hospital within 48 h of the onset of symptoms. A brain computed tomography and/or MRI was performed within the first week of hospital admission. For each patient, demographic data, cardiovascular risk factors, clinical features, neuroimaging findings and early outcome were recorded. Although details of these of these variables have been reported in previous studies [9,21], the more common were alcohol abuse (history of alcohol ingestion of 60 g ethanol/day), heavy smoking (history of daily tobacco use [≥20 cigarettes/day] at least in the 2 years prior to cerebral ischemia), obesity (presence of a BMI >30 kg/m²), lacunar stroke of essential or unknown cause (presence of lacunar stroke in the absence of hypertension, diabetes or other cerebrovascular risk factors as well as in the absence of criteria of cerebral ischemic of cardioembolic origin, atherothrombotic cause or unusual etiology), lacunar stroke-related headache (presence of headache at stroke onset) [22], cardioembolic lacunar stroke (clinical manifestations compatible with a lacunar syndrome, presence of a recent subcortical infarct <20 mm of maximum lesional diameter related to the clinical syndrome, identification of an embolicogenous heart disease in the absence of hypertension and/or diabetes and exclusion of carotid and/or cerebral atherosclerosis or other causes of stroke) [23], atypical lacunar syndrome (proven radiologically absence of one of the five classical lacunar syndromes and presence of another clinical syndrome [e.g., pure dysarthria, isolated hemiataxia, hemichorea–hemibalismus, etc.] [24], and pure motor syndrome (presence of unilateral partial or complete paresis involving at least two of three areas [face, upper limb or lower limb] of the body and no evidence of aphasia, apraxia and agnosia, nor visual field defect, eye movement disturbance, ataxia, sensory loss or evidence of bilateral weakness) [25]. Causes of death were analyzed according to criteria of Silver et al. [26].

**Statistical analysis**

In the univariate analysis, the frequency of each variable in the groups of younger adults (≤55 years) versus older adults (>55 years) with lacunar stroke was compared with the analysis of variance and the chi-square ($\chi^2$) test with Yates and Bonferroni’s correction when necessary. Statistical significance was set at $p < 0.05$. Variables with a $p < 0.10$ in the univariate analysis were included in a logistic regression model and forward stepwise selection, in which lacunar stroke in younger adults was the dependent variable (coded as absent = 0, present = 1). Age was used as a continuous variable with a constant odds ratio for each year. The level of significance to remain in the model was 0.15. The tolerance level was established as 0.0001. The maximum likelihood approach was used to estimate weights of the logistic parameters. The odds ratio and 95% 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 $\chi^2$ test. The SPSS-PC+ and BMDP computer programs were used for statistical analysis.

**Results**

The study cohorts of patients with lacunar stroke included 51 patients aged ≤55 years and 813 aged >55 years. The group of young adults with lacunar stroke (≤55 years of age) accounted for 5.9% of all strokes of the lacunar type ($n = 864$), 1.2% of all ischemic strokes ($n = 4029$) and 1.1% of all acute strokes (ischemic and hemorrhagic; $n = 4597$) collected in the stroke registry over a 24-year period.

The mean (standard deviation [SD]) age was 49.8 (5.2) years (range 34–55 years), and 84.5% were men. Seven patients (13.7%) were in the age range of 34–44 years and the remaining 44 (72.3%) aged between 44 and 55 years. The most frequent cardiovascular risk factors were hypertension (62.7%), diabetes mellitus (62.7%), heavy smoking (45.1%), hyperlipidemia (33.3%), alcohol consumption (23.5%) and obesity (13.7%). The percentage of patients undergoing MRI was 62.7%, and topography of the lesion was documented in 78% of patients. In the remaining patients with unrevealing neuroimaging studies, diagnosis of lacunar stroke was made on clinical grounds. In the first week, computed tomography may have missed cortical and subcortical infarction. The most frequent topographies defined in those patients who had a visible lacunar stroke on computed tomography/MRI were the internal capsule (35.3%), the pons (17.6%), the thalamus (17.6%), the basal ganglia (3.5%), the centrum semiovale (2%) and the mesencephalon (2%).

The lacunar syndromes included pure motor hemiparesis in 18 (35.3%) patients, pure sensory stroke in 15 (29.4%), sensorimotor stroke in 7 (13.7%), dysarthria–clumsy hand in 6 (11.8%), atypical lacunar syndrome in 3 (5.9%) and ataxic hemiparesis in 2 (3.9%). In 9 (17.6%) patients without known vascular risk factors or other etiologies of cerebral ischemia, lacunar stroke was classified as idiopathic or essential.

As shown in Table 1, statistically significant differences between the younger and older lacunar stroke cohorts were
found in the percentages of male patients, heavy smoking (>20 cigarettes/day), alcohol consumption (>60 g/day), chronic liver disease and presence of headache and sensory symptoms at stroke onset, with higher percentages among patients in the younger cohort. Atrial fibrillation was only observed in the older cohort (cardioembolic lacunar stroke). The frequency of the different lacunar syndromes was similar. Also, a higher percentage of patients in the younger age group compared with the older group underwent MRI examination (62.7 vs 47.6%; p = 0.035), echocardiography (60.8 vs 47.0%; p = 0.05), arterial digital subtraction angiography (17.6 vs 2%; p = 0.001) and lumbar puncture with study of the CSF (3.9 vs 0.5%; p = 0.045). Other differences regarding in-hospital mortality, percentage of patients who were symptom-free at discharge (absence of neurological deficit), prolonged hospital stay (>12 days) and transfer to convalescence/rehabilitation units were similar. The percentage of patients with medical complications developed during hospitalization was also similar.

After multivariate analysis (Table 2), alcohol consumption, heavy smoking and obesity (BMI ≥30 kg/m²), essential etiology and presence of headache were independently associated with lacunar stroke in younger adults. Male sex was associated with young lacunar stroke. Results of the receiver operating characteristics curve are shown in Figure 1. The area under the receiver operating characteristics curve representation reinforces the clinical relevance of the multivariate model that helps to differentiate lacunar stroke in younger and older adults.

Discussion
Lacunar stroke is mainly a disease of older patients [27,28] (mean age was 75.9 years in this study). The more advanced age coincides with results reported by Asplund et al. [29], with a mean age at the time of the first stroke of 66.5 years in male and 73.2 in female patients.

In the present series, the incidence of lacunar stroke in younger adults (aged 18–55 years) was low accounting for 5.2% of all patients with lacunar strokes, as well as 1.2% of all ischemic strokes and 1.1% of all first-ever acute strokes. In the study of Rasura et al. [30], lacunar strokes in young patients (14–47 years) accounted for 2.5% of all strokes in young patients, and in the clinical series of 99 patients reported by Dharmasaroja et al. [31], small-vessel disease accounted for 29% of patients aged 41–50 years.

It is unclear whether young patients with lacunar stroke have a distinct clinical profile, with differences in vascular risk

Table 1. Comparative clinical data in the cohorts of acute lacunar stroke patients classified according to age.

<table>
<thead>
<tr>
<th>Data</th>
<th>Younger patients aged ≤55 years (n = 51)</th>
<th>Older patients aged &gt;55 years (n = 813)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, mean (SD)</td>
<td>49.8 (5.25)</td>
<td>75.9 (8.59)</td>
<td>0.001</td>
</tr>
<tr>
<td>Male, sex</td>
<td>43 (84.3)</td>
<td>445 (54.8)</td>
<td>0.001</td>
</tr>
<tr>
<td>Cardiovascular risk factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>32 (62.7)</td>
<td>586 (72.1)</td>
<td>0.152</td>
</tr>
<tr>
<td>Diabetes</td>
<td>16 (31.4)</td>
<td>243 (29.9)</td>
<td>0.823</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>4 (7.8)</td>
<td>109 (13.4)</td>
<td>0.253</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>0</td>
<td>85 (10.5)</td>
<td>0.015</td>
</tr>
<tr>
<td>Heart failure</td>
<td>1 (2.0)</td>
<td>26 (3.2)</td>
<td>0.938</td>
</tr>
<tr>
<td>Valvular heart disease</td>
<td>1 (2.0)</td>
<td>22 (2.7)</td>
<td>1</td>
</tr>
<tr>
<td>Previous TIA</td>
<td>5 (9.8)</td>
<td>80 (9.8)</td>
<td>1</td>
</tr>
<tr>
<td>Previous cerebral infarction</td>
<td>5 (9.8)</td>
<td>128 (15.7)</td>
<td>0.254</td>
</tr>
<tr>
<td>Previous cerebral hemorrhage</td>
<td>2 (3.9)</td>
<td>10 (1.2)</td>
<td>0.329</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>3 (5.9)</td>
<td>69 (8.5)</td>
<td>0.695</td>
</tr>
<tr>
<td>Obesity, BMI ≥30 kg/m²</td>
<td>7 (13.7)</td>
<td>49 (6.0)</td>
<td>0.061</td>
</tr>
<tr>
<td>Heavy smoking (&gt;20 cigarettes/day)</td>
<td>23 (45.1)</td>
<td>89 (10.9)</td>
<td>0.001</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>17 (33.3)</td>
<td>190 (23.4)</td>
<td>0.106</td>
</tr>
<tr>
<td>Intermittent claudication</td>
<td>2 (3.9)</td>
<td>65 (8.0)</td>
<td>0.432</td>
</tr>
<tr>
<td>Alcohol consumption (&gt;60 g/day)</td>
<td>12 (23.5)</td>
<td>16 (2.0)</td>
<td>0.001</td>
</tr>
<tr>
<td>Chronic liver disease</td>
<td>5 (9.8)</td>
<td>16 (2.0)</td>
<td>0.002</td>
</tr>
<tr>
<td>Symptoms at stroke onset</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>9 (17.6)</td>
<td>69 (8.5)</td>
<td>0.050</td>
</tr>
<tr>
<td>Sensory symptoms</td>
<td>23 (45.1)</td>
<td>244 (30)</td>
<td>0.024</td>
</tr>
<tr>
<td>Dysarthria</td>
<td>16 (31.4)</td>
<td>357 (43.9)</td>
<td>0.079</td>
</tr>
<tr>
<td>Symptom-free at discharge</td>
<td>12 (23.5)</td>
<td>170 (20.9)</td>
<td>0.656</td>
</tr>
<tr>
<td>In-hospital death</td>
<td>0</td>
<td>5 (0.6)</td>
<td>1</td>
</tr>
<tr>
<td>Transfer to convalescent/rehabilitation units</td>
<td>1 (2.0)</td>
<td>52 (6.4)</td>
<td>0.327</td>
</tr>
<tr>
<td>Length of stay, mean (SD)</td>
<td>10.9 (8.7)</td>
<td>11.6 (7.7)</td>
<td>0.550</td>
</tr>
<tr>
<td>Prolonged hospital stay &gt;12 days</td>
<td>15 (29.4)</td>
<td>238 (29.3)</td>
<td>0.983</td>
</tr>
</tbody>
</table>

Data as frequencies and percentages in parenthesis unless otherwise stated.
factors, clinical features and early outcome compared with elderly patients. Lacunar stroke constitutes a homogeneous subgroup of cerebral infarctions due to the small size of the lesion (maximal diameter <20 mm) and favorable functional prognosis at hospital discharge, characterized by a lower in-hospital mortality and functional deficit compared with other types of ischemic infarctions, such as those of cardioembolic or atherothrombotic cause [7,32].

In the present study, younger patients with lacunar stroke showed a different clinical profile compared with older patients, with a significantly higher frequency of alcohol consumption, heavy smoking, obesity, undetermined cause of lacunar infarction and headache at stroke onset. Female sex was the only independent clinical predictor associated with lacunar stroke in older age group. These observations are in contrast to the usual profile of cardiovascular risk factors of lacunar stroke, in general, in which hypertension and diabetes are the most common [7,27,33,34]. However, the fact that there is no difference in prevalence of hypertension and diabetes between young and old lacunar stroke patients in the present study does not mean that these risk factors do not play an important role in both young and old patients. In a study cohort (n = 3944) of patients with first-ever ischemic stroke aged 15–49 years from existing hospital- or population-based prospective or consecutive young stroke registries involving 15 cities in 12 European countries, the three most frequent risk factors were current smoking (48.7%), dyslipidemia (45.8%) and hypertension (35.9%) [35]. Therefore, primary preventive strategies for ischemic stroke in young adults – having high rate of modifiable risk factors – should be targeted according to sex and age at continental level [35]. Also, in an investigation of the epsilon4 allele of the apolipoprotein E gene, blood pressure levels and their interaction in relation to subcortical and periventricular white matter lesions in 971 participants in the Rotterdam Scan Study [36], apolipoprotein E epsilon4 carriers were at increased risk for white matter lesions if they suffered from hypertension as well.

Of note, smoking and alcohol consumption (exogenous risk factors) were independently related to lacunar stroke in younger adults, suggesting an earlier lesional predisposition of smoke and alcohol abuse to generate cerebral small-vessel disease, in comparison with arterial hypertension and diabetes that would produce an hypertensive or diabetic angiopathy (either in the form of lipohyalinosis or microatheromatosis) in the long term.

Heavy smoking and alcohol consumption were low among female patients compared with males, a similar finding reported in the study of Megherbi et al. [37]. Current smoking was the most important risk factor present in 48.7% in a relevant study referred to young adults with ischemic stroke in Europe [38]. Alcohol abuse and smoking are more frequent among male patients, as observed in this study. Obesity is another risk factor associated with lacunar stroke in younger adults as already shown in other studies [38]. Obese persons have higher levels of blood pressure, blood glucose, insulin

<table>
<thead>
<tr>
<th>Table 2. Results of the logistic regression analysis: independent predictive variables of lacunar stroke in patients ≤55 years of age.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic, vascular risk factors and clinical variables*</td>
</tr>
<tr>
<td>-------------------------------------------------------------</td>
</tr>
<tr>
<td>Alcohol consumption (&gt;80 g/day)</td>
</tr>
<tr>
<td>Heavy smoking (&gt;20 cigarettes/day)</td>
</tr>
<tr>
<td>Obesity (≥30 kg/m²)</td>
</tr>
<tr>
<td>Essential etiology</td>
</tr>
<tr>
<td>Headache at stroke onset</td>
</tr>
<tr>
<td>Female sex</td>
</tr>
</tbody>
</table>

*β = -3.241; SE (β) = 0.456; goodness-of-fit χ² = 9.48, d.f. = 4, ρ = 0.050.

SE = Standard error.
Clinical characteristics of acute lacunar stroke in young adults

Original Research

Measures to correct these risk factors are particularly important strategies to prevent lacunar infarction and early subcortical vascular dementia [39,40]. Alcohol consumption, heavy smoking and obesity were independently associated with lacunar stroke younger patients.

The incidence of lacunar strokes in younger adults (aged 18–55 years) was only of 5.2% of all patients with lacunar stroke. Lacunar stroke is mainly a disease of older patients (mean age 75.9 years in our study).

The present findings, however, should be interpreted taking into account that the group of young lacunar stroke patients is rather small (n = 51), particularly because lacunar stroke is more frequent in patients older than 70 years of age.

Interestingly, early prognosis was similar in young adults than in older, given that there were no significant differences in the rates of in-hospital mortality, percentage of patients who were symptom-free at discharge or frequency of the different lacunar stroke subtypes. Lacunar stroke can be considered in young adults and older patients as a neurovascular condition with a relatively early favorable functional prognosis.

Key issues

- The ischemic stroke subtype of lacunar infarcts comprises about 25% of all brain infarctions and is a common cause of dementia of vascular origin.
- Lacunar stroke is mainly a disease of older patients (mean age 75.9 years in our study).
- The incidence of lacunar strokes in younger adults (aged 18–55 years) was only of 5.2% of all patients with lacunar stroke.
- Alcohol consumption, heavy smoking and obesity were independently associated with lacunar stroke younger patients.
- Measures to correct these risk factors are particularly important strategies to prevent lacunar stroke and early subcortical vascular dementia, for which lacunar stroke has been identified as a clinically relevant risk factor.

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Financial & competing interests disclosure

M Pulido provided editorial assistance. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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Papers of special note have been highlighted as:
- of interest
- of considerable interest


5. Clinical review of the association between lacunar infarction and vascular dementia.


15. Population-based study of stroke characteristics in the very old.

Other of interest

Interesting clinical study focused on gender differences in stroke patients.

doi: 10.1586/14737175.2015.1049997
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* Update of physiopathological mechanisms, clinical features, treatment and prognosis of lacunar infarction.