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Ischemic stroke subtypes: risk factors, functional outcome and recurrence

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Abstract The etiology of ischemic stroke affects its prognosis, outcome and management. Our aims were to determine risk factors, clinical and imaging variables and prognostic differences in acute ischemic stroke subtypes. In this study, we prospectively investigated 264 consecutive patients with acute ischemic stroke between 1996 and 2000. All of the patients were categorized to one of four major ischemic stroke subtype based on TOAST (Trial of Org 10172 in Acute Stroke Treatment) criteria. The mean age was greater in patients with stroke of undetermined etiology (SUE). Prevalence of hypertension was higher in patients with lacunar infarct (LAC) than other subtypes. Smoking was less frequent in patients with cardioembolism (CARD). The mean infarct size was largest in patients with large artery atherosclerosis (LAA) while there were no differences in location or conversion of the infarct into hemorrhage. The proportion of the patients with milder neurological deficits at entry was higher in patients with LAC subtype. The rate of independent patients were different between subtypes: 62% in LAC, 43% in CARD, 38% in SUE, 35% in LAA at discharge (p=0.01), and 91% in LAC, 69% in CARD, 59% in SUE, 60% in LAA at 6 months (p<0.001). Recurrence rates were not different between groups. We conclude that risk factors, clinical imaging variables are different among ischemic stroke subtypes and that neurological status on admission and during follow-up strongly favors LAC.

Key words Stroke, acute • Stroke classification • Risk factors • Prognosis

Introduction

Ischemic stroke has many causes with different clinical presentations, risk factors, courses and outcomes [1, 2]. Prognosis and management of ischemic stroke is directly related to specific mechanisms of the ischemic lesion. Comparison of clinical characteristics, functional outcomes and mortality rates for specific ischemic stroke mechanisms may allow clinicians to identify those patients who are at higher risk and to evaluate treatment strategies more definitely. Correct classification of subtypes in patients with acute cerebral infarction is crucial for early management and for predicting the prognosis.

We aimed to evaluate the risk factors, clinicoradiological variables and outcomes of patients with common ischemic stroke subtypes in this hospital-based study.

Patients and methods

The study took into consideration 356 patients with acute ischemic stroke admitted consecutively to the neurological department of Bayindir Medical Center, Ankara, Turkey during the 36 months from March 1996 to August 2000. Bayindir Medical Center is a regional hospital, offering secondary-tertiary health care and accepts referrals from small health centers in central Anatolia. All patients who were admitted to the emergency unit with acute ischemic stroke were considered for study. Thirty-six patients diagnosed as having TIAs during hospital stay were excluded from the

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study. Additionally, 54 patients were not included as their evaluation or follow-up was incomplete. Thus, there were 266 patients available for study: 158 men and 108 women, aged 28–95 years (average, 65 years). Consent was obtained from the patient or a family member to record examination scores, standard laboratory test results, radiographic test results, and the physiological parameters for research purposes. All the patients were admitted through the emergency unit and underwent nonenhanced cranial computed tomography (CT) to rule out cerebral haemorrhage.

The Canadian neurological scale [3] was applied in all patients on admission. One study neurologist (MMS) reviewed the clinical history, neurological examination, diagnostic studies, and brain imaging studies of all patients and assigned infarct subtype classifications according to TOAST (Trial of Org 10172 in Acute Stroke Treatment) [4] classification system: 1, large artery atherosclerosis (LAA); 2, cardioembolism (CARD); 3, lacunar infarct (LAC); 4, stroke of other, unusual, determined etiology; and 5, stroke of undetermined etiology (SUE).

Chest X-ray, 12-lead electrocardiography (ECG), and standard blood and coagulation tests were performed in all patients. Special blood tests were done in selected patients. Chemical tests for blood lipids and glucose levels were repeated the next day in fasting conditions. Patients underwent cardiac and large artery investigations as follows: transthoracic echocardiography in 260 patients (98.5%), transesophageal echocardiography in 6 patients (2.3%), Doppler carotid ultrasonography in 235 patients (89%), three-dimensional (3D) magnetic resonance angiography (extracranial and intracranial) in 29 patients (11%), and digital subtraction angiography in 5 patients (1.9%).

CT was repeated in all patients after 48–72 h of the first CT examination or after neurological stabilization in order to confirm the localization and measure the infarct size. Cranial magnetic resonance imaging (MRI) was carried out if the responsible lesion could not be visualized or if its size was not properly assessed on CT. The infarct volume (hypodensity zone consistent with clinical picture) and the infarct topography (anterior circulation, posterior circulation) were assessed. As a result, 183 patients (69%) were assessed with CT and 81 (31%) patients were assessed with MRI. The proportion of patients assessed with MRI was higher among those with small artery disease (15 patients in CARD, 6 patients in LAA, 38 patients in LAC and 22 patients in SUE).

Infarct volume was calculated using the formula 0.5 x a x b x c, with a and b being the largest perpendicular diameters measured with CT or MRI; c refers to slice thickness [5]. This method has good intraobserver and interobserver variabilities [6].

The proportion of mean infarct sizes measured with MRI was not different between the 3 common subtypes (15 patients (17%) in CARD, 6 patients (26%) with LAA and 22 patients (25%) with SUE).

Cerebral tomography was performed on a GE Hilight Advantage and MRI was performed on GE Vectra 0.5 T scanner. Infarct volumes were not calculated in lacunar infarctions.

The patients were treated for associated illnesses and received early rehabilitation. Treatments for hyperglycemia, hypoxia, hyperthermia and high blood pressure were administered in accordance with general directions. In those patients in whom intracranial hypertension was suspected, 20% mannitol or dexamethasone was given intravenously. Low-molecular weight heparin was given to all patients in order to prevent deep venous thrombosis and pulmonary thromboembolism, except for those patients taking unfractionated heparin. The following antithrombotic agents were administered from entry: 53 patients (20%) were given anticoagulants (unfractionated heparin, warfarin), 155 (58.7%) were given antiplatelet agents (aspirin, ticlopidine, clopidogrel) and 56 (21%) were given antiplatelet agents and anticoagulants.

The follow-up was continued for six months after hospital discharge. The Rankin scale (RS) [7] was administered by either of the investigators to surviving patients at discharge and at sixth months to determine functional capacity. RS was performed in 213 patients in control examinations six months after the onset of stroke. Information concerning the neurological status and functional outcome was collected by telephone interview in the remaining 17 patients.

The 266 patients were classified into five infarct subtypes. Two patients with uncommon causes of infarct (subtype 4) were excluded from study because of the small number. These stroke subtypes were compared in terms of the following variables: background characteristics (age, gender, Canadian neurological scale score at entry), risk factors (hypertension, history of hypertension, use of antihypertensive agents, blood pressure consistently >160/90 mmHg during hospital stay, diabetes mellitus, use of insulin or oral hypoglycemic agents, fasting blood glucose ≥140 mg/dl, random blood glucose ≥ 200 mg/dl, smoking habit (e.g. current cigarette smoking or smoking in last 5 years), history of transient ischemic attack or stroke, hypercholesterolemia (total cholesterol >220 mg/dl), radiological data (infarct volumes in three subtypes, hemorrhagic transformation, vascular territory involved), and prognosis (mortality and independency rates at discharge and 6 months after discharge).

The distribution of risk factors, Canadian neurological scale scores on admission (dichotomized as <6.5 versus ≥6.5), infarct localizations (anterior or posterior), functional outcomes and death rates among patients in the 4 subtypes were compared with the χ^2 test. Rankin scores (dichotomized: as independent, RS 1–2 versus dependent, RS 3–5 and death) were analyzed at discharge and after 6 months (after excluding patients who died during hospital stay). Analysis of variance (one-way ANOVA) was used to compare mean ages of patients and the mean infarct size of patients in the groups. The level of significance was chosen to be $p<0.05$.

Results

Two hundred sixty-six patients with ischemic stroke were identified in the study population during a 4-year period. Each of the ischemic strokes was assigned a subtype: CARD, 88 patients (33%); LAA, 23 (9%); LAC, 66 (25%); SUE 87 (33%); and other unusual causes 2 (1%). A probable or certain diagnosis was issued in 47.7% and the diagnosis was not complete in 22.5%. Eighty-eight patients were identified as having a potential cardiac source of embolism (PCSE), including 56 with high-risk PCSE and 32 with medium-risk PCSE. Twenty patients from LAA group and 41 patients from LAC were assessed as having probable etiological causes. Thirty-five patients in SUE had multiple causes, and no identifiable cause was found in the remaining 52 patients. Patients (n=2) with unusual causes of stroke were excluded from the subsequent analysis because of the small number, leaving 264 patients in the study group.

The baseline characteristics, risk factors and neurological status on admission are displayed in Table 1. The mean age was greatest in patients with SUE. Hypertension was more common in the patients with LAC compared with other stroke subtypes; nearly four-fifths of patients with LAC had

hypertension. Smokers were significantly less frequent among the patients with CARD.

The patients with LAC had milder neurological deficits compared to those with other subtypes on admission and on discharge from hospital. Patients with cardioembolic stroke had more severe neurological deficits at the time of stroke, but not at discharge compared with other subtypes. The patients with other two stroke subtypes had nearly the same neurological deficits at the time of stroke and at discharge.

Infarcts in patients with CARD tended to be localized more frequently to the anterior circulation; this trend was observed to a lesser degree for the other subtypes (Table 2). This difference was not statistically significant. Hemorrhagic transformation was more common in patients with LAA, but the rate was not statistically significant. Lacunar infarction was detected in 85 patients (66 with LAC and 19 with SUE). There was no responsible lesion in 17 patients and infarct size could not be measured in 5 patients due to its scattered appearance. As a result mean infarct size could be measured in 157 patients from three subtypes. Within these three subtypes the mean infarct size was larger in LAA than other two groups (Table 2).

Patients receiving anticoagulants more frequently had CARD than other subtypes (64 patients (73%) in CARD, 7 patients (30%) in LAA, 11 patients (16%) in LAC, 27 patients (31%) in SUE; $p<0.001$). In noncardioembolic infarct subtypes, 20 patients received anticoagulants due to progressive stroke (5 patients in LAA, 8 in LAC, 7 in SUE), and 10 were anticoagulated due to recurrent ischemic strokes that developed while taking antiplatelet drugs (2 patients in LAA, 3 in LAC, and 5 in SUE). The remaining 15 patients with SUE having multiple causes were anticoagulated due to PCSE.

Functional independency (Rankin scale scores 1–2) and death rates at discharge from hospital and after 6 months are presented in Table 3. Functional outcome was better in LAC patients than in other stroke subtypes, both on discharge from hospital and after 6 months. Independency rate was 91% in the patients with LAC at 6 months. None of the patients with LAC died during hospital stay or follow-up.

Ischemic stroke recurrencies were observed in 17 patients (6.4%) during the 6-month follow-up: 5 (5.7%) in CARD, 2 (8.7%) in LAA, 3 (4.5%) in LAC, and 8 (9.2%) in SUE. There were no statistical significant differences among stroke subtypes in terms of recurrence ($p=0.8$).

Table 1 Demographic data, baseline characteristics and risk factors for stroke, by ischemic stroke subtype

	CARD (n=88)	LAA (n=23)	LAC (n=66)	SUE (n=87)	*p*
Age, years[a]	63 (12)	60 (16)	64 (10)	69 (12)	0.001
Male, n (%)	47 (53)	13 (57)	43 (65)	55 (63)	0.4
Risk factors, n (%)					
Atrial fibrillation	59 (67)	–	–	16 (18)	<0.001
Hypertension	35 (40)	13 (56)	52 (79)	53 (61)	<0.001
Diabetes	24 (27)	8 (35)	22 (33)	22 (25)	0.6
Smoking	12 (14)	11 (48)	27 (41)	25 (29)	<0.001
Prior TIA or stroke	16 (18)	2 (9)	8 (12)	9 (10)	0.4
Hypercholesterolemia[b]	19 (22)	9 (39)	20 (30)	32 (37)	0.1
CNS score ≥6.5[c]	37 (42)	13 (57)	49 (74)	44 (51)	0.001

[a] Mean (SD)

[b] Cholesterol >220 mg/dl

[c] Canadian neurological scale score on admission

CARD, cardioembolism; *LAA*, large artery atherosclerosis; *LAC*, lacunar infarction; *SUE*, stroke of undetermined etiology; *TIA*, transient ischemic attack

Table 2 Neuroradiological findings in stroke patients, by ischemic stroke subtype

	CARD (n=88)	LAA (n=23)	LAC (n=66)	SUE (n=87)	*p*
Anterior localization, n (%)	71 (81)	17 (74)	41 (62)	58 (67)	0.07
Hemorrhagic infarct, n (%)	12 (14)	6 (26)	–	8 (9)	0.2
Patients with measurable lesion, n	81	20	0	56	–
Infarct size, mean (SD)[a]	66 (95)	91 (116)	–	59 (101)	0.04

[a] Infarct size was measured with MRI in 15 patients with CARD, in 6 patients with LAA and in 22 patients with SUE. Values are mm^3

CARD, cardioembolism; *LAA*, large artery atherosclerosis; *LAC*, lacunar infraction; *SUE*, stroke of undetermined etiology

Table 3 Prognosis among stroke subtypes

	CARD (n=88)	LAA (n=23)	LAC (n=66)	SUE (n=87)	*p*
Rankin scale score 1–2, n (%)					
At discharge	38 (43)	8 (35)	41 (62)	33 (38)	0.01
At 6 months[a]	56 (69)	12 (60)	60 (91)	48 (59)	<0.001
Deaths, n (%)					
In hospital	7 (8)	3 (13)	0	5 (6)	0.02
Total, after 6 months	15 (17)	4 (17)	0	15 (17)	0.003

[a] Excluding patients who died in hospital
CARD, cardioembolism; *LAA*, large artery atherosclerosis; *LAC*, lacunar infraction; *SUE*, stroke of undetermined etiology

Discussion

Categorization of subtypes of ischemic stroke is important in deciding treatment alternatives and forecasting the outcome. Two classification systems are widely used in clinical trials: Oxfordshire community stroke project (OCPS) [8] and TOAST [4]. We used TOAST in this study for its high interobserver agreement and advantage in making etiological diagnoses.

The proportion of patients with cardioembolic stroke was greater (33%) than other identifiable subtypes in our study. Cardioembolic stroke was found to be the most common subtype in one previous study [9], while lacunae constituted the largest subtype in others [10, 11]. The rates of common stroke subtypes are controversial in the literature, especially when considering stroke of undertermined cause [2, 12, 13]. This is mostly due to the composition of different ethnic-racial populations, diagnostic criteria, different study designs and patient-selection methods, i.e. hospital-based studies tend to include patients with more severe strokes and higher mortality, while population-based studies tend to include younger patients [14–16].

Hypertension was found to be the most commonly encountered risk factor for patients with LAC in the current study. Most of the previous studies reported frequent association of hypertension with lacunae [13, 17] and with other risk factors such as diabetes mellitus or hyperlipidemia [10, 18, 19].

Patients with SUE were older than patients with other stroke subtypes. Another interesting finding is that smoking in patients with CARD was less frequent than in other subtypes compared. This may be due to the frequency of previously diagnosed heart disease in this group and to the patients' increased awareness of the harmful effects of smoking.

Lacunar infarcts have the best short- and long-term prognoses with lower mortality and recurrence rates, better admission and follow-up scores and better survival rates [8, 20–25].

Even though our follow-up was shorter than that of some of these studies, this study strongly favors lacunae: none of the patients with lacunar infarct subtype died during hospitalization or follow-up period. The lacunar infarct patients had better functional outcome scores: 9 of 10 patients were independent after 6 months.

Recurrence after stroke may be associated with the mechanism of infarction. Patients with large artery atherosclerosis have higher recurrence rates than other subtypes [19, 22, 26]. Hier et al. [27] reported a 14% cumulative recurrence rate during two years of follow-up with a lower risk of recurrence in patients with an infarct of unknown cause. Landi et al. [28] reported lower recurrence rates among patients with lacunar stroke. Recurrence rate was 6.4% in the current study during a follow-up of six months and it was higher in patients with SUE, yet it was not statistically significant. Our total recurrence rate is in accordance with previous hospital-based studies that reported 1%–4% within 30 days of the first stroke and 5%–25% at 1 year [22, 26, 29].

Only a few studies have compared the mean infarct size between infarct subtypes. This might be due to a low correlation rate with outcome, or to intrinsic limitations of CT technique [30]. Changing of infarct volume with time also causes difficulty in standardizing optimal time from admission to imaging [31]. Three previous studies reported that cardioembolic infarcts were larger than those of other subtypes [31–33], while the difference was not statistically significant between cardioembolic and arterial embolic groups in Timsit et al.'s [32] report. The mean infarct size was larger in patients with large artery atherosclerosis. This finding, to our knowledge, is reported for the first time. Our results should be interpreted with caution, because the number of the patients especially with large artery atherosclerosis was small and the time interval (from first symptom to imaging) was shorter in our study. Further studies with larger patient populations are needed to clarify this observation.

This study has some limitations. Using both CT and MRI prevents standardization and limits our results. However, this may influence our results only slightly, since the same proportions of patients were evaluated with the same method. Strict protocols are unsuitable for hospital-based studies dealing with critical illnesses such as stroke. Rapidly changing clinical situations force physicians to make diagnoses

and to plan treatment strategies at once. It is not practical to wait for days for a second CT examination to visualize the infarct while MRI is available. On the other hand, all patients were not suitable for MRI (e.g. patients with agitation or hypoventilation or those with metallic heart valves). Another restriction was experienced due to relatively small number of patients in our study.

We conclude that risk factors, clinical and imaging variables were different among ischemic stroke subtypes. Patients with LAC had significantly better outcome scores than other subtypes.

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