啓明醫大論文集 第19券 第1號
Keimyung Med J
Vol. 19, No. 1, June, 2000

Cardioembolic Subcortical Infarcts : Clinical Characteristics in 46 Atrial Fibrillation Patients

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=Abstract=

We undertook this study to evaluate the prevalence, risk factors, and clinicoradiological characteristics of cardioembolic subcortical infarcts (SSI). An issue concerning cardioembolism as a cause of SSI has not been settled down. We selected 46 patients with atrial fibrillation (AF) and an isolated CT- or MRI-proven SCI in territory of the internal carotid system. The patients were divided into small (maximal diameter of lesion less than 15 mm) subcortical infarcts [SSI] group (n = 27) and large (maximal diameter of lesion greater than 15 mm) subcortical infarcts [LSI] group (n = 19). We investigated and compared clinical characteristics in both groups. Five (19%) patients in the [SSI] group and 15 (83%) in the [LSI] group had one or more associated neuropsychologic disturbances. In five (19%) patients in the [SSI] group and in 3 (16%) in the [LSI], the lesion was in the centrum ovale. Five (19%) cardiac embolic SSI were found in the [SSI] group (N = 27). The short-term outcome for cardiac embolic SSI was better than for the remaining SSI. A higher frequency of neuropsychological disturbances and better recovery of neurologic deficits characterized cardioembolic SSI vs. SSI due to small vessel disease. Small and large centrum ovale infarcts can be caused by cardiac embolic sources. The prevalence of cardioembolic SSI in the [SSI] group was 19 %.

Key words : small subcortical infarcts, atrial fibrillation, cardioembolic subcortical infarcts

Introduction

Subcortical infarction has been considered synonymous with in situ small vessel disease. Although lacunar infarction accounts for a large proportion of subcortical infarctions, other forms of subcortical infarction have been studied and classified by some investigators (Donnan *et al*, 1993; Bogousslavsky, 1992). Cardiac or carotid embolism as presumed mechanisms of subcortical infarction should not be overlooked (Levin *et al*, 1988; Donnan *et al*, 1991; Ringelstein *et al*, 1992; Hupperts *et al*, 1994). Even in lacunar infarction, which is mainly associated with in situ small vessel disease, several alternative pathogenic mechanisms have been suggested (Aleksic & George, 1973;

Barinagarrementeria & Del Brutto, 1989; Millikan & Futrell, 1990; Park *et al*, 1990; Waterston, *et al* 1990; Bogousslavsky *et al*, 1991; Fredericks *et al*, 1991). In the case of cardioembolic lacunar infarction, a prevalence of up to 18% has been reported (Horowitz *et al*, 1992), and several case reports provide clear radiological and pathologic evidence for embolic lacunar infarction (Futrell *et al*, 1989; Cacciatore & Russo, 1991; Laloux & Brucher, 1991; MacDonald *et al*, 1995). In contrast, other studies suggest that emboliogenic cardiac disease is unlikely to be the cause of lacunar infarction (Foulkes *et al*, 1988; Gandolfo *et al*, 1988; Van Merwijk *et al*, 1990; Norrving & Staff, 1991; Mast *et al*, 1994; Arboix *et al*, 1997). Using the data from the Lausanne Stroke Registry, we retrospectively studied 46 patients with atrial fibrillation (AF), one of the hallmarks of embolism, and an isolated, CT/MRI-proven subcortical infarct.

This study systematically evaluated the prevalence, cardiac and artherosclerotic risk factors, and clinicoradiological characteristics of cardioembolic small subcortical infarcts [SSI] and large subcortical infarcts [LSI].

Materials & Methods

The patients with atrial fibrillation and an isolated CT- or MRI-proven subcortical cerebral infarct in the territory of the internal carotid system were selected. The patients were part of the Lausanne Stroke Registry and were admitted to our primary care centers between 1987 and 1997. In this study, all patients with first-ever stroke were examined by a neurologist, the systematic investigations for each patient including brain CT (up to 4 examinations, the first within 7 days of the stroke) or MRI with or without contrast, Doppler ultrasonography with spectral frequency analysis and B-mode echotomography, 12-lead electrocardiography, blood tests (blood counts, liver and renal function tests, VDRL, total cholesterol, glucose, and sedimentation rate), and two-dimensional echocardiography. Atrial fibrillation was diagnosed on the basis of either ECG results or, in selected patients, of 24 to 48-hour Holter monitoring.

Hypertension was defined by history prior to stroke (two or more blood pressure values >160/95 mmHg), diabetes mellitus (two or more fasting glucose levels of > 6 mmol/l), and hypercholesterolemia (two or more fasting cholesterol levels > 6mmol/l). Concomitant factors, such as regular cigarette smoking (more than 120 packs/year for more than 10 years), history of migraine, or vascular claudication were recorded according to the guidelines in our registry. Neck Doppler findings were grouped into 4 categories of normal, stenosis <50%, stenosis >50%, and occlusion. Coexisting cardiac sources of embolism, other than AF on 2-D echocardiography, included mitral or aortic valvular disease, prosthetic valves, akinetic left ventricular segment with or without thrombus, and global cardiac hypokinesia.

The patients were divided into two groups according to whether the size of the subcortical infarct on CT or MRI was small (small subcortical infarct [SSI] group; maximal diameter of lesion less than 15 mm) or large (large subcortical infarct [LSI] group;maximal diameter of lesion greater than 15 mm). Each group was further divided into 2 sub-

groups by risk factors. Group 1 consisted of patients with AF and coexisting cardiac disease in the absence of the atherosclerotic risk factors (hypertension, diabetes mellitus, smoking, hypercholesterolemia, lower limb claudication, or an elevated hematocrit (>45%). Group 2 consisted of patients with AF and coexisting cardiac disease with any of the above atherosclerotic risk factors. This resulted in 4 subgroups, G1S (group 1, small infarcts), G1L (group 1, large infarcts), G2S (group 2, small infarcts), and G2L (group 2, large infarcts).

The clinical manifestations were classified as one of the four classical lacunar syndromes of pure motor hemiparesis, sensory motor stroke, ataxic hemiparesis, and pure sensory stroke. Associated visual field defects, visuospatial dysfunction (hemineglect and hemianosognosia), speech disturbance, and alteration of mental state were recorded. The number, frequency, side, duration, and time before stroke of transient ischemic attack (TIA) and the pattern of stroke onset were recorded according to the protocol of the Lausanne Stroke Registry (Bogousslavsky *et al*, 1988). Functional status was measured at the times of admission and discharge using a five-point scale with 1 as no disability, 2 mild disability (return to all activities, but with difficulty), 3 moderate disability (return to main activity, but with difficulty), 4 severe disability (impossibility of returning to most activities), and 5 death.

Epidemiological, clinical and radiological features were investigated in 4 subgroups. To determine whether concomitant atherosclerotic risk factors or types of AF or echocardiographic findings or extracranial ICA Doppler ultrasound findings can affect the size of subcortical infarct, those were compared between the [SSI] and [LSI] group. The chi-square test was used for statistical comparison.

Results

Forty-six patients were considered eligible for the study. They consisted of 24 (52%) men and 22 (48%) women, with a mean age of 76 years (range, 56 to 88; standard deviation, 7.0). Groups 1 and 2 consisted of 10 (22%) and 36 (78%) patients, respectively, while the [SSI] and [LSI] groups contained 27 (59%) and 19 (41%) patients, respectively. The mean age and sex distribution of patients in each subgroup are shown in Table 1.

Vascular concomitants : Hypertension was the dominant atherosclerotic risk factor in [SSI] group (95%) and [LSI] group (79%) and both these groups contained 4 patients with diabetes mellitus (Table 1). No statistical difference in the distribution of atherosclerotic risk factors (hypertension, diabetes mellitus, cigarette smoking, hypercholesterolemia, elevated hematocrit, and limb claudication) was seen between [SSI] group and [LSI] group.

Internal carotid artery (ICA) Doppler ultrasound findings : The results of ICA neck Doppler ultrasound examinations are summarized in Table 2.

Types of AF and coexisting cardiac sources : The types of AF and the echocardiographic findings, summarized in Table 3, did not differ statistically between the [SSI] and [LSI] groups. Chronic AF was found in 22 (48%) patients, paroxysmal AF in 18 (39%), and AF was discovered for the first

Table 1. Age, sex, and artherosclerotic risk factors.

	[SSI] group (n=27)		[LSI] group (n=19)	
	G1S	G2S	G1L	G2L
Number	5	22	5	14
Sex (M/F)	4/1	9/13	4/1	7/7
Mean age(yrs)	72	77.9	70.0	76.8
Artherosclerotic risk factors				
HTN	21 (95)		11(79)	
DM	4 (18)		4(29)	
Smoking	2 (9)		4(29)	
HC	3 (14)		2(14)	
Elevated Hct	4 (18)		2(14)	
Claudication	3 (14)		2(14)	

Numbers of patients with the percentage in brackets. [SSI]: small subcortical infarct group, [LSI]: large subcortical infarct, G1S: small infarcts in group 1, G2S: small infarcts in group 2, G1L: large infarcts in group 1, G2L: large infarcts in group 2, M: male, F: female, yrs: years, HTN: hypertension, DM: diabetes mellitus HC: hypercholesterolemia, Hct: hematocrit

Table 2. Internal carotid artery Doppler ultrasound findings.

	[SSI] group (n=27)		[LSI] group (n=19)	
Neck Doppler US	Ipsilat	Contra	Ipsilat	Contra
Normal	8	9	9	9
<50%	18	18	10	10
ICAO	1	0	0	0

US: ultrasound, ICAO: internal carotid artery occlusion, Ipsilat: ipsilateral, Contra: contralateral.

time on admission for stroke in 6 (13%). Cardiac pacemakers were implanted in one patient in the G1S subgroup due to third degree AV block and in one patient in the G1L subgroup due to intermittent bradycardia. The echocardiographic findings in the G1S subgroup were as follows : 1 patient with global hypokinesia with left ventricular thrombus, 1 global hypokinesia without thrombus, 1 prosthetic valve, and the remaining 2 either AV sclerosis or a normal finding. Echocardiography was not performed on one G2S patient because of associated pulmonary disease. Valvular heart disorders were found in 8 (17%) patients, 3 of which had prosthetic mitral valve or rheumatic mitral sclerosis. Coexisting myocardial abnormalities were found in 25 (54%) patients. One G2L patient had a recent (<3 month) myocardial infarction.

Table 3. Types of AF and echocardiographic results.

	[SSI] group (n=27)	[LSI] group (n=19)
Types of AF		
Chronic	15	7
Paroxismal	9	9
Recent	3	3
Echocardiography		
Myocardial abnormality	GH + LVT 1	
	GH - LVT 5	GH - LVT 5
	FLVH - LVT 5	FLVH - LVT 5
Valvular abnormality	Pr MV 1	Pr MV 1
	MS 1	MR 2
	Pr AV 1	MR and AS 1
Myocardial and valvular abnormality	FLVH and MR 1	GH, MR, and TR 1
LA dilatation only	4	3
Normal or insignificant	7	4

GH: global hypokinesia, FLVH: focal left ventricular hypokinesia, LVT: left ventricular thrombosis, MV: mitral valve, MS: mitral stenosis, MR: mitral regurgitation, LA: left atrium, AV: aortic valve, AS: aortic stenosis, TR: tricuspid regurgitation, Pr: prosthetic, +: with, -: without.

Normal or non-significant aortic stenosis (AS) findings were found in 6 (22%) patients in [SSI] group and in 3 (17%) in [LSI] group.

Clinical findings and anatomic locations of infarcts : The lesion was identified by CT in 43 cases and by MRI in 5. In 24 (52%) cases, the lesion was on the right and in 22 (48%) on the left.

[SSI] group : The lesion location and associated clinical features are described in Table 4-1. In the [SSI] group (N=29), 12 (43%) patients showed pure motor stroke; these included 1 patient with faciobrachial motor weakness and 2 (7%) with pure motor hemiparesis with dysphasia. Sensory motor stroke was found in 7 (25%) patients and 2 (7%) showed sensory motor stroke with a visual field defect and speech or neuropsychologic disturbances. Ataxic hemiparesis was found in 4 (14%) patients. One patient showed ataxic hemiparesis, anosognosia, and dysphasia. Associated neuropsychologic dysfunctions were seen in 5 (19%) patients. No patient had a thalamic infarct in the territory of the thalamotuberal artery.

[LSI] group : The lesion locations and associated clinical features are described in Table 4-2. Three patients had lacunar syndromes other than ataxic hemiparesis and pure sensory stroke. One or more associated neuropsychologic disturbances were seen in 15 (83%) patients, and motor sensory stroke with a visual field defect and neuropsychologic disturbances were the most common clinical findings (44%).

Table 4-1. Anatomic locations of infarcts and associated clinical findings in the [SSI] group.

Anatomic locations	N	Neurologic syndromes
G1S		
Lenticular Nu and post IC	1	PM/anos, paraphasia
Lenticular Nu and post IC (hemorrhagic transformation)	1	MS
Extreme capsule	1	PM(FB type)
Centrum ovale (P)	1	MS
Centrum ovale (F)	1	PM
G2S		
Post IC	1	MSH/ disor
	1	MSH/ negl
	4	PM
	2	AH
	1	PM
IC and Lenticular Nu	2	PM
	3	MS
	1	MS/ paraphasia
	1	AH
Paraventricular WM	1	AH
	2	PM
Centrum ovale (F)	1	PM
Centrum ovale (P)	1	AH/anos, motor D
	1	MS

N: number, Nu: nucleus, IC: internal capsule, WM: white matter, F: centrum ovale beneath frontal cortex, P: centrum ovale beneath the parietal cortex, anos: anosognosia, negl: neglect,disor: disorientation, D:dysphasia, PM: pure motor stroke, MS: motor sensory stroke, MSH: motor sensory stroke with visual field defect, AH: ataxic hemiparesis, FB type: faciobrachial typeof motor weakness.

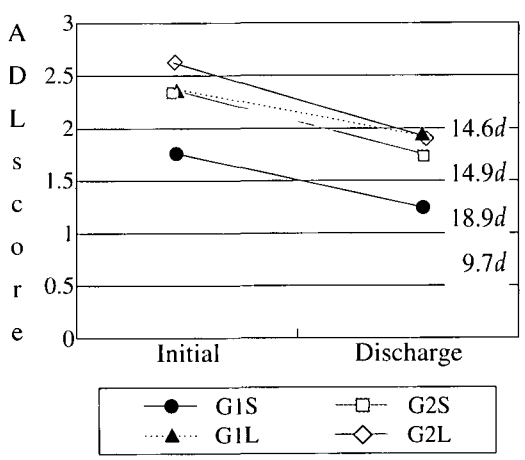
Previous TIAs and stroke onset : Six (13%) patients reported one episode of TIA ipsilateral to their subsequent cerebral infarct. The interval between TIA and the stroke was 1 week to 13 months. The mean duration of TIA was 69 minutes, and 2 patients reported TIAs shorter than 15 minutes. Stroke was immediately completed in 31 (67%) patients, fluctuated in 10 (for < 24 hours in 6 and >24 hours in 4), and progressed gradually in 5 (for < 24 hours in 4 and >24 hours in 1).

Treatment and short-term evolution : Half (23 patients) of all patients were treated with antiplatelet agents, 20 (43%) were anticoagulated, and the remaining 3 were not given antithrombotic therapy because of a bleeding tendency (thrombocytopenia in 2 and a hepatic disorder in 1). One patient died due to cardiac failure 36 days after stroke. In one G1L patient, the clinical symptom worsened on the day 7 of hospitalization, with a favorable recovery at discharge. Figure 1 shows the mean functional disability at the times of admission and discharge and the mean duration of hospitaliza-

Table 4-2. Anatomic locations of infarcts and associated clinical findings in the LSI group.

Anatomic locations	N	Neurologic syndromes
G1L		
IC and Lenticular Nu (hemorrhagic transformation)	1	MSP/negl, drowsy
IC, Caudate Nu, and	1	MSP/negl, visual hallucination
Lenticular Nu	1	PM
IC and Thalamus	1	MSP/negl, global D
Centrum ovale (F)	1	PM(FB type)/motor D
G2L		
IC and Lenticular Nu	1	MSP/drowsy, global D
	1	MSP/drowsy, global D, CGD
	1	MSP/anos
	1	MSP/negl, drowsy, CGD
	1	MS/diso
	1	MSP/motor D
	1	MS/negl
	1	MS
	1	PM/anos, drowsy
	1	PM/negl
IC and Thalamus	1	MS
EC and Putamen	1	PM/drowsy, motor D
Centrum ovale (P)	1	MS/global D
Centrum ovale (F-P)	1	MS/anos

EC: external capsule, CGD: conjugate gaze deviation, F-P: centrum ovale beneath the frontoparietal cortex.



d : days of hospitalization

Fig 1. ADL scores on admission and discharge in 4 subgroups

tion in the 4 subgroups. Of the subgroups, G1S showed the shortest duration of hospitalization (9.7 days) and the lowest ADL scores on admission (1.7) and discharge (1.2).

Discussion

Hypertension was the dominant vascular concomitant in both the [SSI] and [LSI] groups, and the prevalence of atherosclerotic risk factors, types of AF, coexisting echocardiographic findings, and extracranial ICA Doppler ultrasound findings showed no significant difference between the [SSI] and

[LSI] groups. It has been suggested that the constituents or size of an embolus can be responsible for the size of the infarct (Hart *et al*, 1990; Hofmann *et al*, 1990; Wilson *et al*, 1991; Timsit *et al*, 1993; Zanette *et al*, 1995). This study did not find any contributing cardiac and atherosclerotic risk factor nor echocardiographic and ICA neck Doppler finding for predicting small or large subcortical infarcts. This can be partly explained that large part of the patients did not have significant extracranial ICA stenosis. In spite of limited number in the [SSI] and [LSI] groups, this result can suggest that neither type of AF nor coexisting heart disorder nor vascular concomitants affect the size of subcortical infarct.

An issue concerning embolic occlusion of small perforating arteries as a cause of lacunar infarction has been much debated in clinical field partly due to low case fatality rate and lack of a proved cause and effect relation between a demonstration of embolic source and lacunar infarction. The reported prevalence of embolic lacunar infarction was also somewhat various, from 2% up to 18% (Norrving & Staff 1991; Horowitz *et al*, 1992). While not a few investigators do not consider embolism to be a possible mechanism of lacunar infarction (Foulkes *et al*, 1988; Gandolfo *et al*, 1988; Van Merwijk *et al*, 1990; Norrving & Staff, 1991; Mast *et al*, 1994; Arboix et al, 1997), several experimental and clinicoradiological reports as well as Fisher's pathologic study provide a clear evidence for embolic lacunar infarction (Fisher, 1979; Futrell *et al*, 1989; Cacciatore and Russo, 1991; Laloux and Brucher, 1991; MacDonald *et al*, 1995). Recently, one clinical report (Libman *et al*,1997) strongly supported cardioembolic sources as a cause of lacunar infarction (Libman *et al*, 1997). In 29 new infarcts associated with cardiac surgery, 5 (17%) infarcts were lacunar infarcts.

This study found 5 (19%) cardioembolic SSI including 2 small infarcts limited to the territory of deep perforator. In 2 cases in the cardiac embolic SSI, the lesions were in the posterior internal capsule, which agrees with the previous published location in embolic lacunar infarction (Futrell *et al*, 1989; Cacciatore & Russo, 1991; Arboix & Varti-Vilata, 1992). One of the two patients had anosgnosia and paraphasia, while the other showed secondary hemorrhagic transformation on the brain CT. In one G1S case, the lesion was in the extreme capsule, considering the transient faciobrachial motor weakness seen in this case, we cannot rule out the possibility of ischemic damage at other sites, including the cerebral cortex, which was not identifiable by brain imaging.

In the [LSI] group, 15 (83%) patients had one or more associated neuropsychologic disturbances. This result corresponds to published previous studies (Baldin and Berkovic, 1984; Weiller *et al*, 1990; Nicolai *et al*, 1996). Deceased cortical blood flow and ischemic cortical damage which is not visible on CT seem to responsible for neuropsychologic disturbances (Perani *et al*, 1987; Weiller *et al*, 1990). In the [SSI] group, 5 patients out of 27 (19%) had dysphasia or visuospatial dysfunction or disorientation in the absence of thalamic or caudate nucleus infarct, which is not infrequently associated with neuropsychologic disturbances, even in lacunar infarcts. Interestingly, G2S subgroup had 4 patients out of 5

who had neuropsychologic disturbances in the [SSI] group. Lacunar stroke can accompany various neuropsychologic disturbances (Fisher, 1991) and different mechanisms have been proposed (Kobayashi *et al*, 1991; Tatemichi *et al*, 1992). Recently, Lammie *et al* (1998) suggested new pathologic concept of incomplete lacunar infarction presumably caused by transient embolic occlusion of small penetrating artery or small vessel stenosis with reduction in local blood flow. Eight of the ten cases had embolic sources or the autopsy pattern of embolic cerebral infarcts and three of the ten cases had AF, hypertension, and old age as stroke risk factors. Though the majority of incomplete lacunar infarcts are clinically silent, his report can provide a pathologic basis to suggest that embolic occlusion of small penetrating vessel may be more common cause than is generally assumed even in elderly hypertensive patients. In this study, one possible explanation for this higher incidence of neuropsychological disturbances in the [SSI] group is that flow dynamics provide evidence for the preferential lodgement of emboli in pial branches, rather than in the deep perforating arteries (Ringelstein *et al*, 1989), and pathologic studies in SSI have shown that small multiple emboli are also frequently found in the cortex (Futrell *et al*, 1989; Ringelstein *et al*, 1989; Tuszynski & Petito, 1989).

Lacunar infarcts seem characteristically to follow a favorable course and our data agree with published findings (Bamford *et al*, 1987; Arboix *et al*, 1990). Even in the first 2 weeks after stroke onset, the recovery of deficit in the G1S subgroup was better than in the other subgroups. Despite the limited numbers, the results could suggest that embolic SSI have a better short-term outcome than LSI or SSI due to small vessel disease. Less severe ischemia due to early recanalization in single perforating artery could be one explanation for that suggestion.

Two patients in the G1S subgroup and three in the G2S subgroup had small centrum ovale infarcts. These findings are in agreement with recent suggestions that cardiac or carotid embolic sources, in addition to small vessel disease, can be the cause of small centrum ovale infarcts (Ley *at al*, 1994; Read *et al*, 1998). Recently, in a pathologic study, Lamini and Wardlaw (1999) reported that 8 out of 12 cases of small centrum ovale infarct possibly had embolism as the underlying mechanism. In our study, 3 LSI patients had large centrum ovale infarcts, but none of these resulted from hemodynamic disturbances (significant internal carotid stenosis, hypotension, bradycardia, and syncope at stroke onset). The results suggest that large infarcts in the centrum ovale can also be caused by cardioembolic sources. Bogousslavsky and Regli (1992) also found cardiac and carotid embolic sources in a few patients with small and large centrum ovale infarcts.

Summary

To summarize, the prevalence of cardioembolic SSI in the [SSI] group was 19%. This suggests that we should not neglect investigating possible cardiac emboliogenic sources in SSI. Embolic SSI has, to some extent, different clinical features to lacunar infarcts due to small artery disease. Small and large centrum ovale infarcts can be

caused by cardioembolic sources. We expect that studies involving a larger patient series and including brain MRI with functional neuroimaging will confirm these suggestions.

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