

Original articles

Lipids in ischemic stroke subtypes

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Abstract

In secondary prevention, reduction of the risk of recurrent ischemic stroke might be expected with statins if a correlation can be established between hyperlipidemia and ischemic stroke or some specific ischemic stroke/TIA subtypes. However, such correlation remains controversial, and more particularly with the etiologic stroke/TIA subtypes. Few studies have evaluated the plasma lipid profile in different ischemic stroke subtypes, and notably in lacunar infarctions and cardioembolic strokes.

The objectives of this case-control study was to determine (1) which cholesterol fractions is associated with large vessel disease (LVD), small vessel disease (SVD), and cardioembolic disease (CED); (2) whether hypertriglyceridemia is related more to any particular stroke subtype; and (3) whether the lipid profile is different between LVD and SVD which are both responsible for atherothrombotic cerebral ischemia.

From a cohort of 485 patients, were selected 240 consecutive cases with ischemic stroke ($n = 182$) or transient ischemic attack ($n = 58$) due to a single etiology. The levels of total cholesterol (total-C), LDL-cholesterol (LDL-C), HDL-cholesterol (HDL-C), and triglycerides (TG) were measured in 61 patients with LVD, in 65 with SVD, and in 114 with CED, and compared with age- and sex-matched control subjects. Additional analysis was performed to compare the lipid profile between LVD and SVD after adjustment for other risk factors.

Compared to controls, the total-C level was significantly higher in patients with SVD ($p = 0.005$) and LVD ($p = 0.018$). A significant increase in the LDL-C level ($p < 0.004$) and a significant decrease in the HDL-C level ($p = 0.001$) were only observed in the LVD patients. The three stroke subtypes showed higher TG levels than the controls (CED, $p = 0.037$; SVD, $p < 0.001$; LVD, $p = 0.014$). The plasma lipid profile was similar in the SVD and LVD subtypes except for HDL-C, which was significantly lower in LVD than in SVD ($p = 0.047$). Logistic regression adjusted for confounders showed that decreased HDL-C ($p = 0.020$), and smoking ($p = 0.019$) were significant discriminative factors for LVD vs. SVD.

In conclusion, this controlled study shows that hypertriglyceridemia is commonly found in patients with ischemic cerebrovascular disease whatever the etiologic subtype, whereas hypercholesterolemia is related more to SVD and LVD. In addition to hypertension and diabetes, hypercholesterolemia may also be involved in the

etiology of SVD and differs from LVD by a lower decrease in HDL-C.

Key words : Stroke ; subtypes ; lipid ; risk factor ; hyperlipidemia ; cholesterol ; triglycerides ; cerebral ischemia.

Although a prevention trial with simvastatin reported a reduced risk of recurrent stroke (MRC/BHF, 2002), the relationship between plasma lipid abnormalities and ischemic stroke remains controversial. Such an association has been reported in some observational studies (Iso *et al.*, 1989 ; Benfante *et al.*, 1994 ; Sacco *et al.*, 2001), but not in others (Wolf *et al.*, 1991 ; Prospective Studies Collaboration, 1995 ; Crouse *et al.*, 1997). A meta-analysis of 13 Chinese and Japanese cohorts, comprising 125,000 subjects and 1,800 strokes, showed a tendency toward a decreased risk for ischemic stroke as cholesterol levels decreased (Eastern Stroke and Coronary Heart Disease Collaborative Research Group, 1998). Another meta-analysis of 45 prospective cohorts, including 450,000 subjects and 13,000 strokes, found no association between total cholesterol and stroke (Prospective Studies Collaboration, 1995). The conflicting results of these studies may be due to several reasons. In some studies, there might be a masking effect due to the inclusion of patients with cerebral hemorrhage for which an inverse correlation with hyperlipidemia has been reported (Iso *et al.*, 1989 ; Benfante *et al.*, 1994 ; Law *et al.*, 1994 ; Eastern Stroke and Coronary Heart Disease Collaborative Research Group, 1998). In others, the lipid fractions exerted a different influence on stroke risk (Wannamethee *et al.*, 2000 ; Iso *et al.*, 2002), and their effect varied according to whether fatal or non fatal stroke was considered (Wannamethee *et al.*, 2000). Another possible reason is that the impact of hyperlipidemia may be different according to ischemic stroke subtype (Iso *et al.*, 1989). Thus, the relationship between hyperlipidemia and lacunar infarctions, which is due to lipohyalinosis or arteriosclerosis of the small perforating arteries,

remains unclear and little is known about hyperlipidemia in cardioembolic strokes. Few studies have compared the plasma fractions of cholesterol and triglycerides between the main subtypes of ischemic stroke and transient ischemic attacks (TIA). Therefore, the purpose of this study was to compare the plasma lipid profile in patients with large vessel disease (LVD), small vessel disease (SVD), and cardioembolic disease (CED) with age- and gender-matched controls. As atherothrombotic stroke/TIA can be due to SVD or LVD, we also compared the lipid profile between these two specific subtypes.

Methods

STROKE SUBTYPES

All patients had a control CT scan performed at least 48 hours after the stroke onset or MRI (T1, T2, T2*, FLAIR, diffusion sequence, MR-angiography of the intracranial cerebral arteries), standard laboratory tests, ultrasonography of the extracranial and intracranial cerebral arteries, 12-lead electrocardiogram, 24-hour electrocardiographic Holter monitoring, transthoracic echocardiography, and transesophageal echocardiography. MR-angiography or selective arterial angiography of the extracranial cerebral arteries was performed only when ultrasonography identified a presumed $\geq 70\%$ arterial stenosis. According to the TOAST criteria (Adams *et al.*, 1993), etiology of the qualifying ischemic event was considered as LVD (occlusion or $> 50\%$ stenosis of an appropriate large extracranial or intracranial artery or occlusion of appropriate stem, division or branch artery), SVD (recent < 2 cm lacunar infarct on CT or MRI compatible with the clinical deficit or one of the five lacunar syndromes), CED (high and medium risk cardiac-source for cerebral emboli), or undetermined.

RISK FACTORS

The following vascular risk factors were evaluated: age, gender, hypertension (current treatment with anti-hypertensive drugs or two blood pressure values $\geq 140/90$ mmHg at least 5 days after the stroke onset), smoking within the last 5 years, alcohol consumption (> 2 drinks per day), and diabetes mellitus (fasting glucose level ≥ 6.0 mmol/l).

MEASUREMENT OF PLASMA LIPIDS

The fasting lipid profile was evaluated within 2 days after the stroke onset (Aull *et al.*, 1996) and consisted of plasma total cholesterol (total-C), high-density lipoprotein cholesterol (HDL-C), and triglycerides (TG). Low-density lipoprotein cholesterol (LDL-C) values were calculated using

Friedenwald's formula. Apolipoprotein A-I, apolipoprotein B, and lipoprotein (a) were not evaluated in this study.

SUBJECTS

This study prospectively evaluated 485 consecutive patients admitted in a stroke unit with a first-ever ischemic stroke or TIA as defined by the National Institute of Neurological Disorders and Stroke (National Institute of Neurological Disorders and Stroke, 1990). Of the initial 485 cases, the etiologic subtype was undetermined in 245 patients and those patients were excluded from the study. The remaining 240 cases with a single identified cause were thus evaluated. The control group included 240 age- and gender-matched subjects who were hospitalized in the department of rheumatology, orthopedics, and geriatric medicine. They had no history of cardiovascular or cerebrovascular disease and were not taking lipid-lowering drugs.

STATISTICS

Numerical data are expressed as mean \pm SD. Homogeneity between the three stroke subtypes was studied by a chi-square test for categorical, and an analysis of variance for numerical, variables. Patient and control subject variables were compared by a paired t-test. Comparison between LVD and SVD subtypes was evaluated using unpaired t-test for univariate analysis and Wald test for logistic regression after adjustment for covariates. All statistical tests were two-tailed. Data analysis was performed with SPSS statistical software (SPSS Inc., Chicago, IL).

Results

Fifty-eight of the 240 patients presented with a TIA and 182 with an ischemic stroke. Race was Caucasian in all patients. There were 148 men and 92 women. Mean age was 66.2 ± 12.0 years (range, 17 to 90 years). In this selected cohort, the etiologic subtype was considered as SVD in 65 patients, LVD in 61, and CED in 114. Cardioembolic disease was atrial fibrillation in 44 patients, left atrial stasis or left ventricular thrombus in 32, ischemic heart disease in 9, prosthetic valve in 6, patent foramen ovale in 42, and atrial septal aneurysm in 37 (some patients fitted into more than one category).

Age, gender, diabetes, and alcohol consumption were not significantly different among the three stroke/TIA subtypes (table 1). Hypertension was more frequent in patients with SVD than in those with CED ($p = 0.013$), but there were no differences in the presence of hypertension between patients with LVD and SVD or between LVD and

Table 1

Risk factors in the three stroke subtypes

Risk factors	CED n = 114	SVD n = 65	LVD n = 61	P
Mean age, y	68.0 ± 12.3	64.1 ± 12.0	65.0 ± 10.8	n.s.
Male, n (%)	62 (54.4)	45 (69.2)	41 (67.2)	n.s.
Diabetes, n (%)	17 (14.9)	14 (21.5)	10 (16.4)	n.s.
Hypertension, n (%)	43 (37.7)	37 (56.9)	30 (49.2)	SVD-CE, = .013
Smoking, n (%)	29 (25.4)	25 (38.5)	34 (55.7)	LVD-CE, < .001
Alcohol intake, n (%)	16 (14.0)	9 (13.8)	6 (9.8)	LVD-SVD, = .052
				n.s.

CED : cardioembolic disease ; LVD : large vessel disease ; SVD : small vessel disease.

CED patients. Smoking was significantly associated with LVD when compared to CED ($p < 0.001$), and tended to be more frequent in SVD patients when compared with LVD but this did not reach statistical significance ($p = 0.052$).

Compared to the control group, the stroke/TIA patients had a significantly higher level of total-C (217.7 ± 49.7 vs. 202.3 ± 45.8 mg/dl ; $p = 0.001$), LDL-C (144.6 ± 44.0 vs. 132.5 ± 40.3 mg/dl ; $p = 0.002$), and TG (156.6 ± 67.8 vs. 123.79 ± 61.9 mg/dl ; $p < 0.001$), and a lower HDL-C (41.5 ± 12.1 vs. 45.9 ± 17.7 mg/dl ; $p = 0.010$). When the different stroke/TIA subtypes were considered, the CED patients had a significantly higher level only in TG ($p = 0.037$) (table 2). Those with SVD had higher levels of total-C ($p = 0.005$) and TG ($p < 0.001$), whereas LDL-C tended to be higher but without reaching statistical significance ($p = 0.057$). In LVD patients, total-C ($p = 0.018$), LDL-C ($p = 0.004$), and TG ($p = 0.014$) were higher and HDL-C ($p = 0.001$) lower than in controls. When the plasma lipid profile was compared between the SVD and LVD subtypes, only HDL-C was discriminating, with a significantly lower level in patients with LVD than in those with SVD (37.4 ± 10.6 vs. 41.7 ± 13.4 mg/dl ; $p = 0.047$). After adjustment for age, gender, hypertension, diabetes, smoking, and alcohol intake, logistic regression analysis showed that decreased HDL-C ($p = 0.020$), and smoking ($p = 0.019$) were significant discriminative factors for LVD vs. SVD.

Discussion

In the HPS study, simvastatin significantly reduced the risk of any major vascular event (including stroke) in patients with a history of cerebrovascular disease (MRC/BHF, 2002). However, this trial does not provide data about the efficacy of simvastatin in reducing the risk of ischemic stroke in patients with a history of ischemic cerebrovascular disease, or about variations in the degree of reduced risk according to the etiology of the stroke. In secondary prevention, reduction of the risk of recurrent ischemic stroke might be expected with statins (at least through their lipid-lowering effect)

if a correlation can be established between hypercholesterolemia and ischemic stroke or some specific ischemic stroke/TIA subtypes. However, such correlation remains controversial, and more particularly with the etiologic stroke/TIA subtypes.

In several studies, ischemic stroke was associated with hypercholesterolemia (Iso *et al.*, 1989 ; Qizilbash *et al.*, 1991 ; Benfante *et al.*, 1994 ; Amarenco *et al.*, 1998 ; Sacco *et al.*, 2001 ; Koren-Morag *et al.*, 2002), a low level of HDL-C (Qizilbash *et al.*, 1991 ; Sidharam, 1992 ; Lindgren *et al.*, 1992 ; Lindenstrom *et al.*, 1994 ; Tanne *et al.*, 1997 ; Wannamethee *et al.*, 2000 ; Tanne *et al.*, 2001 ; Sacco *et al.*, 2001 ; Koren-Morag *et al.*, 2002), and hypertriglyceridemia (Nubiola *et al.*, 1981 ; Salonen and Puska, 1983 ; Qizilbash *et al.*, 1991 ; Lindgren *et al.*, 1992 ; Lindenstrom *et al.*, 1994 ; Hachinski *et al.*, 1996 ; Tanne *et al.*, 2001 ; Iso *et al.*, 2002). However, not all studies reported an association with hypercholesterolemia (Noma *et al.*, 1979 ; Tilvis *et al.*, 1987 ; Iso *et al.*, 2002) or hypertriglyceridemia (Gordon *et al.*, 1981 ; Rhoads and Feinleib, 1983 ; Aronow *et al.*, 1988 ; Wolf *et al.*, 1991 ; Sidharam, 1992 ; Wannamethee *et al.*, 2000 ; Sacco *et al.*, 2001). In some, only a severe hypercholesterolemia (total-C levels > 8 mmol/L) was associated with ischemic stroke (Lindenstrom *et al.*, 1994) or non fatal stroke in men (Wannamethee *et al.*, 2000). Whereas a low HDL-C level has been reported to be associated with ischemic stroke in many studies, this was not observed in the Framingham study except for men. In another, hypertriglyceridemia was weakly associated with ischemic stroke in women but not in men (Njolstad *et al.*, 1996). Our controlled study shows that ischemic stroke/TIA is associated significantly with a higher level of total-C, LDL-C, HDL-C (inversely), and TG. Therefore, these results confirm that hypercholesterolemia and hypertriglyceridemia may be a risk factor for ischemic cerebrovascular disease. However, the issue of whether hyperlipidemia is related more to any particular stroke subtype remains unsettled. Although two studies have shown that a high level of total-C and TG was significantly associated with atherothrombotic stroke as compared to control

Table 2

Plasma lipid profile in the three stroke subtypes and controls

	CED		SVD		LVD	
	Patients	Control	Patients	Control	Patients	Control
Total C	208.1 ± 52.4	200.3 ± 43.5	229.8 ± 40.4†	205.1 ± 52.8	222.7 ± 50.6*	203.1 ± 42.2
LDL-C	137.0 ± 45.2	130.7 ± 41.5	152.2 ± 36.8	138.2 ± 43.2	150.8 ± 46.9†	129.7 ± 34.3
HDL-C	43.5 ± 11.7	46.6 ± 18.1	41.7 ± 13.4	44.1 ± 18.7	37.4 ± 10.6†	46.4 ± 16.0
TG	137.4 ± 60.5*	120.9 ± 57.0	179.9 ± 62.8‡	118.0 ± 51.9	167.7 ± 76.0*	134.9 ± 78.1

Significance of differences between patients and controls : * $P < .05$; † $P < .01$; ‡ $P < .001$.

Values are expressed as mean ± SD and given in units of mg/dl.

CED : cardioembolic disease ; LVD : large vessel disease ; SVD : small vessel disease ; Total-C : total cholesterol ; LDL-C : low-density lipoprotein cholesterol ; HDL-C : high-density lipoprotein cholesterol ; TG : triglycerides.

subjects (Hachinski *et al.*, 1996) or cardioembolic stroke (Dahl *et al.*, 2000), the issue of whether triglycerides and the different fractions of cholesterol can be considered as risk factor for the three main etiologic stroke/TIA subtypes remains a matter of debate.

Some studies (Lindgren *et al.*, 1992 ; Ryu *et al.*, 1992 ; Palomaki *et al.*, 1993 ; Hachinski *et al.*, 1996 ; Sharrett *et al.*, 1999), but not all (Bogousslavsky *et al.*, 1985 ; Ford *et al.*, 1985 ; Shintani *et al.*, 1993 ; Iso *et al.*, 2002), have reported a significant association between hypertriglyceridemia and extracranial arterial atherosclerosis. A positive association with lacunar infarction or cardioembolic stroke has also been reported in one study (Lindgren *et al.*, 1992), but not in another (Iso *et al.*, 2002). Our controlled study shows that hypertriglyceridemia is significantly associated with LVD, SVD, and CED, and therefore does not seem to be related to one particular stroke/TIA etiology. These findings support the hypothesis that hypertriglyceridemia may play a role in atherosclerosis not only of large cerebral vessels but also of small penetrating arteries.

The Framingham study showed a good correlation between increasing serum cholesterol and an increased risk of cardiovascular disease (Gordon *et al.*, 1981). Cardioembolic stroke may be due in part to ischemic heart disease, leading to emboligenic conditions such as myocardial infarct or arrhythmia (Pearson, 1984). Therefore, an association between CED and hyperlipidemia might be expected. Our study, like two others (Lindgren *et al.*, 1992 ; Iso *et al.*, 2002), does not demonstrate any evidence for an association between CED and hypercholesterolemia, but the TG level was however higher than in the control group. An increased TG level in cardioembolic strokes has also been observed in one study (Lindgren *et al.*, 1992), but not in another (Iso *et al.*, 2002).

In large artery atherosclerotic disease, total-C and LDL-C increase the carotid intima-media thickness, while HDL-C exerts a protective effect (Ford *et al.*, 1985 ; Lindgren *et al.*, 1992 ; Palomaki *et al.*, 1993 ; O'Leary *et al.*, 1996 ; Hachinski *et al.*,

1996 ; Sacco *et al.*, 2001). Several reports (Bogousslavsky *et al.*, 1985 ; Ford *et al.*, 1985 ; Salonen *et al.*, 1988 ; Tell *et al.*, 1988 ; Handa *et al.*, 1990 ; Heiss *et al.*, 1991 ; Tell, 1991 ; Homer *et al.*, 1991 ; Palomaki *et al.*, 1993 ; Kontishi *et al.*, 1993 ; Fine-Edelstein *et al.*, 1994 ; Fabris *et al.*, 1994 ; Sacco *et al.*, 1995 ; O'Leary *et al.*, 1996 ; Wilson *et al.*, 1997 ; Amarenco *et al.*, 1998), though not all (Ingall *et al.*, 1991 ; Lindgren *et al.*, 1992 ; Iso *et al.*, 2002), have shown a correlation between LVD and high levels of total-C and LDL-C. However, this association is not uniform across the different studies. In 121 consecutive patients who underwent cerebral angiography (Ford *et al.*, 1985), the extent of carotid bifurcation atherosclerosis was inversely associated with HDL-C, but there were no correlations with total-C or LDL-C concentrations. In a controlled study (Bogousslavsky *et al.*, 1985), the mean level of total-C was only associated with carotid occlusion but not with stenosis. In other reports, the association disappears after adjustment for confounding factors (Palomaki *et al.*, 1993 ; Fabris *et al.*, 1994). In the GENIC case-control study (Amarenco *et al.*, 1998), hypercholesterolemia (LDL-C > 1.6 g/l or current lipid-lowering therapy) was found in 27.9% of patients with atherothrombotic infarction and 6.3% of controls, and was also significantly associated with > 30% carotid stenosis. Similarly, our study demonstrates that LVD is strongly related to elevated total- and LDL-C, and decreased HDL-C.

The relationship between hypercholesterolemia and SVD remains controversial. Hypercholesterolemia was more frequent in lacunar infarctions than in controls (32.1% vs. 6.3%) in the GENIC study (Amarenco *et al.*, 1998). Other controlled studies were negative (Kazui *et al.*, 2000 ; Iso *et al.*, 2002) or showed an association with decreased HDL-C but not with total-C (Lindgren *et al.*, 1992 ; Shintani *et al.*, 1993). In contrast, our study shows higher total-C levels and a trend towards increased LDL-C in SVD patients compared to controls. This suggests that hypercholesterolemia may be involved in the etiology of SVD, in addition to hypertension and diabetes mellitus.

Few studies have compared the plasma lipid profiles of patients with LVD and SVD which are both responsible for atherothrombotic strokes. In a cohort of patients with ischemic stroke (Bogousslavsky *et al.*, 1988), hypercholesterolemia (> 6.5 mmol/l) was more often observed in patients with SVD (15%) than in those with LVD (4.4%). In two studies (Lindgren *et al.*, 1992 ; Cerrato *et al.*, 2002), there were no statistical differences for total-C, LDL-C, and TG. Our study shows that cholesterol and TG levels are similar in these two subtypes, but the univariate analysis shows that LVD differs from SVD by a greater decrease in HDL-C. Moreover, the logistic regression analysis still retains HDL-C, in addition to smoking, as a discriminative parameter for LVD after adjustment for vascular risk factors. This result suggests that the protective effect of HDL-C against atherosclerosis cannot be as marked in the penetrating arteries as in the large extracranial arteries. Similarly, Lindgren *et al.* (1992) found that the HDL-C level was the lowest in the LVD subtype, although the difference with the SVD subgroup was not significant.

In conclusion, this controlled study shows that hyperlipidemia is associated with ischemic stroke/TIA as a whole. Hypertriglyceridemia is commonly found in ischemic cerebrovascular disease whatever the etiologic subtype, whereas hypercholesterolemia is more related to SVD and LVD. In addition to hypertension and diabetes, hypercholesterolemia may be involved in the etiology of SVD and differs from LVD by a lower decrease in HDL-C. Our study supports the view that the therapeutic targets in atherothrombotic stroke should be total-C and HDL-C, and lowering triglycerides should be targeted in all stroke types.

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