Risk factors for and incidence of subtypes of ischemic stroke

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Summary

The TOAST classification divides patients with ischemic stroke into five subgroups according to the presumed etiological mechanism. The aims of the present study were to evaluate the distribution of the different etiological stroke subtypes in a hospital-based sample of stroke patients, and to investigate the association between important risk factors and stroke subtypes.
A total of 210 patients with a first-ever ischemic stroke admitted to the stroke unit of Asker and Bærum Hospital in Norway between February 2007 and July 2008 were enrolled in the study. Information on vascular risk factors was collected at admittance, examination of neurological deficits was carried out during their stay, and classification was made according to the TOAST criteria. According to the TOAST classification, 24 (11.4%) of the patients suffered from large vessel disease, 66 (31.4%) from cardioembolic disease, 66 (31.4%) from small vessel disease and 54 (25.7%) from a stroke of undetermined etiology. The presence of hyperlipidemia and atrial fibrillation varied significantly between the different subtypes. In multivariate analyses, hyperlipidemia [odds ratio (OR) 2.46, 95% confidence interval (CI) 1.32-4.60] and current smoking (OR 2.06, 95% CI 1.04-4.08) were the only variables that were related to small vessel disease.
Small vessel disease was observed more frequently and large vessel disease less frequently than previously reported. Small vessel disease was significantly associated with hyperlipidemia and current smoking. Our study supports the view that the etiology of lacunar strokes is multifactorial.

KEY WORDS: cerebrovascular disease, stroke, risk factors for stroke

Introduction

The Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification was introduced in 1993 to improve the subclassification of ischemic stroke (1). Differentiation between etiological subgroups of cerebral infarction has therapeutic implications, and makes it easier to predict prognosis. The TOAST classification divides patients with ischemic stroke into five subgroups according to the presumed etiological mechanism: cardioembolic disease, large vessel disease, small vessel disease, unusual causes of stroke and stroke of undetermined etiology. Stroke of unusual etiology is caused by mechanisms such as hypercoagulable conditions or hematological disorders. Stroke of undetermined etiology has either no probable etiology or more than one potential cause. The TOAST classification is based on clinical and radiological findings as well as supplementary investigations such as color duplex of precerebral arteries, electrocardiogram (ECG), echocardiography and blood samples. The TOAST classification has been found to be valid and reliable (2).
Traditionally, it has been estimated that cardioembolic disease is the cause in 20%, large vessel disease in 50%, and small vessel disease in 25% of all cerebral infarctions (3). Most studies fail to identify a definite cause in 25-39% of patients (4). In more recent studies, small vessel disease has been reported to be more frequent and large vessel disease less frequent than previously estimated (5-9), but different studies diverge (10).
There has been some disagreement regarding the association between risk factors and various stroke subtypes. Different risk factor profiles are differently associated with different subtypes, but the contribution of each single risk factor has hardly been evaluated. According to the initial definition of lacunar stroke syndrome, patients had to suffer from hypertension and diabetes in order to fulfill the diagnostic criteria (11). Hypertension and cigarette smoking are known to be main risk factors for all ischemic strokes (8), and cigarette smoking has been reported to be significantly associated with infarctions due to atherosclerosis (8). In 2001, Kolominsky-Rabas found lower frequencies of large vessel disease (15.3%) and higher frequencies of small vessel disease (30.2%) than earlier reported (6). The major risk factors for small vessel disease were hypertension and diabetes, while smoking was associated with large vessel disease. A later study reported that hypertension was the strongest risk factor for all ischemic stroke subtypes (10). Changes in the prevalence of vascular risk factors may influence the etiology, prevalence and management of acute ischemic stroke. It is therefore necessary to study the distribution across etiological subtypes repeatedly and in different populations.
Thus, the aims of the present study were to evaluate the distribution of the different etiological stroke subtypes in

a hospital-based sample of first-ever stroke patients, and to investigate the association between possible risk factors and stroke subtypes.

Materials and methods

Patients

All patients surviving their first-ever stroke admitted to the stroke unit of Asker and Bærum Hospital between February 2007 and July 2008 were invited to participate in a prospective study. The hospital has a policy of admitting all stroke patients directly to the acute stroke unit which serves two communities with a total population of approximately 160,000 inhabitants. These two communities are among the most affluent in Norway, and the inhabitants have good access to their general practitioner. Exclusion criteria were known cognitive decline as indicated by a score ≥3.7 on the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) (12), previous stroke or transient ischemic attack (TIA), and a diagnosis of subarachnoid hemorrhage. In addition, patients who did not speak Norwegian and patients with an estimated life expectancy of less than one year were excluded.

Diagnosis of ischemic stroke and TIA

The diagnosis of stroke and the classifications according to the TOAST criteria were based on the history of symptoms and their acute presentation, clinical examination, and cerebral CT scans. The clinical criteria for small vessel disease included the presence of a lacunar syndrome, characterized either by pure motor stroke, pure sensory stroke, sensory motor stroke, ataxic hemiparesis or the dysarthria-clumsy hand syndrome. Patients diagnosed with small vessel disease should be free from aphasia, apraxia and visuospatial disturbance, and present no neglect phenomena or visual field defects. Lesions on CT or MRI should be less than 1.5 cm. For a diagnosis of large vessel disease to be made, there should be paraclinical signs including duplex or arteriographic signs of a significant (>50%) stenosis or occlusion of the internal carotid artery or middle cerebral artery on the symptomatic side. A diagnosis of a cardioembolic stroke requires paraclinical signs of a source of cardiac embolism. The most frequent cardioembolic sources are atrial fibrillation, prosthetic heart valves, recent myocardial infarction, dilated cardiomyopathy, intracardiac tumors, rheumatic mitral stenosis and infective endocarditis. A patent foramen ovale (PFO) without any other source of embolism was classified as cardioembolic disease according to Warlow el al. (3).
Stroke patients with a clinical stroke syndrome but no corresponding lesion on brain imaging were classified according to the clinical presentation and paraclinical findings. A clinical presentation of a lacunar syndrome (see above) with no signs of large vessel disease or cardioembolic disease was diagnosed as small vessel disease. Stroke syndromes with signs of cortical affection but without a source of embolism were classified as stroke of undetermined etiology. Patients with either no probable etiology or more than one potential cause were also classified as stroke of undetermined etiology.

All the patients but one were examined with a precerebral color duplex scan and all the patients underwent an ECG at admittance and on day 1. Ninety-two (44%) had a cerebral MRI and 85 (41%) an echocardiography. The protocol of our hospital states that a CT scan should be carried out in all patients in the acute setting, and MRI in selected patients (13). Patients with cortical symptoms and no source of embolism on ECG or echocardiography were monitored with a 24-hour ECG. All paraclinical assessments were performed during the stay or within 14 days if the patients had an early discharge.
Patients under 60 years with no findings on routine ECG, echocardiography or precerebral duplex scan, and selected patients with cortical symptoms without a source of embolism, were screened for thrombophilia. The same patients, in total 13, were assessed with a transeosophageal echocardiography (TEE).

Assessments

Known vascular risk factors such as treated hypertension, hyperlipidemia [total cholesterol >5 mmol/l, low density lipoprotein (LDL)-cholesterol >3 mmol/l], diabetes mellitus, atrial fibrillation, coronary heart disease (present angina pectoris or previous myocardial infarction), alcohol use, smoking and a family history of vascular disease, were recorded. The duration of treated hypertension was not recorded. Regarding primary prevention, 28.6% of the patients were on statin therapy prior to the cerebrovascular event, 38.1% on antiplatelet therapy, 11.4% used oral anticoagulation, 8.6% used oral anti-diabetic medication, and 3.3% were insulin-dependent. During the hospital stay**,** weight and height were recorded. Overweight was defined as a body mass index (BMI=weight/height squared) over 25 (14). Neurological impairments were measured by the National Institute of Health Stroke Scale (NIHSS) (15). The neurological examination was performed on the first day after admittance by an experienced stroke physician. We screened for pre-stroke cognitive impairment using the 26-question version of the IQCODE. When possible, the questionnaire was filled in by first-degree relatives. The NIHSS was re-assessed at discharge by a stroke physician. Activities of daily living (ADL) were assessed at discharge by dedicated stroke nurses using the Barthel ADL index (16). The Oxfordshire Community Stroke Project (OCSP) (17) and TOAST classifications as well as the modified Rankin Scale score (16) were recorded at discharge in accordance with the routine stroke unit practice at our hospital. Due to somewhat different definitions of lacunar stroke, this subtype was coded as small vessel disease in the TOAST classification and as lacunar circulation infarction or posterior circulation infarction in the OCSP classification.
This study was approved by the Regional Committee for Ethics in Medical Research and by the data protection authorities. Patients gave their written informed consent before inclusion. First-degree relatives gave consent on behalf of patients with reduced capacity.

Statistical analysis

Statistical analyses including table analyses, and bivariate and multivariate logistic regression analyses, were

performed using the SPSS package version 18 (SPSS Inc., Chicago, IL, USA). Variables that were associated with the outcome with a p-value below 0.2 in bivariate analyses were subjected to multivariate logistic regression analyses by forward selection and backward elimination, in order to identify risk factors independently associated with the different TOAST subtypes. The vascular risk factors were dichotomized into pathological or normal according to American Heart Association recommendations (18) and the European Stroke Initiative Recommendation from 2003 (19). The results are presented as the odds ratio (OR) with 95% confidence intervals (CI).

Results

Of the 253 patients invited to take part in the study, 250 agreed. Of these, 23 patients were excluded: 12 did not meet the inclusion criteria (six had an IQCODE score ≥3.7, one did not speak Norwegian, one had an infarct in the spinal cord, one had suffered a previous TIA, two withdrew their consent and one died before signing the consent) and another 11 patients were diagnosed with diseases other than stroke. Of the 227 remaining patients, 174 (76.7%) had a cerebral infarction, 36 (15.9%) had suffered a TIA and 17 (7.5%) were diagnosed with a cerebral hemorrhage. Only patients with ischemic cerebrovascular disease, i.e. infarction or TIA, were included in statistical analyses regarding the TOAST classification. The patient characteristics are shown in Table 1.

According to the TOAST classification, 24 (11.4%) of the patients suffered from large vessel disease, 66 (31.4%) from cardioembolic disease and 66 (31.4%) from small vessel disease, whereas 54 (25.7%) had a stroke of undetermined etiology. No patient had stroke of unusual etiology. Echocardiography did not detect any plaques in the aortic arch. Regarding the cardioembolic strokes, 52 patients had atrial fibrillation during the hospital stay, four were diagnosed with atrial fibrillation during follow up, three suffered from PFO, three on inadequate anticoagulation had a possible embolism from a mechanical valve, two had akinesia of the left ventricle, one suffered endocarditis with valve vegetations and one had a myxoma in the left atrium.

The prevalence of risk factors in the different TOAST subtypes is shown in Table 2 (over). Differences between subtypes were statistically significant regarding hyperlipidemia ($p<0.02$, most prevalent among patients with small vessel disease) and atrial fibrillation ($p<0.01$, most prevalent among patients with cardio embolic stroke).

The relationships between the potential risk factors and the different stroke subtypes are displayed in Tables 3, 4 and 5 (over). When small vessel disease was compared to the other ischemic stroke subtypes, hyperlipidemia and current smoking, but not diabetes and hypertension, were found to be significant predictors, when adjusted for the other risk factors (Table 3). Cardioembolic stroke, on the other hand, was significantly associated with atrial fibrillation and a BMI ≥25 as shown in Table 4. Regarding large vessel disease, the only association was a borderline significant association with hyperlipidemia (Table 5). No statistically significant relationships were identified between stroke of unusual etiology, compared to the other subtypes, and the various risk factors (data not shown).

Table 1 - Baseline characteristics of patients (n=210)

	n(%) if not otherwise specified
Demographics	
Male	106 (51)
Mean age, years (SD)	73.1 (11.9)
Fewer than nine years of education	53 (25)
Risk factors	
Hypertension (treated)	126 (60)
Hyperlipidemia	116 (55)
Diabetes mellitus	26 (12)
Cigarette smoking (current)	48 (23)
Coronary heart disease	49 (23)
Atrial fibrillation	71 (34)
Daily alcohol use	38 (18)
BMI>25	115 (55)
Mechanical heart valve	4 (2)
OCSP classification	
TACI	22 (11)
PACI	97 (46)
LACI	64 (31)
POCI	27 (13)
Topography	
Right hemisphere	81 (39)
Left hemisphere	103 (49)
Cerebellum/brainstem	26 (12)
Assessments	
NIHSS day one, mean (SD)	4.0 (6.2)
NIHSS at discharge, mean (SD)	2.4 (4.5)
BI, mean (SD)*	17.5 (4.9)
mRS ≤2	164 (78)

Abbreviations and definitions: Hyperlipidemia=total cholesterol >5 or LDL-cholesterol >3; LDL=low density lipoprotein; Coronary Heart Disease=previous myocardial infarction or present angina pectoris; BMI=body mass index; OCSP=Oxfordshire Community Stroke Project classification; TACI=total anterior circulation infarction; PACI=partial anterior circulation infarction; LACI=lacunar circulation infarction; POCI=posterior circulation infarction; NIHSS=National Institutes of Health Stroke Scale; BI=Barthel Activities of Daily Living Index; mRS=modified Rankin scale

* The BI data are based on n=205

Discussion

In this study the incidence of small vessel disease and cardioembolic disease as the cause of stroke was found to be higher than reported in previous studies, whereas the incidence of large vessel disease was lower. Compared to other ischemic stroke subtypes, small vessel disease was significantly associated with hyperlipidemia and current smoking. Cardioembolic disease was more strongly associated with atrial fibrillation and overweight than were the other etiological stroke subtypes.

In 1997, up to 40% of stroke patients were treated outside hospital (20,21). Thus, earlier hospital-based studies tended to include patients with more severe strokes, and, consequently, the mortality was higher. Today a higher proportion of stroke patients are hospitalized, including those with minor strokes, and more patients undergo etiological examinations. The diagnosis of stroke and TIA is still essentially clinical, but more patients re-

Table 2 - Prevalence of risk factors in patients with stroke of different TOAST subtypes

Risk factor	Small vessel disease n (%)	Cardioembolic disease n (%)	Large vessel disease n (%)	p-value*
Hypertension (treated)	38 (58)	45 (68)	15 (63)	0.31
Hyperlipidemia	46 (70)	34 (52)	9 (38)	0.02
Daily smoking	21 (32)	11 (17)	4 (17)	0.17
Diabetes	8 (12)	11 (17)	3 (13)	0.50
Atrial fibrillation	0	52 (79)	6 (25)	<0.01
Overweight	36 (55)	42 (64)	11 (46)	0.28
Coronary heart disease	10 (15)	21 (32)	7 (29)	0.12
Daily alcohol use	10 (15)	13 (20)	4 (17)	0.87
Mechanical heart valve	0	3 (5)	0	0.24

Definitions: Hyperlipidemia=total cholesterol >5 or LDL-cholesterol >3; Overweight=BMI ≥25; Coronary heart disease=previous myocardial infarction or present angina pectoris

*Pearson's chi-square

Table 3 - Associations between cardioembolic disease and potential risk factors (reference: cardioembolic disease, large vessel disease and stroke of unusual etiology)

Explanatory variables	Bivariate analyses		Multivariate analyses		p-value*
	OR	95% CI	OR	95%CI	
Age over 75 years	0.65	0.36-1.16			
Male gender	1.03	0.57-1.84			
Body Mass Index ≥25	0.99	0.55-1.77			
Current smoking*	2.02	1.04-3.94	2.06	1.04-4.08	0.038
Coronary heart disease	0.48	0.22-1.04			
Hypertension (treated)	0.86	0.48-1.56			
Diabetes	0.97	0.40-2.35			
Hyperlipidemia	2.43	1.31-4.51	2.46	1.32-4.60	0.005

Definitions: Coronary heart disease=previous myocardial infarction or present angina pectoris; Hyperlipidemia=total cholesterol >5 or LDL-cholesterol >3.

*Reference category: ex-smokers and non-smokers

Table 4 - Associations between cardioembolic disease and potential risk factors (reference: small and large vessel disease and stroke of unusual etiology)

Explanatory variables	Bivariate analyses		Multivariate analyses		p-value*
	OR	95% CI	OR	95%CI	
Age over 75 years	1.31	0.73-2.36			
Male gender	1.12	0.63-2.01			
Body Mass Index ≥25	1.70	0.94-3.10	2.51	1.11-5.66	0.027
Current smoking*	0.58	0.27-1.22			
Coronary heart disease	1.93	1.00-3.75			
Hypertension (treated)	1.67	0.90-3.08			
Diabetes	1.72	0.74-3.98			
Hyperlipidemia	0.80	0.45-1.44			
Atrial fibrillation	24.4	11.4-52.4	27.7	12.4-62.0	<0.001

Definitions: Coronary heart disease=previous myocardial infarction or present angina pectoris; Hyperlipidemia=total cholesterol >5 or LDL-cholesterol >3.

*Reference category: ex-smokers and non-smokers

Table 5 - Associations between large vessel disease and potential risk factors (reference: small vessel disease, cardioembolic disease and stroke of unusual etiology)

Explanatory variables	Bivariate analyses	
	OR	95% CI
Age over 75 years	1.37	0.58-3.24
Male gender	1.02	0.44-2.39
Body Mass Index ≥25	0.67	0.28-1.57
Current smoking*	0.65	0.21-1.99
Coronary heart disease	1.41	0.55-3.63
Hypertension (treated)	1.13	0.47-2.71
Diabetes	1.01	0.28-3.66
Hyperlipidemia	0.44	1.18-1.06

Definitions: Coronary heart disease=previous myocardial infarction or present angina pectoris; hyperlipidemia=total cholesterol >5 or LDL-cholesterol >3.

*Reference category: ex-smokers and non-smokers

ceive an MRI during the acute phase. Accordingly, lacunar lesions are detected more frequently. In the present sample of patients with acute stroke, the two main risk factors, hypertension and diabetes, were well controlled. A combination of a higher frequency of hospitalization among stroke patients, more advanced investigations and better control of risk factors may have contributed to the high incidence of small vessel disease found in the present study.

Cardioembolic disease is reported to be more frequent in hospitalized than in non-hospitalized patients. In our sample, the main cause of cardioembolic disease was atrial fibrillation. The main risk factor for developing atrial fibrillation is age. The mean age in our sample was higher (72.1 years) than reported in previous studies (8), possibly explaining the high incidence of cardioembolic disease found. Furthermore, a high BMI is a well-known risk factor for atrial fibrillation (22). More than fifty percent of the patients in our study had a BMI ≥ 25. As shown by Abbot et al., the risk of stroke in patients with asymptomatic arteriosclerosis of the carotid artery has declined in recent decades due to better medical treatment and a decline in the frequency of smoking (23). Many of the patients in our study were already on treatment for known vascular risk factors when they suffered their first stroke. This may explain why the incidence of large vessel disease was lower than previously reported.

The two risk factors most strongly related to a diagnosis of small vessel disease in the present study were current smoking and hyperlipidemia. Risk factors for ischemic stroke are well known (8,24,25), but the risk factor profiles for different subtypes is still under discussion. Petty et al. did not find hypertension and diabetes to be associated with lacunar infarctions (9), whereas Kolominsky-Rabas et al. and Khan et al. did find an association between hypertension and small vessel disease (6,26). In these studies, smoking was associated with large vessel disease. The high proportion of patients with well-regulated hypertension in the present sample may indicate that the etiology of lacunar infarcts is more complex than supposed by the lacunar hypothesis.

It is of clinical importance that small vessel disease, compared to other ischemic stroke subtypes, was significantly associated with hyperlipidemia and current smoking, since these risk factors are modifiable through lifestyle interventions and medical therapies. The findings regarding risk factors and their association with ischemic stroke subtypes should encourage physicians to focus on both primary and secondary prevention directed towards modifiable risk factors.

Cardioembolic disease, as compared to other stroke subtypes, was significantly associated with a BMI ≥25. Overweight and obesity in high-income countries are dramatically on the rise, and may lead to serious health consequences including risk for cardiovascular disease. Obesity may be preventable, and recommendations include more physical activity and a diet with decreased intake of energy-dense foods that are high in fat and sugar.

Our study has some limitations. The TOAST classification is under discussion (27,28). However, currently no other etiological classification system of ischemic stroke is available. Although the diagnosis of stroke is clinical, supplementary investigations such as cerebral MRI play an increasingly important role. We included only first-ever stroke patients without known pre-stroke cognitive decline. In addition, only patients who survived the acute phase in the stroke unit (day 7-10) were eligible. Therefore, some patients with the most severe strokes were not included. This may have led to an overrepresentation of lacunar stroke (29). PFO was classified as cardioembolic stroke, but could also have been classified as an unusual cause (3). A diagnosis of PFO was based on TEE with intravenously administered contrast, and not on additional transcranial Doppler or transcranial color coded duplex sonography with intravenous contrast (30).The high socio-economic level in this sample does not necessarily reflect the stroke population in all Western countries. The vascular risk factors are inconsistently defined in different studies, and this may influence the contribution of each risk factor to each ischemic stroke subtype. Finally, since we had no control group without stroke, our reported relationships are relative and may reflect the risk factors that had the strongest impact on the respective subtypes compared to the others.

In conclusion, we observed a higher incidence of small vessel disease and cardioembolic disease, and a lower incidence of large vessel disease in our sample of stroke patients compared to previous studies. Small vessel disease, in contrast to the other subtypes, was significantly associated with hyperlipidemia and current smoking. Our study supports the assumption that the etiology of lacunar infarcts may be more multifactorial than originally believed. In times when vascular risk factors are better controlled and lifestyle-related risk factors are expected to become more prevalent, we have to focus on all the known vascular risk factors and optimize the risk factor intervention for each patient. Studies on stroke mechanisms, prevention and treatment are needed to improve the long-term follow up of these patients, especially regarding modifiable vascular risk factors.

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