Ischaemic stroke subtypes and associated risk factors: a French population based study

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Received 24 March 2008
Revised 20 May 2008
Accepted 8 June 2008
Published Online First 27 June 2008

ABSTRACT

Background: There is little reliable population based information about the distribution of risk factors among the various ischaemic stroke subtypes, even though determining risk factor profiles is of major importance to develop targeted preventive strategies.

Methods: The distribution of first ever ischaemic stroke subtypes was established in a prospective population based study conducted in Dijon, France (152 606 inhabitants). Cases were collected between January 2005 and December 2006, and were classified using TOAST classification. Vascular risk factors were recorded to determine a risk factor profile for each subtype.

Results: 332 patients with first ever ischaemic stroke (150 men and 182 women) were recorded. Adjusted incidence to world population was 54/100 000/year. The distribution of ischaemic stroke subtypes was as follows: 119 (35.8%) cases of large artery atherosclerosis, 89 (26.8%) small artery occlusions, 81 (24.4%) cardioembolisms and 43 (13%) other and undetermined causes. The most frequent vascular risk factor was hypertension, irrespective of the ischaemic stroke subtype, with a total prevalence of 62%. Using multivariate regression, a positive association between cardioembolism and age (OR 1.051; 95% CI 1.026 to 1.076; $p<0.001$) was demonstrated and between small artery occlusion and either high blood pressure (OR 1.86; 95% CI 1.06 to 3.27; $p = 0.03$) or hypercholesterolaemia (OR 2.23; 95% CI 1.33 to 3.76; $p = 0.02$).

Conclusion: This comprehensive prospective population based study has demonstrated that vascular risk factors exhibit a particular distribution according to the ischaemic stroke subtypes. These findings, as well as the great frequency of hypertension among stroke patients, have implications for prevention strategies, the design of clinical trials and the organisation of health care services.

Ischaemic stroke is characterised by great heterogenicity since various pathophysiological mechanisms are usually involved. Worldwide disparities in the proportion of ischaemic stroke subtypes have been observed as a result of a few studies using the aetiological TOAST classification.[1–7] For this reason, it is essential to have a clear understanding of the distribution of subtypes in a geographically or ethnically defined population, all the more so since the prognosis in terms of mortality and handicap varies according to the nature of the stroke.[1 7–10] In addition, it is important to know the different risk factor profiles with regard to the aetiology of ischaemic stroke as the frequency of vascular risk factors differs according to the various stroke subtypes.[5 11 12] However, there is some disagreement in the findings of different studies, perhaps because of the inclusion of either hospitalised or non-hospitalised patients, which could have led to bias in the generalisation of the data.[5] Only a few reliable population based studies focusing on this issue are available, and the results of these studies need to be confirmed to target new preventive strategies based on the association between ischaemic stroke subtypes and particular risk factor profiles. These data also need to be taken into account in the design of future clinical trial.[1 2 5]

The Stroke Registry in Dijon, France, was set up to evaluate the epidemiology of stroke.[13] In the present study, we aimed to determine the proportion of stroke subtypes and their related risk factors in an unselected urban population in cases presenting between January 2005 and December 2006.

MATERIALS AND METHODS

Ischaemic stroke subtypes and their related risk factors were studied from 1 January 2005 to 31 December 2006 in the prospective population based Stroke Registry of Dijon, which complies with the "standard ideal criteria" for population based stroke studies.[14 15]

Study area and population

The study population comprised all residents of the city of Dijon, a town located in east France with a total population of 152 606 inhabitants (69 872 men and 82 734 women). The proportion of individuals aged 65 years or more was 15.8% whereas it was 3.1% for individuals aged over 85 years. To be included, patients who had a first ever stroke had to reside in the city of Dijon at the time of the stroke.

Definition and classification of ischaemic stroke

Stroke was defined according to World Health Organization (WHO) recommendations[16] as "rapidly developing clinical symptoms and/or signs of focal, and at times global, loss of cerebral function, with symptoms lasting more than 24 h or leading to death, with no apparent cause other than that of vascular origin". Clinical diagnosis was always validated on the basis of either CT or MRI, which makes it possible to identify ischaemic strokes. Only first ever ischaemic strokes (ie, occurring for the first time in a patient's lifetime) were considered. All subsequent strokes, occurring 28 days or more after first stroke onset, were recorded as recurrent stroke and were not included in this study. The diagnosis of ischaemic stroke subtype was always performed by a committee of

Table 1 Crude and age standardised to the World population incidence rates of first ever ischaemic strokes in 2005 and 2006 in Dijon, France

Age (year)	n	Proportion (%)	Incidence rate (95% CI)
Men			
<40	3	2	3.6 (0.7–10.6)
40–49	10	7	54.5 (26.1–100.2)
50–59	19	13	117.6 (70.8–183.6)
60–69	20	13	227.3 (138.8–351.0)
70–79	53	35	571.1 (427.8–747.0)
⩾80	45	30	1090.1 (795.1–1458.7)
Total	150	100	107.3 (90.8–126.0)
Adjusted to world population			63.5 (52.3–74.8)
Women			
<40	7	4	7.7 (3.1–15.8)
40–49	8	4	37.4 (16.1–73.7)
50–59	9	5	51.9 (23.7–98.5)
60–69	22	12	209.7 (131.4–317.4)
70–79	40	22	252.3 (180.2–343.5)
⩾80	96	53	1048.1 (849.0–1280.0)
Total	182	100	110.0 (94.6–127.2)
Adjusted to world population			47.1 (38.1–56.1)
Men and Women			
<40	10	3	5.7 (2.8–10.6)
40–49	18	5	45.3 (26.8–71.6)
50–59	28	8	83.6 (55.5–120.8)
60–69	42	13	217.7 (156.9–294.3)
70–79	93	28	370.0 (298.6–453.3)
⩾80	141	43	1061.2 (893.3–1251.5)
Total	332	100	108.8 (97.4–121.1)
Adjusted to world population			53.8 (46.8–60.8)

neurologists on clinical and cerebral imaging data using the original TOAST (Trial of ORG 10172 in Acute Stroke Treatment) criteria.[7] Hence we distinguished five major categories of ischaemic stroke: large artery atherosclerosis (LAA), cardioembolism (CE) originating from atrial fibrillation or other rhythm trouble, valve disease, patent foramen ovale or spontaneous intracavitar thrombus, small artery occlusion (SAO), stroke of other determined cause (OC) and stroke of undetermined cause (UND).

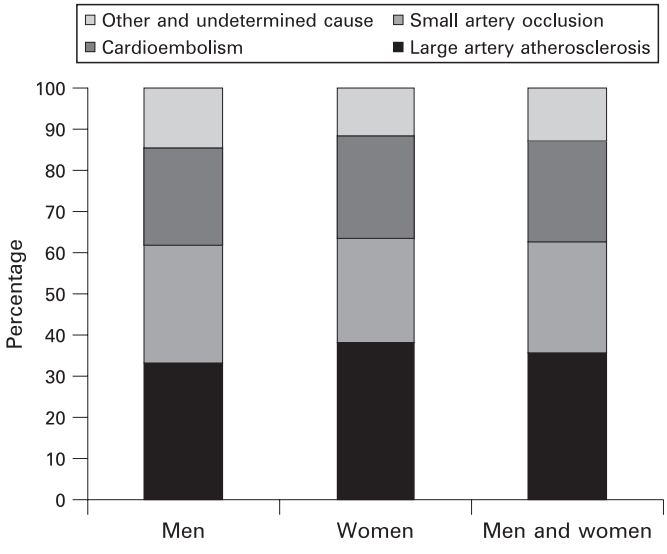

Figure 1 Proportions of stroke subtypes among total ischaemic strokes.

Case ascertainment

To ensure its completeness, case ascertainment was both active and passive. Hence information was provided by six sources[17]: (1) from the emergency rooms, and all of the clinical and radiological departments of Dijon University Hospital, with diagnosis of stroke made by one of the neurologists of the Department of Neurology, where the Stroke Registry is located; (2) from the emergency rooms and all of the clinical departments of the three private hospitals of the city and its suburbs, with diagnosis made by private neurologists working in these establishments; (3) from the patient's home or from the nursing homes of the city, with diagnosis assessed by the 250 general practitioners of the city with the help of an outpatient clinic with either a public or private neurologist who notified and registered the case; (4) from the three private radiological centres, where the medical records were reviewed to identify missed cases that had not been transferred to the registry by the general practitioners; (5) from the ultrasound Doppler centres of the University Hospital and private centres, where medical records were reviewed; (6) from the death certificates obtained from the local Social Security Office responsible for registering all deaths in the community in order to identify fatal strokes occurring in non-hospitalised patients. Hence all of the information collected by the various correspondents was continuously centralised in the Stroke Registry.

We collected classical vascular risk factors using the same methodology previously described.[13–17] Hypertension was listed if there was a previous history of known hypertension with or without antihypertensive treatment, with systolic blood pressure ⩾160 mm Hg and/or diastolic blood pressure ⩾95 mm Hg. Diabetes mellitus was recorded if a glucose level of ⩾7.8 mmol/l had been reported in the medical history of the patient or was

Table 2 Demographic data and risk factors in patients with various ischaemic stroke subtypes.

	LAA	SAO	CE	OC and UND	Overall ischaemic strokes
n	119	89	81	43	332
Age					
Mean (95% CI)	71.5 (20.9–98.6)	73.7 (39.6–95.0)	80.0 (47.7–98.0)	71.8 (29.4–98.5)	74.2 (20.9–98.6)
Male sex					
Yes (n (%))	44 (49.4)	50 (42.0)	33 (40.7)	23 (53.5)	150 (45.2)
Hypertension					
Yes (n (%))	70 (58.8)	65 (73.0)	44 (54.3)	27 (62.8)	206 (62.1)
OR (95% CI)	0.95 (0.63–1.44)	1.67 (1.06–2.64)	0.59 (0.37–0.95)	1.01 (0.51–2)	
p Value	0.8	0.027	0.032	0.97	
Diabetes					
Yes (n (%))	26 (21.9)	17 (19.1)	11 (13.6)	3 (7.0)	57 (17.2)
OR (95% CI)	1.43 (0.86–2.36)	1.13 (0.66–1.91)	0.82 (0.45–1.5)	0.32 (0.1–1.09)	
p Value	0.16	0.66	0.52	0.07	
Previous TIA					
Yes (n (%))	5 (4.2)	10 (11.2)	3 (3.70)	2 (4.7)	20 (6.0)
OR (95% CI)	0.58 (0.25–1.33)	2.82 (1.37–5.81)	0.58 (0.23–1.45)	0.62 (0.14–2.71)	
p Value	0.2	0.005	0.24	0.52	
Hypercholesterolaemia					
Yes (n (%))	55 (46.2)	54 (60.7)	26 (32.1)	16 (37.2)	151 (45.5)
OR (95% CI)	1 (0.68–1.48)	2.3 (1.52–3.48)	0.44 (0.27–0.71)	0.68 (0.36–1.31)	
p Value	0.99	<0.001	0.001	0.25	
Smoking					
Yes (n (%))	26 (21.9)	27 (30.3)	13 (16.1)	13 (30.2)	79 (23.8)
OR (95% CI)	0.74 (0.39–1.41)	2.07 (1.09–3.92)	0.6 (0.27–1.31)	0.81 (0.32–2.9)	
p Value	0.36	0.03	0.6	0.65	
Previous (n (%))	19 (16.0)	11 (12.4)	9 (11.1)	5 (11.6)	44 (13.3)
OR (95% CI)	1.53 (0.79–2.95)	1.23 (0.61–2.47)	0.59 (0.27–1.29)	0.53 (0.17–1.65)	
p Value	0.21	0.56	0.18	0.28	

Odds ratios obtained from univariate analysis.
Missing data for overall ischaemic strokes: hypertension, 0.6%; diabetes, 0.9%; previous TIA, 0%; hypercholesterolaemia, 0.6%; smoking, 9.9%.
CE, cardioembolism; LAA, large artery atherosclerosis; OC, stroke of other determined cause; SAO, small artery occlusion; TIA, transient ischaemic attack; UND, stroke of undetermined cause.

found in the blood sample taken at the time of the stroke (patients who had been treated with insulin or oral hypoglycaemic agents were also considered diabetics). Similarly, hypercholesterolaemia was recorded for total cholesterol ⩾5.7 mmol/l or triglyceride level ⩾1.6 mmol/l, or if patients had been treated with lipid lowering therapy. We also recorded smoking (more than 1 cigarette per day, current or former habit). Atrial fibrillation was diagnosed on ECG or Holter recordings. Two dimensional echocardiography (transthoracic or transoeosophageal cardiography) was performed to detect other cardioembolic sources. Carotid and vertebral ultrasonography as well as standard blood and urine tests were performed. A history of transient ischaemic attack (TIA), defined as sudden development of signs and symptoms affecting motor, sensory, sensorial and speech, brainstem and cerebellum functions lasting less than 24 h was considered as a cerebrovascular risk factor.

Ethics

Our registry was approved by the National Ethics Committee (CNIL) and complied with national rules on informed consent of patients.

Statistical analyses

Data were stored in a computerised database in separate anonymous files. The crude incidence rate per age group and the standardised rate in terms of world populations were calculated for every year and according to sex using the direct method with the SEGI 1996 World population.[18] We assumed Poisson distribution for the annual number of events to calculate 95% confidence intervals (CI) for the rates. We determined the association between stroke subtype and each of the risk factors after adjustment for differences in age and sex in univariate and multivariate logistic regression analyses. Smoking was excluded from the mutlivariate analysis because >10% of the data were missing. Statistical analysis was performed with STATA 9.0 software.

RESULTS

Over the 2 year period, 332 first ever ischaemic strokes were recorded (table 1). Among these, 150 (45%) patients were men and 182 (55%) were women. Mean age at stroke onset was 74.2 years. Of these 332 cases, 246 (74.1%) were hospitalised at the University Hospital, 47 (14.2%) were managed in a private hospital and 39 (11.7%) were treated at home with a consultation performed by a neurologist in 28 cases. Either CT scan (328 patients) or MRI (88 patients) examination was done in 332 patients. Cervical artery ultrasonography was performed in 87% of patients managed at the University Hospital, in 79% of patients managed in a private hospital and in 72% of patients treated at home. For echocardiography, the values were 72%, 59% and 45%, respectively, and only one patient treated at home did not undergo an ECG or Holter recording.

The overall crude annual incidence was 109/100 000/year (107/100 000/year in men and 110/100 000/year in women). After adjustment to the world population, values were

Table 3 Multivariate association of risk factors with each subtype of ischaemic stroke after adjustment for any differences in age and sex

	LAA	SAO	CE	OC and UND	LV vs SAO	LV vs CE	SAO vs CE
Age							
OR	0.979	0.993	1.051	0.991	0.995	0.952	0.948
95% CI	0.964–0.995	0.974–1.011	1.026–1.076	0.969–1.012	0.976–1.016	0.928–0.976	0.917–0.980
p Value	0.011	0.435	<0.001	0.395	0.687	<0.001	0.001
Male sex							
OR	0.74	1.14	1.03	1.44	0.76	0.79	1.05
95% CI	0.46–1.19	0.68–1.9	0.59–1.80	0.74–2.79	0.42–1.35	0.42–1.49	0.52–2.13
p Value	0.213	0.61	0.91	0.28	0.346	0.46	0.89
Hypertension							
OR	0.95	1.86	0.52	1.14	0.6	1.72	2.34
95% CI	0.58–1.54	1.06–3.27	0.30–0.90	0.57–2.29	0.32–1.12	0.90–3.27	1.14–4.81
p Value	0.827	0.03	0.019	0.714	0.11	0.1	0.021
Diabetes							
OR	1.78	0.98	0.75	0.34	1.35	1.74	1.13
95% CI	0.98–3.24	0.51–1.89	0.35–1.60	0.10–1.17	0.66–2.77	0.77–3.95	0.44–2.93
p Value	0.6	0.947	0.46	0.087	0.41	0.185	0.795
Previous TIA							
OR	0.69	2.86	0.44	0.73	0.37	1.75	3.33
95% CI	0.24–1.98	1.10–7.42	0.12–1.61	0.16–3.35	0.12–1.15	0.38–7.96	0.78–14.18
p Value	0.49	0.03	0.216	0.689	0.085	0.471	0.103
Hypercholesterol							
OR	0.97	2.23	0.53	0.73	0.55	1.7	2.67
95% CI	0.61–1.55	1.33–3.73	0.30–0.93	0.37–1.43	0.31–0.99	0.90–3.21	1.35–5.31
p Value	0.897	0.02	0.028	0.356	0.045	0.101	0.005

CE, cardioembolism; LAA, large artery atherosclerosis; OC, stroke of other determined cause; SAO, small artery occlusion; TIA, transient ischaemic attack; UND, stroke of undetermined cause.

54/100 000/year (64/100 000/year in men and 47/100 000/year in women).

Each of the 332 ischaemic strokes was assigned a subtype (fig 1). The distribution of subtypes was as follows: 119 (35.8%) LAA, 89 (26.8%) SAO, 81 (24.4%) CE, 43 (13%) other and undetermined causes.

Table 2 reports demographic data and the frequency of risk factors according to stroke subtypes. Mean age at stroke onset was lowest in LAA and highest in CE stroke. The most common risk factor was hypertension with a prevalence of 59% in LAA, 73% in SAO, 54% in CE and 63% in other and undetermined strokes.

The association between risk factors and each ischaemic stroke subtype was evaluated using multivariate regression (table 3). There was a positive association between CE stroke and age (OR 1.051; 95% CI 1.026 to 1.076; p<0.001). SAO was associated with high blood pressure (OR 1.86; 95% CI 1.06 to 3.27; p = 0.03) but the association was no longer significant when SAO was compared with LAA. In addition, there was a positive association between SAO and hypercholesterolaemia (OR 2.23; 95% CI 1.33 to 3.76; p = 0.02). There was no difference between the subtypes of ischaemic stroke with regard to diabetes mellitus and male sex.

DISCUSSION

In our population, the incidence of ischaemic stroke was lower than that reported in other studies.[1–3 6 19 20] Nevertheless, except for LAA, the distribution of stroke subtypes was quite similar to that observed in other Western countries. Indeed, the proportion of LAA in our study was greater than that reported in OXVASC,[5] OCSP,[5] Erlangen,[1] Rochester,[2] Auckland[6] or Nueces County.[21] These differences could be attributed to race, sex and age differences between the patients with ischaemic stroke in our community and those enrolled in the studies cited above. Race/ethnic differences in the proportions of ischaemic stroke subtype have been evaluated elsewhere.[3 4 6] The differences in risk factors observed between ethnic populations could reflect variations in socioeconomic and environmental status, which may modify the risk of stroke and the distribution of its subtypes.[6] Another explanation for these discrepancies could be variations in case ascertainment and classification. In our study, the proportion of UND is particularly low. This could be due to the fact that, when several causes were possible, a meeting of the neurologists of our department was organised to determine the most likely one. Consequently, we may have overestimated LAA and underestimated UND strokes. Another explanation is that a large proportion of patients (74%) were managed at the university hospital, a tertiary hospital with easy access to a number of investigations (such as carotid ultrasound, transcranial Doppler, echocardiography, etc) which may have led to more frequent classification of ischaemic strokes in one of the different categories.

Our study revealed the great frequency of hypertension whatever the ischaemic stroke subtype. As in other studies, this major risk factor was found in more than 60% of ischaemic strokes in our study,[1–3 5 6] which underlines the need for the development of both efficient screening and therapeutic strategies within the population.[22]

Several consistent associations between risk factors and particular subtypes of stroke were found. There was a strong positive correlation between age and CE (table 3). In a systematic review of the OXVASC, OCSP, Rochester and Erlangen population based studies, this association was also reported,[5] and is undoubtedly explained by the fact that atrial fibrillation accounts for more than half of CE strokes, and that the prevalence of this risk factor in the general population shows a marked correlation with age[23]: AF is found in 6% of people older than 65 years of age, and this increases to 9% in those between 80 and 89 years.[23 24] In contrast with these studies, we found no particular association between LAA and

either male sex or a history of TIA but we found an association with young age. Furthermore, our study showed an association between SAO and hypertension. Only the Erlangen study reported similar findings.[1] However, unlike the Erlangen study, this association only persisted when SAO was compared with CE stroke. The German Stroke Data Bank[12] found a strong association between microangiopathy and both hypertension and diabetes. This study, however, was hospital based, which makes comparison with our study difficult because of differences in the prevalence of risk factors between hospitalised and non-hospitalised patients.[5] Similar results were reported in a review of studies assessing risk factor profiles in various ischaemic stroke subtypes.[25] Nevertheless, there were statistical discrepancies between the results of the individual studies, which may be due to the fact that results from hospital based studies were mixed with those from population based studies and that there were differences in the classifications used. We also found an association between hypercholesterolaemia and SAO, whereas this risk factor was strongly related to LAA in the combined data of OXVASC and OCSP.[5]

Our study fulfils the key methodological criteria for the evaluation of stroke epidemiology.[14 15] The strength of our population based registry was that uniform registration and diagnostic criteria established by the WHO[16] were strictly applied, and stroke diagnosis was precise, as neuroimaging was performed in more than 99% of cases. In addition, the TOAST classification[7] was prospectively used. Although this classification is frequently used by studies investigating the epidemiology of ischaemic stroke, it has some limitations. Its reliability depends on access to diagnostic investigations (such as neuroimaging, echocardiography, carotid ultrasound, etc), which can explain the wide range in the proportions of patients in the ''undetermined'' subtype category and thus the differences between studies.[25] Moreover, this category contains cases in which there is more than one potential cause of stroke. That is why, in our registry, we decided to choose between the most probable cause when several were possible, in order to limit the proportion of patients in the ''undetermined'' category.

We only evaluated ischaemic stroke subtypes over a 2 year period even though the Dijon Stroke Registry has been functioning continuously since 1985. In fact, TOAST classification was introduced in our community based study in January 2005, and ischaemic stroke subtypes were determined retrospectively for the period before. Hence, we chose to limit our study to the period when TOAST classification was used prospectively in order to avoid diagnostic bias. Another limitation was that our population was predominantly White with a high socioeconomic level, and this prevented us from making comparisons of stroke subtype distribution according to ethnic groups. Moreover, we were not able to include smoking in the multivariate regression analysis as 10% of the data were missing (table 3).

In conclusion, we have demonstrated in a comprehensive, prospective and well documented population based study that vascular risk factors exhibit a particular distribution according to the ischaemic stroke subtype. Hence the various mechanisms of ischaemic stroke are probably influenced by different combinations of risk factors, which determine a risk factor profile for each stroke subtype. These findings, as well as the high frequency of hypertension among stroke patients, have implications for prevention strategies, the design of clinical trials and the organisation of health care services.

Acknowledgements: We thank Mr Philip Bastable for reviewing the English.

Competing interests: None.

Ethics approval: Our registry was approved by the National Ethics Committee (CNIL).

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