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ORIGINAL COMMUNICATION

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Age-dependent differences in demographics, risk factors, co-morbidity, etiology, management, and clinical outcome of acute ischemic stroke

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Abstract *Background* Comparisons between younger and older stroke patients including co-morbidities are limited. *Methods* Prospective data of consecutive patients with first ever acute ischemic stroke were compared between younger (≤45 years) and older patients (>45 years). *Results* Among 1004 patients, 137 (14%) were ≤45 years. Younger patients were more commonly female (57% versus 34%; p<0.0001), had a lower frequency of diabetes (1% versus 15%; p<0.0001), hypercholesterolemia (26% versus 56%; p<0.0001), hypertension (19% versus 65%; p<0.0001), coronary heart disease (14% versus 40%; p<0.0001), and a lower mean Charlson co-morbidity index (CCI), (0.18 versus 0.84; p<0.0001). Tobacco use was more prevalent in the young (39% versus 26%; P<0.0001). Large artery disease (2% versus 21%; p<0.0001), small artery disease (3% versus 12%; p=0.0019) and atrial fibrillation (1% versus 17%; p=0.001) were less common in young patients, while other etiologies (31% versus 9%; p<0.0001), patent foramen ovale or atrial septal defect (44% versus 26%; p<0.0001), and cervical artery dissection (26% versus 7%; p<0.0001) were more frequent. A favorable outcome (mRS 0 or 1) was more common (57.4% versus 46.9%; p=0.023), and mortality (5.1% versus 12%; p=0.009) was lower in the young. After regression analysis, there was no independent association between age and outcome (p=0.206) or mortality (p=0.073). Baseline NIHSS score (p<0.0001), diabetes (p=0.041), and CCI (p=0.002) independently predicted an unfavorable outcome. *Conclusions* Younger patients were more likely to be female, had different risk factors and etiologies and fewer co-morbidities. There was no independent association between age and clinical outcome or mortality.

Key words stroke · outcome · mortality

Introduction

Stroke in young adults is rare. The majority of strokes in the younger age group are cerebral infarcts, and their etiologies are manifold and often remain undetermined [1–3].

Clinical functional outcome has been considered more favorable and survival rates are higher in younger than in older individuals, but severe and fatal strokes may occur at any age and co-morbidities have not been systematically analyzed in previous studies [1].

In recent years, new insights in stroke epidemiology, aetiology and prognosis in young stroke patients have been gained [4–7]. However, comparisons between younger and older patients with ischemic stroke includ-

ing risk factors, extensive diagnostic investigations to determine etiology, management, co-morbidities, and outcomes are still limited. Therefore we aimed to compare younger and older patients with first-ever ischemic strokes in a large cohort of consecutive patients.

Methods

The study sample included consecutive patients older than 16 years who suffered a first ever acute ischemic stroke and had been admitted to The Berne Stroke Unit from January 2000 to July 2006. Our University Hospital-based Stroke Unit has a catchment population of about 1.5 million.

Data were collected prospectively and entered continuously in the hospital-based Bernese stroke database.

Stroke was defined according to the World Health Organization criteria as an acute focal neurological deficit with symptoms lasting longer than 24 hours [8]. Clinical data of some patients were reported previously [3].

All patients underwent a standard investigation protocol immediately upon admission, including blood tests (determination of red cell, white cell and platelet counts, prothrombin time, activated partial thromboplastin time, serum electrolytes, glucose, urea, creatinine, transaminases, and cholesterol levels), 12-lead ECG, cranial computed tomography (CT) and/or conventional magnetic resonance imaging (MRI) (1.5 Tesla system providing axial T1, T2, and proton density weighted images, and gadolinium- enhanced T1-weighted images. All patients were investigated by neurovascular ultrasound or magnetic resonance angiography (MRA) or digital subtraction angiography (DSA) of the brain supplying arteries upon admission or during their hospital stay. The following ancillary investigations were carried out at the discretion of the treating stroke neurologist: a search for vasculitis (including C reactive protein, erythrocyte sedimentation rate, antinuclear antibodies, and antiphospholipid antibodies), transthoracic echocardiography, transesophageal echocardiography, 24-hour ECG monitoring, cervical MRI with fat suppression technique, diffusion-weighted and perfusion-weighted MRI. We assessed etiologic stroke subtype according to the TOAST criteria (trial of ORG 10172) [9]. The frequency of atrial fibrillation, cervical artery dissection, foramen ovale or atrial septal defect and atrial septal aneurysm (in patients undergoing TEE), coagulopathy and vasculitis were analyzed separately.

In addition infarctions were categorized according to the Oxfordshire Community Stroke Project (OCSP) classification [10]. The following risk factors were assessed: sex, hypertension (defined by pre-admission history and medical records), diabetes mellitus (fasting venous plasma glucose values ≥7.0 mmol/l on at least two separate occasions, and/or ≥11.1 mmol/l 2 hours after intake of 75 g of oral glucose and on one other occasion during the 2 hour test, or pre-admission history of diabetes), current cigarette smoking, hypercholesterolemia (total venous plasma cholesterol concentration >5 mmol/l), and coronary heart disease.

Pre-existing co-morbid conditions were assessed using the Charlson Co-morbidity Index (CCI) [11]. The term "myocardial infarction" was replaced by "coronary heart disease" proved by coronary angiography or electrocardiography [12]. The severity of the neurological deficit was assessed at admission by a neurologist using the National Institutes of Health Stroke Scale (NIHSS) [13].

Antithrombotic therapy and secondary prevention was performed according to a standardized protocol similar to international guidelines [14, 15].

Clinical follow-up information of ischemic stroke patients was obtained by neurological examination (n = 307) or a structured telephone interview (n = 680) by different neurologists 3 months after stroke onset. The modified Rankin scale score (mRS) was recorded [16].

Seventeen patients (1.7 %) were lost to follow-up because they had moved or were living in foreign countries.

Statistical analysis

Statistical analysis was performed with SPSS 10 for Macintosh statistical software (2001; SPSS Inc). The following variables were analyzed and compared between younger (≤45 years) and older patients (>45 years): gender; smoking; hypertension; diabetes mellitus; hypercholesterolemia; family history of stroke; NIHSS score on admission; Charlson Co-morbitidy Index; stroke etiology; intravenous and intra-arterial thrombolysis; antithrombotic treatment; overall frequency of transesophageal echocardiography (TEE), transthoracic echocardiography (TTE), and 24-hour ECG; duration of hospital stay; discharge to home; 3 months functional clinical outcome; and mortality.

For comparison of outcome we divided patients into two groups with favorable (mRS score 0 to 1) and non-favorable (mRS score 2 to 6) outcome. The χ^2 test was performed for cross tabulation. Mann-Whitney U test was used for non-categorical variables. Logistic regression analysis with a forward stepwise method was performed including the NIHSS score on admission and the variables that showed significant associations or trends ($p < 0.20$) with age when tested with univariate analyses, to determine an independent association between age and functional outcome or mortality.

Results

Among 1004 patients with acute ischemic stroke, 137 (14 %) younger patients (≤45 years) and 867 (86 %) older patients (>45 years) were identified.

The mean age was 35.8 years (SD 7.3) in the younger and 64.7 years (SD 9.9) in the older patients.

The percentage of women was higher in younger than in older patients (57 % versus 34 %; $p < 0.0001$). Risk factors, stroke severity on admission and co-morbidities are shown in Table 1: Younger patients had a lower overall frequency of diabetes mellitus (1 % versus 15 %; $p < 0.0001$), hypercholesterolemia (26 % versus 56 %; $p < 0.0001$), hypertension (19 % versus 65 %; $p < 0.0001$), and coronary heart disease (14 % versus 40 %; $p < 0.0001$) but were more often current smokers (39 % versus 26 %;

Table 1 Demographics, risk factors, stroke severity, and co-morbidity in younger (<45 years) and older (>45 years) patients

Characteristic	Younger patients n (%)	Older patients n (%)	P-value
No. of patients	137 (14)	867 (86)	
Female sex	78 (57)	291 (34)	p < 0.0001
Family history of stroke	24 (22)	183 (28)	p = 0.155
Diabetes mellitus	2 (1)	128 (15)	p < 0.0001
Current smoking	52 (39)	221 (26)	p = 0.002
Hypertension	26 (19)	562 (65)	p < 0.0001
Hypercholesterolemia	34 (26)	474 (56)	p < 0.0001
Coronary heart disease	19 (14)	347 (40)	p < 0.0001
Mean NISS score on admission (SD)	8.5 (7.7)	8.6 (7.2)	p = 0.845
Mean Charlson Co-morbidity Index (SD)	0.18 (0.45)	0.84 (1.36)	p < 0.0001

P < 0.0001) than older patients. The NIHSS score on admission did not differ between younger and older patients (mean 8.5 (SD 7.7) versus 8.6 (SD 7.2; p = 0.845). Mean CCI was lower in the younger age group (0.18 versus 0.84; p < 0.0001).

Younger patients more often underwent TEE [(98 patients (72 %) versus 442 (56 %); p < 0.0001)] and less frequently TTE [15 (11 %) versus 174 (20 %) patients; p = 0.011]. A 24-hour ECG was performed in 105 (77 %) younger and in 704 (81 %) older patients (p = 0.21).

Strokes due to large artery disease (2 % versus 21 %; p < 0.0001) and small artery disease (3 % versus 12 %; p = 0.0019) were less frequent, and strokes due to other etiologies (31 % versus 9 %; p < 0.0001) were more common in the younger age group. Patent foramen ovale or atrial septal defect (44 % versus 26 %; p < 0.0001), and cervical artery dissection were more common (26 % versus 7 %; p < 0.0001), and atrial fibrillation less frequent (1 % versus 17 %; p = 0.001) among younger patients. The stroke etiology remained undetermined in 27 % of the younger and in 25 % of the older patients (Table 2).

There was no significant association between age and OCSP categories (p = 0.120). However, a trend towards a higher frequency of lacunar syndromes (16 % versus 12 %; 0.250) and total anterior circulation syndromes (16 % versus 9 %; p = 0.062) and a lower frequency of partial anterior circulation syndromes (45 % versus 53 %; p = 0.098) in the older patients was observed (Table 2).

Twenty-eight patients (20 %) ≤45 years and 235 patients (27 %) > 45 years were treated with local intra-arterial thrombolysis (p = 0.099), and 6 (4 %) younger and 20 (2 %) older patients with intravenous thrombolysis (p = 0.156).

Stroke treatment and prevention included aspirin in 84 younger (61 %) and 572 (66 %) older patients (p = 0.29). Twenty-six older patients received clopidogrel (3 %). Heparin in therapeutic dose and/or warfarin was given to 53 (39 %) younger and 269 (31 %) older patients (p = 0.074).

Statins were given to 28 (20 %) younger and 395 (46 %) older patients (p < 0.0001).

The duration of hospital stay (10.3 (SD 7.5) days in the young versus 9.9 (SD 6.5) days in the elderly; p = 0.154) and the frequency of discharge at home (41 % in the young versus 35 % in the elderly; p = 0.21) were similar in both groups

At three months 107 (78 %) younger and 631 (73 %) older patients were living at home (p = 0.19). At univari-

Table 3 Three-month clinical outcome in 136 younger (< 45 years) and 851 older (> 45 years) patients with ischemic stroke

Modified Rankin Scale Score	Younger patients n (%)	Elderly patients n (%)	P-value univariate	P-value Regression analyses
0	**45 (33.1)**	**195 (22.9)**	**0.023**	**0.258**
1	**33 (24.3)**	**204 (24.0)**		
2	28 (20.6)	168 (19.7)		
3	12 (8.8)	102 (12.0)		
4	5 (3.7)	74 (8.7)		
5	6 (4.4)	6 (0.7)		
6	**7 (5.1)**	**102 (12.0)**	**0.009**	**0.051**

Table 2 Stroke etiology according to TOAST classification and Oxfordshire Community Stroke Project Subtype in younger (< 45 years) and older (> 45 years) patients

Characteristic	Younger patients n (%)	Older Patients n (%)	P-value
Atrial fibrillation	2 (1)	147 (17)	< 0.0001
PFO or atrial septal defect	43 (44)	129 (26)	< 0.0001
Atrial septal aneurysm	5 (5)	27 (6)	0.44
Cervical artery dissection	35 (26)	62 (7)	< 0.0001
Coagulopathy	1 (1)	2 (0.2)	0.99
Vasculitis	2 (1.5)	4 (0.5)	0.16
TOAST criteria			
Large artery disease	3 (2)	181 (21)	< 0.0001
Cardioembolic	51 (37)	284 (33)	0.30
Small artery disease	4 (3)	101 (12)	0.0019
Other determined etiology	42 (31)	78 (9)	< 0.0001
Undetermined, complete examination	37 (27)	214 (25)	0.56
Undetermined, incomplete examination	0 (0)	3 (0.3)	0.33
More than one cause	0 (0)	6 (0.7)	0.33
OCSP criteria			
Total anterior circulation syndrome	13 (9)	135 (16)	0.062
Partial anterior circulation syndrome	72 (53)	390 (45)	0.098
Lacunar syndrome	17 (12)	141 (16)	0.250
Posterior circulation syndrome	35 (26)	201 (23)	0.544

PFO patent foramen ovale; *p* the difference between subgroups by χ^2 test or Mann-Whitney-test; *TOAST* trial of ORG 10172 in acute stroke treatment; *OCSP* Oxfordshire Community Stroke Project

ate analysis, younger patients were more likely to have a favorable outcome (modified Rankin scale Score ≤ 1) after 3 months (57 % versus 47 %; p = 0.023) and had a lower mortality (5 % versus 12 %; p = 0.009).

After regression analysis, there was no independent association between age and outcome (p = 0.206) or mortality (p = 0.073). Higher baseline NIHSS score (p < 0.0001), higher CCI (p = 0.002) and diabetes (p = 0.041) were the only independent predictors of an unfavorable clinical functional outcome. Mortality was independently associated with higher baseline NIHSS score (p < 0.0001), higher CCI (p = 0.001), diabetes (p = 0.008), cardioembolic etiology (p = 0.001) or stroke due to other etiology (p = 0.015).

Discussion

In this hospital-based study the overall percentage of younger patients ≤ 45 years of age was 14 %. The higher percentage of younger patients compared with population-based studies reporting less than 5 % young stroke rates probably reflects a selection bias [1, 17]. In Switzerland, younger patients are more likely to be admitted to a stroke unit.

The percentage of women was higher in younger than in older patients (57 % versus 34 %).

These age-dependent gender differences are difficult to explain and may be partly due to higher stroke incidences in men in the sixth and seventh decade [18]. Another reason may be that elderly women are less likely to be admitted to a stroke unit than elderly men because of a gender-based selection bias [19]. A sex-based selection bias in the young is unlikely because in Switzerland young adults with ischemic stroke are usually referred to a stroke center independent of their sex.

Hypertension, diabetes, hypercholesterolemia, and coronary heart disease were more common among older patients. This reflects the higher prevalence of these risk factors among older subjects in the general population. Only smoking was more frequent among young stroke patients. The fact that more than one third of the younger group were current smokers indicates that smoking is a particularly important modifiable risk factor in younger subjects. This emphasizes the need to enforce preventive strategies to target behavioral risk factors in this age group.

One of the strengths of this study is a complete evaluation including echocardiography and 24-hour ECG to determine stroke etiology in almost all patients. Three fourths of the younger and more than half of the older patients underwent TEE. This explains the lower frequency of stroke with undetermined etiology compared with other series [20–22]. The etiology of stroke differed greatly between younger and older patients. Cardiac embolism and other determined etiologies such as cervical internal carotid and vertebral artery dissections were the most common causes in younger patients. These results are in agreement with previous studies [2, 23]. Atrial fibrillation was more frequent in older patients as reported previously [24]. PFO or atrial septal defect were detected by TEE in 44 % among younger and in only 26 % among older patients. These findings support the current hypothesis that a right to left shunt may play a more important role in the pathogenesis of stroke in the young, whereas other etiologies such as atrial fibrillation, large and small vessel disease are the principal causes of stroke in older patients.

Previous reports on clinical functional outcome in ischemic stroke in the young are contradictory. In a French study, 86.8 % of young adults were independent 3 years after ischemic stroke [2]. In contrast, functional outcome was worse in other studies reporting 37 % to 47 % moderate or severe disabilities in young ischemic stroke patients [1, 25]. In our study, a favorable outcome (mRS 0 or 1) was more common (57.4 % versus 46.9 %), and case fatality (5.1 % versus 12 %) was lower in the young compared with older patients. The low mortality rates in our young adults is in agreement with previous studies reporting case fatality rates ranging from 4.9 % to 7.7 % in young stroke patients [1, 2]. However, after regression analysis, there was no independent association between age and clinical outcome or mortality in our patients. Higher baseline NIHSS score, higher CCI and diabetes were the only independent predictors of an unfavorable outcome. These results emphasize the need to analyze co-morbidities such as the CCI in stroke studies aiming to predict clinical outcome or mortality.

The main limitation of this hospital-based study is a selection bias. Our cohort had a lower mean age than patients in population-based studies. However, in contrast to most population-based studies the strength of this study is a more extensive diagnostic investigation including neurovascular ultrasound or MRA of the brain supplying arteries, echocardiography and 24-hour ECG in most patients.

In conclusion, in this hospital-based study with a potential selection bias, young adult stroke patients were more likely to be female than older patients and had different stroke etiologies and vascular risk factors. More than one third of the young stroke patients were current smokers. Co-morbidities were less common in the young. After correction for other variables including CCI, there was no independent association between age and clinical outcome or mortality.

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