Journal of the Neurological Sciences 339 (2014) 41–46

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Risk factors and acute ischemic stroke subtypes

Aliaksei Kisialiou [a,1], Rodolfo Grella [b,1], Albino Carrizzo [c], Giordana Pelone [b], Michelangelo Bartolo [d], Chiara Zucchella [d,e], Francesco Rozza [k], Giovanni Grillea [f], Claudio Colonnese [f,g], Luigi Formisano [h], Maria Lembo [i], Annibale A. Puca [j,k], Carmine Vecchione [c,k,*]

[a] Clinical Epidemiology & Biostatistics Unit, Innomed Srl, Località Camerelle, Pozzilli, IS, Italy
[b] Stroke Unit, IRCCS INM Neuromed, Pozzilli, IS, Italy
[c] Vascular Physiopathology Unit, IRCCS INM Neuromed, Pozzilli, IS, Italy
[d] NeuroRehabilitation Unit, IRCCS INM Neuromed, Pozzilli, IS, Italy
[e] Department of Brain and Behavioral Sciences, University of Pavia, Pavia, Italy
[f] Diagnostical & Therapeutical NeuroRadiology Unit, IRCCS INM Neuromed, Pozzilli, IS, Italy
[g] Department of Neuroradiology, Umberto I Hospital, University Sapienza, Rome, Italy
[h] Department of Science and Technology, University of Sannio, Benevento, Italy
[i] Department of Medicine and Surgery, University of Rome, La Sapienza, Italy
[j] IRCCS MultiMedica, Milan, Italy
[k] Department of Medicine and Surgery, University of Salerno, Salerno, Italy

ARTICLE INFO

Article history:
Received 23 August 2013
Received in revised form 9 December 2013
Accepted 9 January 2014
Available online 15 January 2014

Keywords:
Stroke
Epidemiology
Risk factors
Men
Women
Cohort study

ABSTRACT

Background: Acute ischemic stroke (AIS) is influenced by gender, age, and the brain site affected. Better characterization of AIS is necessary for improving guidelines, prevention, and destination of resources.
Methods: Demographics, prestroke conditions, etiology, subtypes, specific hospital outcome, clinical and laboratory parameters, and mortality rates were prospectively registered in 105 southern Italian patients.
Results: AIS became more frequent in women than in men after age 65 years. Cryptogenic AIS decreased with age independently of sex and lesion site. Cerebellum–brainstem stroke was more prevalent in men, whereas anterior AIS was more frequent in women. There were no overall differences in 6- and 12-month survival rates based on site or sex; however, mortality rates were high after age 80 years. Chronic kidney disease was more frequent in patients with cerebellum–brainstem stroke, and its prevalence increased significantly with age independently of sex. Association of AIS with arterial hypertension, diabetes, and previous myocardial infarction increased with age, whereas that with active smoking decreased with age, independently of sex and site.
Conclusion: Specific AIS etiology and blood characteristics associated independently to the youngest and oldest AIS patients, respectively. Chronic kidney disease was a specific predictor of cerebellum–brainstem AIS. AIS mortality showed peculiar association with the oldest patients.

1. Introduction

Acute ischemic stroke (AIS) imparts a tremendous medical, emotional, and fiscal burden on society. Moreover, annual costs for stroke care are increasing. According to the World Health Organization statistics, the incidence and prevalence of stroke are 9.0 million and 30.7 million, respectively, with a higher incidence found in the eastern Pacific, Europe, and southeast Asia. Due to advances in Western healthcare, the prevalence of stroke since 1970 has decreased 42%, whereas it has more than doubled in low-income to middle-income countries [1]. However, fatal stroke remains the third cause of death worldwide, accounting for 10% (5.5 million) of deaths; cancer, the first cause, accounts for 12% (7.1 million). In addition, AIS produces severe dependency after 4 weeks in approximately one-third of patients hospitalized [2]. Non-fatal stroke is the main cause of disability in Italy [3].

Stroke (ICD-9 codes: 430–438) is associated with the elderly and the female sex. The frequency of AIS increases usually after 40 years of age [4], and in the West it is estimated that only a quarter of stroke-affected people are under the age of 65 years. It is considered one of the diseases that develops due to long-lasting exposure to risk factors associated with the "modern" lifestyle, such as smoking cigarettes, alcohol/drugs abuse, an unbalanced diet and obesity, diabetes, constant stress, and not taking regular medical check-ups [5]. The incidence and mortality of AIS are also affected by disparities in access to high-quality care and education [6], by misdiagnosing venous thromboembolism and, therefore, failing to administer prophylaxis during admission to Stroke Units (SU) [7], by the antithrombotic drug prescribed, and by AIS

* Corresponding author at: Vascular Physiopathology Unit, IRCCS INM Neuromed, Pozzilli, IS, Italy. Tel.: +39 0865915229; fax: +39 0865927575.
E-mail addresses: vecchione@neuromed.it, cvecchione@unisa.it (C. Vecchione).
[1] These authors contributed equally to this work.

0022-510X/$ – see front matter © 2014 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.jns.2014.01.014

survivors missing rehabilitation follow-ups after discharge from the SU [8].

The disease severity profiles have changed over the last decade on account of the expansion of primary and secondary prevention, but AIS continues to be the main complication of atrial fibrillation [9], internal carotid artery occlusion [10], myocardial infarction (MI) [11], atherosclerotic vascular disease [12], diabetes mellitus (DM) [13], chronic kidney disease (CKD) [14], chronic obstructive pulmonary disease [15], metabolic dysfunction [16], and dyslipidemia [17]. The accurate clinical evaluation of AIS patients on admission by the SU team is therefore fundamental for developing an appropriate strategy for care in the intermediate- and long-term. Unfortunately, clinicians use non-standardized approaches for AIS prognosis based on clinical experience and knowledge gathered from the international and national guidelines. These guidelines are based on the characteristics of well-studied populations, especially from northern Europe, such as Scandinavians [18,19]. In fact, nationwide characterization of well-known prestroke and stroke factors in all social backgrounds is essential if we are to have an impact on the rapid increase of AIS in our aging populations [20]. However, populations can differ significantly not only in their socio-behavioral, legal, and geographical conditions, but also from other, historically understudied, cohorts [21]. The Italian population is one that has not been fully characterized over the last decade. In particular, Molise is one of the remaining regions in Europe without stroke registry surveillance, and, as such, is of great interest for the characterization of AIS patients from geographical and socio-behavioral points of view.

Here, we characterize AIS in patients from the Molise region, stratifying data for age, sex, and lesion site.

2. Methods

For detailed methodology, please see the online-only supplementary material.

3. Results

The principal patient characteristics stratified by age are given in Table 1. Cardioembolism was the main cause of AIS in our population: it was more common after 80 years of age and, considering the Oxfordshire Community Stroke Project (OCSP) classification, was associated with total anterior circulation syndrome (TACS) and partial anterior circulation syndrome (PACS). Moreover, very old AIS patients had a significantly higher erythrocyte sedimentation rate (ESR) and a lower

Table 1
Characteristics of patients who developed acute ischemic stroke stratified by age group.

Characteristics (%)	≤49.9 years	50–80 years	>80 years	p^*
No.	20	71	14	
6-month mortality	ND	8.5	21.4	NA
12-month mortality	ND	1.4	49.9	NA
Prestroke				
Active smoking status	40.0	12.7	7.2	<0.001
Arterial hypertension	55.0	87.3	100.0	0.003
Aspirin use	10.0	21.1	35.7	0.06
Contraceptive use	5.0	4.2	ND	NA
Chronic kidney disease	25.0	45.1	71.4	0.007
Diabetes mellitus II type	10.0	43.7	57.1	0.003
Dyslipidemia	35.0	56.3	14.3	0.18
Family risk assessment	20.0	5.6	ND	NA
Hyperhomocysteinemia	10.0	5.6	ND	NA
Infection inflammatory status	ND	22.5	28.6	NA
Migraine history	5.0	5.6	ND	NA
Previous stroke	10.0	11.3	7.2	0.77
Thrombophilic screening abnormalities	10.0	ND	ND	NA
Transient ischemic attack	5.0	2.8	7.2	0.80
Weekend admission	55.0	45.1	35.7	0.27
Stroke related				
Arteriosclerotic vascular disease	15.0	21.1	14.3	0.95
Cardioembolism	15.0	35.2	78.6	<0.001
Cryptogenic etiology	55.0	32.4	7.1	0.004
Disease of the small vessels	10.0	9.9	7.1	0.77
Anterior stroke	45.0	62.0	64.3	0.26
Blood characteristics				
Albumin lowest quartile	5.0	23.9	64.3	<0.001
ESR highest quartile	5.0	23.9	28.6	0.05
Fibrinogen 3rd quartile	15.0	25.4	21.4	0.63
Triglycerides 3rd quartile	10.0	26.8	28.6	0.16
Medical complications				
Atrial septum aneurysm	5.0	4.2	ND	NA
Carotid pathology including carotid stenosis <70%	35.0	66.2	64.3	NA
Chronic atrial fibrillation	ND	7.0	57.1	NA
Dilated cardiomyopathy	ND	11.3	14.3	NA
Heart failure	ND	2.8	14.3	NA
Myocardial infarction less than 3 months	ND	4.2	ND	NA
Paroxysmal atrial fibrillation	ND	14.1	7.1	NA
Patent foramen ovale	35.0	11.3	ND	NA
Peripheral artery disease	ND	1.4	ND	NA
Previous myocardial infarction >3 months	5.0	14.1	35.7	0.02
Thrombus in the atrium	ND	8.5	7.1	NA
Valvular prosthesis	ND	2.8	ND	NA

* $p < 0.05$ between aged ≤49.9 years and aged ≥80 years.

albumin level. In particular, the quartile of high ESR resulted associated with PACS and with posterior circulation syndrome (POCS), while the quartile of low albumin level was associated with TACS. Active smoking and a cryptogenic etiology were more common before age 50, whereas aspirin use, arterial hypertension, DM, CKD, and a history of MI were more common after age 80. OCSP analysis revealed that arterial hypertension was associated with TACS and lacunar syndrome (LACS).

Dyslipidemia was more prevalent in the adult and old groups compared with the young and very old groups (data not shown). Smoking is known to enhance atherosclerosis leading to large-vessel disease [22]: we found that the proportion of smokers was the greatest in the young AIS group, and decreased from adult to the very old patients (>80 years). The highest 6- and 12-month mortality rates were found in very old patients.

The principal stroke characteristics stratified by sex are given in Table 2. AIS increased in prevalence in women after age 65 and in men before age 65. The proportion of women with anterior stroke was greater than that of men, whereas the majority of men presented with cerebellum–brainstem stroke. The mean age for women AIS patients was greater than that for men. Cardioembolism was more common in women than in men. In women, AIS was associated with an elevated ESR and high fibrinogen levels. The 6- and 12-month mortality rates were not found significantly different between men and women. However, higher 6-month mortality was found for men, whereas higher 12-month mortality was found for women. Familial risk was more common in men. The anterior brain was found to be significantly more affected in women than in men. The presence of patent foramen ovale (PFO) was significantly greater in women. The principal patient characteristics stratified for stroke location are given in Table 3. The 6- and 12-month mortality rates were not significantly different for anterior- and cerebellum–brainstem-stroke patients. Patients with <70% carotid stenosis more commonly developed stroke of the cerebellum–brainstem. Using

Table 2
Characteristics of patients who developed acute ischemic stroke stratified by gender.

Characteristics (%)	Total	Women	Men	p^*
No.	105	46	59	
6-month mortality	8.6	6.5	10.2	0.51
12-month mortality	16.2	19.6	13.6	0.17
Age category (years)				
≤49.9	19.1	15.3	22.0	0.006
≥50–64.9	34.3	21.7	44.1	
≥65–79.9	33.3	41.3	27.1	
≥80	13.3	21.7	6.8	
Prestroke				
Active smoking status	17.1	10.9	22.0	0.13
Arterial hypertension	82.9	84.8	81.4	0.64
Aspirin use	20.9	26.1	16.9	0.25
Contraceptive use	3.8	8.7	NA	ND
Chronic kidney disease	44.8	45.7	44.1	0.87
Diabetes mellitus II type	39.1	41.3	37.3	0.67
Dyslipidemia	46.7	54.3	40.6	0.16
Family risk assessment	7.6	4.3	10.2	0.06
Hyperhomocysteinemia	5.7	4.3	6.8	0.59
Infection inflammatory status	19.1	21.7	16.9	0.38
Migraine history	4.8	6.5	3.4	0.45
Previous stroke	10.5	13.0	8.5	0.44
Thrombophilic screening abnormalities	1.9	2.2	1.7	0.85
Transient ischemic attack	3.8	ND	6.8	ND
Weekend admission	45.7	54.3	38.9	0.12
Stroke related				
Arteriosclerotic vascular disease	19.0	17.4	20.3	0.15
Cardioembolism	37.1	45.6	30.5	0.11
Cryptogenic etiology	33.3	26.1	38.9	0.16
Disease of the small vessels	9.5	10.9	8.5	0.67
Anterior stroke	59.1	71.7	49.2	0.02
Blood characteristics				
Albumin lowest quartile	23.8	30.4	18.6	0.15
ESR highest quartile	25.7	34.8	18.6	0.06
Fibrinogen 3rd quartile	22.9	19.6	8.5	0.09
Platelets 3rd quartile	23.8	23.9	23.7	0.98
Triglycerides 3rd quartile	24.8	23.9	25.4	0.85
Medical complications				
Atrial septum aneurysm	3.8	8.7	ND	ND
Carotid pathology including carotid stenosis <70%	60.0	60.9	59.3	0.87
Chronic atrial fibrillation	17.1	23.9	11.9	0.10
Dilated cardiomyopathy	9.5	8.7	10.2	0.79
Heart failure	3.8	4.3	3.4	0.79
Myocardial infarction less than 3 months	2.9	ND	5.1	ND
Paroxysmal atrial fibrillation	10.5	10.9	10.2	0.9
Patent foramen ovale	14.3	23.9	6.8	0.01
Peripheral artery disease	0.9	ND	1.7	ND
Previous myocardial infarction >3 months	14.3	15.2	13.6	0.80
Thrombus in the atrium	6.7	8.7	5.1	0.46
Valvular prosthesis	1.9	4.3	ND	ND

* $p < 0.05$ between women and men.

Table 3
Characteristics of patients who developed acute ischemic stroke stratified by brain site location.

Characteristics (%)	Anterior	Cerebellum–brainstem	p^*
No.	62	43	
6-month mortality	9.6	6.9	0.62
12-month mortality	14.6	18.6	0.32
Age category (years)			
≤49.9	14.5	25.6	0.80
≥50–64.9	38.7	27.9	
≥65–79.9	32.3	34.9	
≥80	14.5	11.6	
Prestroke			
Active smoking status	17.7	16.3	0.84
Arterial hypertension	87.1	76.7	0.17
Aspirin use	19.4	23.3	0.63
Contraceptive use	3.2	4.7	0.70
Chronic kidney disease	37.1	55.8	<0.05
Diabetes mellitus II type	38.7	39.5	0.93
Dyslipidemia	53.2	37.2	0.11
Family risk assessment	8.1	6.9	0.84
Hyperhomocysteinemia	4.8	6.9	0.64
Infection inflammatory status	21.0	16.3	0.54
Migraine history	3.2	6.9	0.37
Previous stroke	8.1	13.9	0.33
Thrombophilic screening abnormalities	1.6	2.3	0.79
Transient ischemic attack	4.8	2.3	0.50
Weekend admission	41.9	51.2	0.35
Stroke related			
Arteriosclerotic vascular disease	22.6	13.9	0.27
Cardioembolism	38.7	34.9	0.69
Cryptogenic etiology	29.0	39.5	0.26
Disease of the small vessels	9.6	9.3	0.95
Blood characteristics			
Albumin lowest quartile	22.6	25.6	0.72
ESR highest quartile	24.2	27.9	0.67
Fibrinogen 3rd quartile	27.4	16.3	0.18
Platelets 3rd quartile	25.8	20.9	0.56
Triglycerides 3rd quartile	21.0	30.2	0.28
Medical complications			
Atrial septum aneurysm	6.5	ND	ND
Carotid pathology including carotid stenosis <70%	53.2	69.8	0.08
Chronic atrial fibrillation	19.4	13.9	0.47
Dilated cardiomyopathy	8.1	11.6	0.54
Heart failure	4.8	2.3	0.51
Myocardial infarction less than 3 months	17.7	9.3	0.22
Paroxysmal atrial fibrillation	11.3	9.3	0.74
Patent foramen ovale	12.9	16.3	0.63
Peripheral artery disease	1.6	ND	ND
Previous myocardial infarction >3 months	1.6	4.7	0.36
Thrombus in the atrium	4.8	9.3	0.37
Valvular prosthesis	3.2	ND	ND

* $p < 0.05$ between Anterior and Cerebellum–brainstem.

the OCSP classification (Table 4), we found that hyperhomocysteinemia and migraine history were significantly associated with LACS and POCS. Transient ischemic attack, the 3rd quartile of platelets, and triglycerides were associated with LACS. Finally, chronic atrial fibrillation was more frequently associated with TACS and PACS. No other significant differences were found between age groups, sexes, or lesion sites.

4. Discussion

Here we assess the age and gender variances of stroke in different brain sites and the risk factor profile with clinical outcome. Compared with the young onset group, the old onset group had significantly different risk profiles and stroke features. Several stroke risk factors were more prevalent in the elderly (infection, DM, hypertension, CKD, carotid pathology including carotid stenosis, transient ischemic attack, chronic atrial fibrillation, dilated cardiomyopathy, and previously studied blood biomarkers). Six- and 12-month mortality rates in the very old population contributed, respectively, to one-fifth and one-half of deaths in our study. Aspirin use before stroke was more common in the very old population, in particular in the women of this group, and was associated with the incidence of AIS. Other studies support that regular aspirin use may be associated with increased rates of ischemic stroke in low-risk populations [23], with increased systolic blood pressure, and with antagonization of the effect of certain antihypertensive drugs [24,25]. The thrombogenic effects of aspirin have been demonstrated experimentally, particularly at high doses, and possibly relate to inhibition of endothelial-derived prostacyclin synthesis or, in some patients, to an increase in platelet adhesiveness [26]. However, the mechanisms by which frequent aspirin use could increase ischemic stroke are still not well defined.

In our population, hypertension remained a prominent risk factor for AIS, and, as expected, the risk of stroke increased with age, as for other populations [27,28]. However, this increase in risk was most notable in individuals without evidence of hypertension at the beginning of their follow-up period; thus, while the risk of stroke rose with age in hypertensive men, it increased more rapidly in normotensive men. The percentage of stroke attributable to hypertension also declined significantly with age, again secondarily to the increasing importance of stroke in men without hypertension. Thus, while hypertension remains an important risk factor for stroke in the elderly [29], it appears that other factors associated with aging have an increasing role in the causation of stroke in other individuals.

On this point, studies have reported that DM independently increases the risk of death by a factor of 1.5 to 2 [30]. Our findings demonstrate that ischemic stroke was significantly more correlated with DM in our very old population, which had the greatest 12-month mortality level. Moreover, the risk of stroke was significantly associated CKD in the old age group, independently of demographics, lipid levels, smoking, and other known factors that predict stroke. Interestingly, CKD

Table 4
Oxfordshire Community Stroke Project (OCSP) classification.

Characteristics (%)	TACS(%)	PACS(%)	LACS(%)	POCS(%)	TACS vs PACS	TACS vs LACS	TACS vs POCS	PACS vs LACS	PACS vs POCS	LACS vs POCS	p^*
No.	17	34	16	36							
Prestroke											
Active smoking status	11.8	23.5	18.75	13.9	n.s	n.s	n.s	n.s	n.s	n.s	0.15
Arterial hypertension	88.2	85.3	87.5	75	n.s	n.s	0.025	n.s	n.s	0.037	0.05
Aspirin use	11.8	23.5	25	22.2	n.s	n.s	n.s	n.s	n.s	n.s	0.11
Contraceptive use	5.9	2.9	6.2	2.8	n.s	n.s	n.s	n.s	n.s	n.s	0.65
Chronic kidney disease	64.7	29.4	31.2	55.5	<0.001	<0.001	n.s	n.s	<0.001	<0.001	<0.001
Diabetes mellitus II type	35.3	38.2	43.7	38.9	n.s	n.s	n.s	n.s	n.s	n.s	0.91
Dyslipidemia	47.0	50.0	56.2	38.9	n.s	n.s	n.s	n.s	n.s	n.s	0.13
Family risk assessment	11.8	5.9	6.2	8.3	n.s	n.s	n.s	n.s	n.s	n.s	0.54
Hyperhomocysteinemia	0.0	2.9	12.5	5.6	n.s	n.s	0.05	0.023	n.s	n.s	<0.05
Infection inflammatory status											
Migraine history	5.9	0.0	12.5	5.6	0.04	n.s	n.s	<0.001	0.05	n.s	0.04
Previous stroke	0.0	11.8	12.5	13.9	0.001	<0.001	<0.05	n.s	n.s	n.s	0.003
Thrombophilic screening abnormalities	0.0	11.8	12.5	13.9	n.s	n.s	<0.05	0.023	n.s	n.s	0.014
Transient ischemic attack	0.0	2.9	12.5	2.7	n.s	<0.001	n.s	0.023	n.s	0.02	<0.001
Weekend admission	35.3	52.9	43.7	44.4	n.s	n.s	n.s	n.s	n.s	n.s	0.12
Stroke related											
Arteriosclerotic vascular disease	29.4	20.6	18.7	13.9	n.s	n.s	0.01	n.s	n.s	n.s	0.068
Cardioembolism	47.0	44.1	18.7	36.1	n.s	<0.001	n.s	<0.001	n.s	0.01	<0.001
Cryptogenic etiology	23.5	23.5	50	38.9	n.s	<0.001	0.02	<0.001	0.02	n.s	<0.001
Disease of the small vessels	0	11.8	12.5	8.3	0.001	<0.001	0.009	n.s	n.s	n.s	<0.001
Blood characteristics											
Albumin lowest quartile	41.2	17.6	12.5	27.8	<0.001	<0.001	n.s	n.s	n.s	0.01	<0.05
ESR highest quartile	11.8	23.5	12.5	27.8	0.04	n.s	0.008	n.s	n.s	0.01	0.007
Fibrinogen 3rd quartile	29.4	23.5	25	22.2	n.s	n.s	n.s	n.s	n.s	n.s	0.91
Platelets 3rd quartile	5.9	32.3	37.5	19.4	<0.001	<0.001	<0.001	n.s	0.05	0.008	<0.05
Triglycerides 3rd quartile	5.9	17.6	43.7	30.6	<0.01	<0.001	<0.001	<0.001	0.04	n.s	<0.05
Medical complications											
Atrial septum aneurysm	5.9	5.9	6.25	0	n.s	n.s	n.s	n.s	n.s	n.s	0.12
Chronic atrial fibrillation	35.3	23.5	0	11.1	n.s.	<0.001	<0.001	<0.001	0.03	n.s	0.002
Paroxysmal atrial fibrillation	11.8	8.8	12.5	11.1	n.s.	n.s.	n.s.	n.s.	n.s.	n.s	n.s
Patent foramen ovale	17.6	11.8	12.5	16.7	n.s.	n.s.	n.s.	n.s.	n.s.	n.s	0.761
Previous myocardial infarction >3 months	23.5	14.7	12.5	11.1	n.s.	n.s.	n.s.	n.s.	n.s.	n.s	0.088

Chi-square test was used to compare values of all parameter. TACS indicates total anterior circulation syndrome; PACS, partial anterior circulation syndrome; LACS, lacunar syndrome; and POCS, posterior circulation syndrome.

* P value is statistically significant.

was associated with cerebellum–brainstem-localized AIS independently of gender and, using the OCSP classification, it resulted associated with POCS.

We also found significant evidence of association of hypertension, DM, and CKD with AIS. In particular, there was a 2-fold increase for hypertension, an ~6-fold increase for DM, and an ~3-fold increase for CKD in the very old population compared with the young group.

When analyzing extravascular pathologies, a significant association was found in very old patients between AIS and MI occurring <3 months previously. In particular, the prevalence of stroke in this group was more than 7-fold that in young patients, independently of gender or the site of lesion. This fact indicates that an appropriate follow-up of elderly patients should be performed after non-fatal MI by a multidisciplinary team of cardiologists and neurologists. In addition, PFO, which is present in >25% of the adult population [31], was significantly associated with incidence of major ischemic stroke in women. Patients with PFO are probably more susceptible to atrial arrhythmias and intra-atrial thrombus formation, which lead to stroke. Of note, cardioembolism was significantly associated with stroke in the very old group, independently of gender or lesion site. Thus, cardioembolism and PFO may be important risk factors for stroke in the elderly and in women, respectively.

In a previous paper [32], we reported an association between the extent of ischemia and albumin levels and ESR. In the present study, we further highlight this association, showing that low albumin levels and high ESR are characteristics of a very old population with stroke, and increase the risk of cerebral damage in this group. In females, we also found association of stroke with high ESR and normal–high fibrinogen levels. This finding should be addressed in future studies.

The presence of undetermined stroke etiology in the young patient group could be due to a genetic background not analyzed in our study or to problems with anamnesis in this group of patients (drug abuse, alcohol abuse, work stress, asocial lifestyle, etc.). Particularly, 20% of the young population had a family risk of stroke, and 10% had a history of previous stroke. In addition, previous stroke and thrombophilic screening abnormalities were found associated with POCS. Moreover, 55% experienced stroke during a weekend, indicative of an association with lifestyle and, in particular, with substance abuse. In fact, we found that ischemic stroke was associated with active smoking and a cryptogenic etiology in young patients, rather than with hypertension, DM, MI, CKD, cardioembolism, low plasma albumin, or ESR, as for very old patients.

In conclusion, prospective epidemiologic profiling (by age, sex, and lesion site) of AIS patients is fundamental for characterization of our historically understudied population. The trends identified in this pilot study and all the findings, like the key outcomes that should be further studied and replicated for use in good clinical practice guidelines of SUs, will be addressed in a clinical stroke registry.

Conflicts of interest

The authors declare that they have no competing interests.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.jns.2014.01.014.

References

[1] Murray CJ, Vos T, Lozano R, Naghavi M, Flaxman AD, Michaud C, et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 2012;380:2197–223.

[2] Lin HJ, Wolf PA, Kelly-Hayes M, Beiser AS, Kase CS, Benjamin EJ, et al. Stroke severity in atrial fibrillation The Framingham Study. Stroke 1996;27:1760–4.

[3] Sans S, Kesteloot H, Kromhout D. The burden of cardiovascular diseases mortality in Europe. Task Force of the European Society of Cardiology on Cardiovascular Mortality and Morbidity Statistics in Europe. Eur Heart J 1997;18:1231–48.

[4] Reynolds MR, Panagos PD, Zipfel GJ, Lee JM, Derdeyn CP. Elements of a stroke center. Tech Vasc Interv Radiol 2012;15:5–9.

[5] O'Donnell MJ, Xavier D, Liu L, Zhang H, Chin SL, Rao-Melacini P, et al. Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries (the INTERSTROKE study): a case-control study. Lancet 2010;376:112–23.

[6] Kothari R, Sauerbeck L, Jauch E, Broderick J, Brott T, Khoury J, et al. Patients' awareness of stroke signs, symptoms, and risk factors. Stroke 1997;28:1871–5.

[7] Tapson VF, Decousus H, Pini M, Chong BH, Froehlich JB, Monreal M, et al. Venous thromboembolism prophylaxis in acutely ill hospitalized medical patients: findings from the International Medical Prevention Registry on Venous Thromboembolism. Chest 2007;132:936–45.

[8] Wissel J, Olver J, Sunnerhagen KS. Navigating the poststroke continuum of care. J Stroke Cerebrovasc Dis 2013;22:1–8.

[9] Kimura K, Minematsu K, Yamaguchi T. Atrial fibrillation as a predictive factor for severe stroke and early death in 15,831 patients with acute ischaemic stroke. J Neurol Neurosurg Psychiatry 2005;76:679–83.

[10] Paciaroni M, Balucani C, Agnelli G, Caso V, Silvestrelli G, Grotta JC, et al. Systemic thrombolysis in patients with acute ischemic stroke and Internal Carotid ARtery Occlusion: the ICARO study. Stroke 2012;43:125–30.

[11] Toole JF, Malinow MR, Chambless LE, Spence JD, Pettigrew LC, Howard VJ, et al. Lowering homocysteine in patients with ischemic stroke to prevent recurrent stroke, myocardial infarction, and death: the Vitamin Intervention for Stroke Prevention (VISP) randomized controlled trial. JAMA 2004;291:565–75.

[12] Goldstein LB, Adams R, Alberts MJ, Appel LJ, Brass LM, Bushnell CD, et al. Primary prevention of ischemic stroke: a guideline from the American Heart Association/American Stroke Association Stroke Council: cosponsored by the Atherosclerotic Peripheral Vascular Disease Interdisciplinary Working Group; Cardiovascular Nursing Council; Clinical Cardiology Council; Nutrition, Physical Activity, and Metabolism Council; and the Quality of Care and Outcomes Research Interdisciplinary Working Group. Circulation 2006;113:e873–923.

[13] Stevens RJ, Coleman RL, Adler AI, Stratton IM, Matthews DR, Holman RR. Risk factors for myocardial infarction case fatality and stroke case fatality in type 2 diabetes: UKPDS 66. Diabetes Care 2004;27:201–7.

[14] Abramson JL, Jurkovitz CT, Vaccarino V, Weintraub WS, McClellan W. Chronic kidney disease, anemia, and incident stroke in a middle-aged, community-based population: the ARIC Study. Kidney Int 2003;64:610–5.

[15] Feary JR, Rodrigues LC, Smith CJ, Hubbard RB, Gibson JE. Prevalence of major comorbidities in subjects with COPD and incidence of myocardial infarction and stroke: a comprehensive analysis using data from primary care. Thorax 2010;65:956–62.

[16] Milionis HJ, Rizos E, Goudevenos J, Seferiadis K, Mikhailidis DP, Elisaf MS. Components of the metabolic syndrome and risk for first-ever acute ischemic nonembolic stroke in elderly subjects. Stroke 2005;36:1372–6.

[17] Tziomalos K, Athyros VG, Karagiannis A, Mikhailidis DP. Dyslipidemia as a risk factor for ischemic stroke. Curr Top Med Chem 2009;9:1291–7.

[18] Appelros P, Nydevik I, Seiger A, Terent A. High incidence rates of stroke in Orebro, Sweden: further support for regional incidence differences within Scandinavia. Cerebrovasc Dis 2002;14:161–8.

[19] Truelsen T, Piechowski-Jozwiak B, Bonita R, Mathers C, Bogousslavsky J, Boysen G. Stroke incidence and prevalence in Europe: a review of available data. Eur J Neurol 2006;13:581–98.

[20] Paolucci S, Antonucci G, Grasso MG, Morelli D, Troisi E, Coiro P, et al. Early versus delayed inpatient stroke rehabilitation: a matched comparison conducted in Italy. Arch Phys Med Rehabil 2000;81:695–700.

[21] Lindsay P, Bayley M, McDonald A, Graham ID, Warner G, Phillips S. Toward a more effective approach to stroke: Canadian Best Practice Recommendations for Stroke Care. CMAJ 2008;178:1418–25.

[22] Vermeer SE, Longstreth Jr WT, Koudstaal PJ. Silent brain infarcts: a systematic review. Lancet Neurol 2007;6:611–9.

[23] Flaker GC, Eikelboom JW, Shestakovska O, Connolly SJ, Kaatz S, Budaj A, et al. Bleeding during treatment with aspirin versus apixaban in patients with atrial fibrillation unsuitable for warfarin: the apixaban versus acetylsalicylic acid to prevent stroke in atrial fibrillation patients who have failed or are unsuitable for vitamin K antagonist treatment (AVERROES) trial. Stroke 2012;43:3291–7.

[24] Mazya M, Egido JA, Ford GA, Lees KR, Mikulik R, Toni D, et al. Predicting the risk of symptomatic intracerebral hemorrhage in ischemic stroke treated with intravenous alteplase: safe Implementation of Treatments in Stroke (SITS) symptomatic intracerebral hemorrhage risk score. Stroke 2012;43:1524–31.

[25] Cox D, Maree AO, Dooley M, Conroy R, Byrne MF, Fitzgerald DJ. Effect of enteric coating on antiplatelet activity of low-dose aspirin in healthy volunteers. Stroke 2006;37:2153–8.

[26] Kronmal RA, Hart RG, Manolio TA, Talbert RL, Beauchamp NJ, Newman A. Aspirin use and incident stroke in the cardiovascular health study. CHS Collaborative Research Group. Stroke 1998;29:887–94.

[27] Grube MM, Koennecke HC, Walter G, Thummler J, Meisel A, Wellwood I, et al. Association between socioeconomic status and functional impairment 3 months after ischemic stroke: the Berlin Stroke Register. Stroke 2012;43:3325–30.

[28] Wolfe CD, Crichton SL, Heuschmann PU, McKevitt CJ, Toschke AM, Grieve AP, et al. Estimates of outcomes up to ten years after stroke: analysis from the prospective South London Stroke Register. PLoS Med 2011;8:e1001033.

[29] Kario K, Ishikawa J, Pickering TG, Hoshide S, Eguchi K, Morinari M, et al. Morning hypertension: the strongest independent risk factor for stroke in elderly hypertensive patients. Hypertens Res 2006;29:581–7.

[30] Almdal T, Scharling H, Jensen JS, Vestergaard H. The independent effect of type 2 diabetes mellitus on ischemic heart disease, stroke, and death: a population-based study of 13,000 men and women with 20 years of follow-up. Arch Intern Med 2004;164:1422–6.
[31] Homma S, Sacco RL. Patent foramen ovale and stroke. Circulation 2005;112:1063–72.
[32] Kisialiou A, Pelone G, Carrizzo A, Grillea G, Trimarco V, Marino M, et al. Blood biomarkers role in acute ischemic stroke patients: higher is worse or better? Immun Ageing 2012;9:22.