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ORIGINAL COMMUNICATION

Prestroke dementia in patients with atrial fibrillation

Frequency and associated factors

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Abstract *Background and purpose* Prestroke dementia is frequent but usually not identified. Non-valvular atrial fibrillation (NVAF) is independently associated with an increased risk for dementia. However, the frequency and determinants of prestroke dementia in patients with NVAF have never been evaluated. *Objective* The aim of this study was to determine the frequency of prestroke dementia and associated factors in patients with a previously known NVAF. *Methods* This is an ancillary study of Stroke in Atrial Fibrillation Ensemble II (SAFE II), an observational study conducted in patients with a previously known NVAF, consecutively admitted for an acute stroke in French and Italian centers. Prestroke dementia was evaluated by the IQCODE in patients with a reliable informant. Patients were considered as demented before stroke when their IQCODE score was ≥ 104. *Results* of 204 patients, 39 (19.1 %; 95 % confidence interval [CI]: 13.7 %–24.5 %) patients met criteria for prestroke dementia. The only variable independently associated with prestroke dementia was increasing age (adjusted odds ratio for 1 year increase in age: 1.10; 95 % CI: 1.04–1.17), and there was a non-significant tendency for previous ischemic stroke or TIA and arterial hypertension. *Conclusion* One fifth of stroke patients with a previously known NVAF were already demented before stroke. The main determinant of prestroke dementia is increasing age. A large cohort is necessary to identify other determinants.

Key words prestroke dementia · IQCODE · atrial fibrillation · stroke

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Introduction

Many patients are already demented before stroke [21, 25]. The 4 studies [1, 12, 15, 23] including a systematic and standardized evaluation of the preexisting cognitive status of consecutive stroke patients found that: (i) prestroke dementia is often unrecognized in the absence of a systematic evaluation; (ii) prevalence rates of prestroke dementia range from 12 to 16 % in patients recruited within 48 hours, with a mean age of 75 years; (iii) factors the most frequently associated with prestroke dementia are female sex, previous ischemic stroke, lower education level, family history of dementia, leukoaraiosis, global cerebral atrophy, and medial temporal lobe atrophy; and (iv) prestroke dementia is associated with more severe clinical deficits at onset, and higher short-term mortality rates.

Non-valvular atrial fibrillation (NVAF) is frequent in the elderly [9], leads to a 5-fold increased risk of stroke [27, 28], and accounts for nearly 25 % of strokes occurring after 80 years of age [28]. NVAF is also associated with cognitive impairments [14, 18, 22, 26], even in the absence of stroke [8, 14]. Patients with NVAF have a 1.8-fold increased risk of Alzheimer's disease, but no significant increased risk of vascular dementia [19]. In the 4 studies with a systematic and standardized evaluation of the prevalence of prestroke dementia, NVAF accounted only for approximately 20 % of the whole study population. Although prestroke dementia is frequent, and NVAF is associated with an increased risk for dementia, the frequency and determinants of prestroke dementia in patients with NVAF remain unknown.

The aim of this study was to determine the frequency of prestroke dementia and associated factors in patients with a previously known NVAF.

Method

This study was performed in the Italian and French centers participating in the Stroke in Atrial Fibrillation Ensemble II (SAFE II) study. SAFE II was a prospective, multicenter and observational study conducted in 40 centers from 5 European countries, whose primary objective, design and results have been published elsewhere [7]. We included only patients who had a reliable informant. Participating centers, investigators and steering committee members are listed in the appendix.

Participating centers recruited all consecutive patients of any age and both sexes, who were admitted for an acute stroke (ischemic or hemorrhagic), or transient ischemic attack (TIA), as defined below, and who had had a NVAF (permanent or not) proven by an ECG less than 24 months before. Patients whose NVAF was not previously known, or had not been proven by an ECG before admission were not eligible. Ischemic stroke was defined as clinical signs of focal cerebral dysfunction lasting more than 24 hours or leading to death, with no apparent cause other than of vascular origin, and no sign of relevant primary intracerebral hemorrhage on computed tomography (CT), or on T2*-weighted magnetic resonance imaging (MRI) sequences. Hemorrhagic stroke was defined as the presence of clinical symptoms or signs of stroke plus a relevant primary intracerebral hemorrhage on a CT or MRI. Patients with hemorrhagic changes within an infarct were classified as having an infarct. TIA was defined as an episode of focal cerebral dysfunction, lasting less than 24 hours and followed by return to normality, without any relevant lesion on CT or MRI, other than ischemic. The presence of silent infarcts was defined according to Mounier-Vehier criteria [17]. The presence of leukoaraiosis and multiple infarcts (≥ 2 arteries) was evaluated on CT.

Patients were managed according to the local rules in all centers, without any investigation or treatment performed specifically for the study. Patients were examined by a neurologist as soon as possible after admission. All patients had non-contrast CTor MRI at admission, routine biological tests (at least blood ionogram and cell count), 12-lead electrocardiogram, cervical Doppler ultrasonography, and a transthoracic echocardiography. Other diagnostic procedures (magnetic resonance angiography, transcranial Doppler, 24-hour electrocardiogram monitoring, digitalized angiography, etc.) were optional and performed according to local rules.

Medical history was determined from all available records (GP's letter or telephone call) and sources (patient, family, GP, or cardiologist). We prospectively collected the following data: age; sex; education level (< 8 years of schooling vs. 8 years or more); previous stroke or TIA. NVAF was classified as paroxysmal when its duration was less than 7 days; and previous depression according to the GP's opinion. Vascular risk factors were defined as arterial hypertension (defined as current treatment with antihypertensive drugs); diabetes mellitus (defined as serum glucose level > 1.26 g/l or current use of antidiabetic drugs); hyperlipidemia (defined as fasting serum level of triglycerides > 1.5 g/l, or fasting total cholesterol serum level > 2.3 g/l, or current hypolipemiant therapy for another reason than a previous MI); cigarette smoking (more than 10 cigarettes a day or cessation less than 5 years earlier); alcohol abuse (more than 300 g/week). When available, previous echocardiographic data were also collected, with left ventricular dysfunction defined as an ejection fraction ≤ 25 %. Current medications before stroke onset, and previous cardioversion (electrical, pharmacological or both) were recorded.

The assessment of preexisting dementia was conducted within 48 hours of stroke onset by means of a French translation of the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) [12, 13]. This questionnaire, administered to a close relative, consists of 26 questions concerning the changes experienced by the patient over the last 10 years in aspects of daily behavior requiring memory and other intellectual abilities. Each item carries a score of 1 to 5 (1, has become much better; 2, has become a bit better; 3, has not changed; 4, has become a bit worse; and 5, has become much worse). The global score, the addition of the scores of all items, ranges from 26 to 130 points. The informant should have known the patient for at least 10 years and meet him or her at least once a week. Patients with IQCODE scores ≥ 104 were considered as being previously demented [12, 13].

The first step of the statistical analysis consisted of a description of the percentage of patients with preexisting dementia, with 95 % confidence intervals (CI). The second step consisted of a bivariate analysis comparing demographic features, NVAF characteristics, medical history, vascular risk factors, treatments before admission, and stroke characteristics, between patients with and without prestroke dementia (Chi square test, with Yates' correction, or Fisher's exact test when appropriate, and Mann-Whitney's U test). The third step consisted of a logistic regression analysis [2] with preexisting dementia (quoted 1 when present and 0 when absent), as dependent variable. The independent variables included in the analysis were selected from the bivariate analysis, with a 0.25 level as a screening criterion for the selection of candidate variables [11]. Correlations between variables were checked for possible colinearity between variables (defined as $r > 0.6$). Adjusted odds ratios (aOR) and 95 % confidence interval (CI) were calculated from the logistic regression analysis. Accordingly, treatments were not included in the regression model because they could have been influenced by the cognitive status, and previous depression was also not included, because we cannot exclude the possibility that several patients with prestroke dementia were misdiagnosed as depressed.

Results

The study population consisted of 204 patients, with the following baseline characteristics: median age: 78.5 years (range: 54–101); 120 women (58.8 %); 70 patients with schooling ≥ 8 years: (34.3 %); median interval between the onset of NVAF and stroke: 36 months (range: 0.5–300 months); 174 patients with ischemic stroke (85.3 %); 13 patients with primary intra-cerebral hemorrhages (6.4 %); 17 patients with TIA (8.3 %); and 72 patients with previous stroke or TIA (35.3 %). This study population accounts for 55.1 % of all patients included in SAFE II: the reasons for not being included in the dementia sub-study were: not having been recruited in French or Italian centers for 95 patients (25.7 %), and not having a reliable informant for 71 patients (19.2 %). The 204 patients included in the dementia sub-study did not differ from the 166 remainders, for age ($p = 0.10$), gender ($p = 0.85$), education level ($p = 0.51$), and interval between the onset of NVAF and stroke ($p = 0.83$). However, they were more likely to have intra-cerebral hemorrhages (6.4 % vs. 1.8 %; $p = 0.03$) or prior stroke or TIA (35.3 % vs. 24.7 %; $p = 0.03$).

Of 204 patients included in the study, 39 (19.1 %; 95 % CI: 13.7 %–24.5 %) had prestroke dementia. The breakdown of IQCODE scores in the study population is shown in Fig. 1.

The results of the bivariate comparison of demographic features, NVAF characteristics, medical history, stroke risk factors, treatments received before admission and stroke characteristics between patients with prestroke dementia and those without, are shown in Table 1. Patients with prestroke dementia were older, more likely to have had a previous stroke or TIA, and to receive digoxin, and less likely to have more than 8 years of education, to have paroxysmal NVAF, hyperlipidemia, history of cardioversion, or to be receiving beta-blockers.

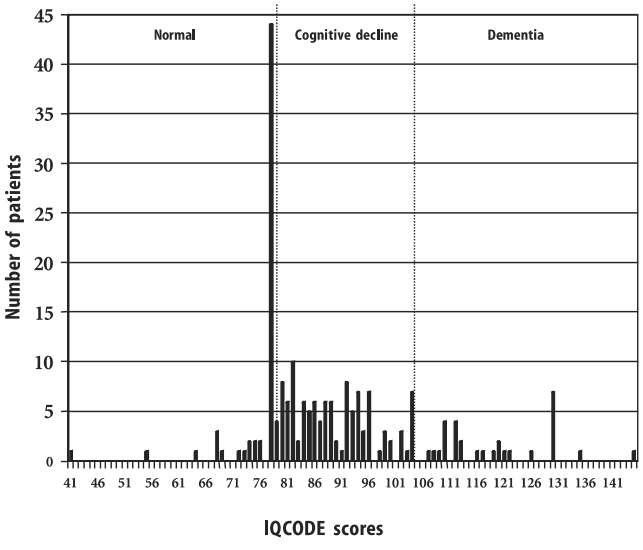

Fig. 1 Breakdown of the IQCODE scores in the study population of 204 patients. A score of 78 indicates normality. Scores between 79 and 103 indicate cognitive decline. Scores of 104 and above indicate dementia

The logistic regression analysis found increasing age as only variable independently associated with prestroke dementia (aOR for 1-year increase in age: 1.10; 95 % CI: 1.04–1.17). The details of the logistic regression analysis are given in Table 2. There was a non-significant tendency for previous ischemic stroke or TIA, and arterial hypertension, to be associated with prestroke dementia.

Discussion

The SAFE II dementia sub-study is, to our knowledge, the first study with a systematic evaluation of the prestroke cognitive status in patients with NVAF. This study showed that: (i) one fifth of patients met criteria for prestroke dementia; (ii) the only factor independently associated with prestroke dementia was increasing age; and (iii) there was a tendency for having previous ischemic stroke or TIA, and arterial hypertension to be associated with prestroke dementia.

We did not perform any test specially for this study, without being part of the current practice in the centers. The major advantage of such an observational design is to evaluate patients in "true life", and to include all consecutive patients admitted during the study period. Nevertheless, this study probably suffers recruitment bias. Not all patients recruited in the SAFE II study were included in the dementia sub-study. Austrian, Belgian and Portuguese centers were not included because the IQCODE is not validated or not used routinely for German, Dutch and Portuguese speakers. One of the 2 Belgian centers, located in a French-speaking area, was however not asked to participate in the dementia sub-study. Finally, only French and Italian SAFE II centers were involved in the dementia sub-study: there is no reason for this to have introduced a bias, because the 4 previous studies with a systematic evaluation of the frequency of prestroke dementia in non-selected stroke patients found similar prevalences in different countries [1, 12, 15, 23], when only patients recruited within 48 hours of stroke onset were taken into account. There is no reason, therefore, why Italian and French patients might have different prevalence rates of prestroke dementia from patients from the other 3 countries. A more important potential selection bias is that patients without reliable informant could not be included. Although this bias may have influenced the results, it should be minimized for the following reasons: (i) the same bias occurred in all studies using the IQCODE and cannot be avoided, allowing a comparability between studies; (ii) the com-

Table 1 Crude comparison between patients with and without prestroke dementia for demographic features, non-valvular atrial fibrillation (NVAF) characteristics, medical history, stroke risk factors, treatments before admission and stroke characteristics

	Prestroke dementia		p values
	Present (n = 39)	Absent (n = 165)	
Demographic features			
Age (median and range)(years)	86 (64–101)	78 (54–95)	< 0.001**
Male sex	13 (33.3)	71 (43.0)	0.268
Education level ≥ 8 years	6 (15.4)	64 (39.0)	0.005
NVAF characteristics			
Paroxysmal	1 (2.6)	26 (15.8)	0.029
Delay since onset (median and range)*	36 (4–156)	36 (0.5–300)	0.955**
Medical history			
LV dysfunction***	2 (8.7)	13 (8.8)	1.000
Previous ischemic stroke or TIA	20 (51.3)	52 (31.5)	0.020
Depression	10 (25.6)	7 (4.2)	0.036
Stroke risk factors			
Congestive heart failure	3 (7.7)	17 (10.3)	0.846
HTN	33 (84.6)	119 (72.1)	0.107
Diabetes mellitus	4 (10.3)	35 (21.2)	0.118
Hyperlipidemia	8 (20.5)	68 (41.2)	0.016
Smoking	4 (10.3)	17 (10.3)	1.000
Alcohol abuse	2 (5.1)	8 (4.8)	0.942
Treatments before admission			
Cardioversion	2 (5.1)	31 (18.8)	0.037
Beta-blockers	0 (0.0)	36 (21.8)	0.001
Calcium blockers	6 (15.4)	39 (23.6)	0.264
ACE inhibitors	19 (38.8)	64 (48.7)	0.256
Diuretics	83 (59.0)	75 (45.5)	0.129
ARA II	0 (0.0)	5 (3.0)	0.586
Digoxin	27 (69.2)	80 (48.5)	0.020
Nitrates	9 (23.1)	43 (26.1)	0.701
Antiarrythmic therapy	7 (17.9)	41 (24.8)	0.361
Antidiabetic therapy	4 (10.3)	20 (12.1)	0.961
Hypolipemiant therapy	0 (0)	8 (4.8)	0.358
Stroke characteristics			
Cerebral infarct	33 (84.6)	141 (85.5)	0.894
Intracerebral hemorrhage	3 (7.7)	10 (10.5)	0.717
TIA	3 (7.7)	14 (13.8)	0.872
Multiple infarcts	14 (35.9)	44 (26.7)	0.250
Silent infarcts	10 (25.6)	57 (34.5)	0.287
Leukoaraiosis	18 (46.2)	59 (35.8)	0.228

HTN arterial hypertension; *LV* left ventricular. Values are numbers (percentages) of patients, unless specified. p values were calculated with Chi-square tests (with Yates' correction, or exact test when appropriate) unless specified

* clearly identified in 139 patients only; ** Mann-Whitney U test; *** evaluated in 170 patients. See text for definition of variables when not detailed in the legend

parison of the main baseline characteristics of SAFE II patients included and non-included in the dementia sub-study showed no significant differences for age, the only major predictor of dementia found in this study. Therefore the selection of patients has probably not significantly influenced the results.

This hospital-based study did not take into account NVAF patients who did not develop a stroke during the study period, and stroke patients who died before admission. Therefore, the proportion of patients who were not properly treated is probably much higher in this study than in the community. Conversely, we cannot exclude the possibility that a few patients with TIA were not identified, or not admitted, or referred to cardiological wards. However, the demographic profile of our study population did not differ from that of stroke patients with NVAF included in a European community-based stroke registry [9]. Moreover, TIA patients accounted for only 8% of the study population. If we compare our study population with the population of

Table 2 Results of the logistic regression analysis with prestroke dementia as dependent variable (quoted 1 when present and 0 when absent). Adjusted comparison between patients with and without prestroke dementia for demographic features, non-valvular atrial fibrillation (NVAF) characteristics, medical history, stroke risk factors, treatments at admission, and stroke characteristics

	$_a$OR	95% CI. $_a$OR
Age*	1.10	1.04–1.17
Education level ≥ 8 years	0.44	0.16–1.23
Paroxysmal NVAF	0.19	0.02–1.55
Previous ischemic stroke or TIA	2.07	0.94–4.58
HTN	2.70	0.83–7.78
Diabetes mellitus	0.51	0.15–1.72
Hyperlipidemia	0.67	0.25–1.77
Multiple infarcts	1.03	0.44–2.41
Leukoaraiosis	0.98	0.44–2.21

HTN arterial hypertension
* for 1 year increase of age. See text for definition of variables when not detailed in the legend, and for the details of the selection of variables. $_a$OR means adjusted odds ratio

acute stroke patients with atrial fibrillation recruited in the HAEST study [3], our patients were slightly younger (79 years vs. 80 years), and more likely to be women (59% vs. 55%), to have diabetes mellitus (19% vs. 15%), to be non-smokers (90% vs. 82%) and to have already had a stroke or TIA (35.3 vs. 24%).

Prestroke dementia was diagnosed according to the IQCODE, which requires the participation of a close relative. Information provided by relatives has been shown to be pertinent for the diagnosis of dementia when recorded in a structured interview [5, 6]. However, we have probably underestimated the frequency of prestroke dementia because we used a cut-off score at 104 for the IQCODE, as did Jorm [13] and as we did in the Lille Stroke Dementia Study [12], to increase the specificity of the test. However, the best cut-off to discriminate between demented and non-demented patients is probably lower [16].

Our study is, to our knowledge, the only one in which the prevalence of prestroke dementia has been evaluated in a structured way in a population of stroke patients with a previously known atrial fibrillation. The baseline frequency of prestroke dementia was 19.1%. This frequency tended to be slightly higher than the 12–16% reported in consecutive stroke patients of any type and cause, and approximately the same age and method of evaluation [1, 12, 15, 23].

Vascular risk factors and silent infarcts were not independently associated with preexisting dementia. However, cerebral atrophy and family history of dementia, factors usually associated with degenerative dementia and found associated with prestroke dementia in the Lille Stroke Dementia study [12] were not analyzed in SAFE II.

Although increasing age is an independent determinant of post-stroke dementia [4, 24], it was not clearly associated with prestroke dementia in the 4 studies conducted in non-selected stroke patients [1, 12, 15, 23]. A lack of statistical power is possible in these studies where the prevalence of dementia was slightly lower, and the study population smaller. In the SAFE II dementia sub-study, increasing age was the only factor independently associated with prestroke dementia. A possible explanation could be that our study population was slightly older than in previous studies – because NVAF occurs in the elderly – and therefore improved the statistical power. Therefore, age is likely to play a more important role in the pathogenesis of prestroke dementia in patients with NVAF than in patients with other types of stroke. This finding may reflect the increased prevalence of Alzheimer's disease with age, and the influence of stroke as a trigger of the clinical expression of a disease which was still at a pre-clinical stage [20]. In the Rotterdam study, subjects below 75 years of age who have NVAF, had an increased prevalence of dementia [19], and NVAF was not significantly associated with vascular dementia, but with Alzheimer disease associated with cerebrovascular lesions [19]. Although, it did not reach the threshold of significance, there was a tendency for an independent association between prestroke dementia and previous ischemic stroke or TIA and arterial hypertension. This tendency is coherent with previous studies [12]. We did not exclude from our study patients with previous stroke or TIA for the following reasons: (i) previous studies with a systematic evaluation of prestroke dementia also included patients with prior strokes, and we wanted to make comparisons between studies; (ii) the exclusion of 35% of patients would have led to a study population which is not representative of stroke patients with NVAF; (iii) in our previous study conducted in non-selected patients [12], and in this one, prior stroke was not a major contributor to prestroke dementia, leading to the hypothesis that many dementia syndromes are of degenerative origin; (iv) our study aiming to identify the determinants of prestroke dementia, and stroke being a possible determinant, exclusion of patients with history of stroke would have modified the results.

With the aging of the population in western countries, NVAF is a more and more important public health issue. One fifth of stroke patients with a previously known NVAF were already demented before stroke. The main determinant of prestroke dementia is increasing age. A large cohort is necessary to identify other determinants.

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