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Atrial Fibrillation and Dementia: Results from the São Paulo Ageing & Health Study

Liz Andrea Kawabata-Yoshihara[1], Márcia Scazufca[2,3], Itamar de Souza Santos[2], Aristarcho Whitaker[1], Vitor Sérgio Kawabata[1], Isabela Martins Benseñor[1,2], Paulo Rossi Menezes[2], Paulo Andrade Lotufo[1,2]

Hospital Universitário da Universidade de São Paulo[1]; Faculdade de Medicina da Universidade de São Paulo[2]; Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo[3], São Paulo, SP – Brazil

Abstract

Background: Atrial fibrillation (AF) is a controversial risk factor for dementia.

Objective: The objective of this study was to assess the association between AF and dementia in the "Sao Paulo Ageing & Health" (SPAH) study participants.

Methods: SPAH is a cross-sectional, population-based study of elderly people living in a deprived neighborhood in Sao Paulo, Brazil. Dementia diagnosis was performed according to the 10/66 study group protocol based on Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria. Diagnosis of AF was made using a 12-lead electrocardiogram (ECG) recording, which was assessed by two cardiologists. Data on demographics and cardiovascular risk factors were also obtained.

Results: Dementia was diagnosed in 66 (4.3%) and AF in 36 (2.4%) of 1,524 participants with a valid ECG. The crude odds ratio (OR) for dementia in participants with AF was 2.8 (95% confidence interval [CI]: 1.0–8.1; p=0.06) compared with individuals without AF. When analyzing data according to sex, a positive relationship was found in women (OR 4.2; 95% CI: 1.24–15.1; p=0.03). After age-adjustment, however, this association was no longer significant (OR 2.2; 95% CI: 0.6–8.9; p=0.26).

Conclusion: There was no independent association between AF and dementia in this sample. The prevalence of AF may be low in this population owing to premature cardiovascular death. (Arq Bras Cardiol 2012;99(6):1108-1114)

Keywords: Atrial fibrillation; cardiovascular disease; dementia.

Introduction

It is estimated that most people with dementia already live in low- and middle-income nations[1]. However, there is very little data about risk factors for dementia in these populations[2].

The role of atrial fibrillation (AF) as a risk factor for dementia is still the subject of intense debate and conflicting results. Because dementia may be of vascular origin (even in the absence of documented stroke), some studies evaluated a possible role of AF in the development of dementia. The Rotterdam Study[3] showed an association between AF and risk of dementia and/or impaired cognitive function with a relative risk (RR) of 2.3 and a 95% confidence interval (95% CI) of 1.4–3.7. Tilvis et al. found a positive association between AF and cognitive decline in a population-based sample of 650 individuals aged 75 years and older after 5 years (but not after 10 years) of follow-up[4]. Forti et al.[5], studying individuals with mild cognitive impairment (MCI), found a 10.5/100 person-years conversion rate to dementia in this setting. The presence of AF was associated with a 4.6-fold higher risk in this group compared with individuals without AF (95% CI: 1.7–12.5).

On the other hand, Park et al. found no difference in cognitive function in individuals aged 60 years or older in the Cognition and Atrial Fibrillation Evaluation (CAFE) study at baseline[6] or after a three-year follow-up[7]. The Vantaa 85+Study[8] included residents aged 85 years or older (N=553) and found no difference in the frequency of dementia in subjects with and without AF at baseline (41.0% *vs*. 38.1%) and no difference in dementia incidence in individuals with AF after a mean follow-up of 3.5 years.

There is conflicting data about this subject in medical literature. In addition to recent reports on AF prevalence in the elderly[9], there is no information on the association between AF and dementia in the Brazilian population. The objective of this study was to assess a possible association between AF and dementia in a population of elderly people living in a deprived neighborhood in a metropolitan area of the city of São Paulo.

Mailling Address: Itamar de Souza Santos •
Center for Clinical and Epidemiological Research
Av. Prof. Lineu Prestes, 2565, Cidade Universitária. Postal Code 05508-000, São Paulo, SP – Brazil
E-mail: itamarss@usp.br, itamarss@gmail.com
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Methods

The "São Paulo Ageing & Health" (SPAH) Study included a cross-sectional, one-phase, population-based study carried out in all residents aged 65 years or older living in an economically-deprived area of São Paulo, Brazil. The main objective of the SPAH Study was to evaluate the prevalence of dementia as part of a collaborative program developed by the 10/66 Dementia Research Group. The study protocol is detailed elsewhere[10,11]. A substudy addressing ECG patterns was published previously[9].

Population and sample

SPAH focused on all residents aged 65 years and older in 66 census sectors (smallest administrative areas) in the district of Butanta. The selected sectors were the most deprived ones in the district, including slums. Identification and recruitment was made by systematic knocking on doors of all households. Eligibility was based exclusively on age at time of recruitment. With the exception of institutionalized individuals, who were not included, all were invited to join the study. Whenever a census sector was selected, all residents were invited to participate in the study.

Of 2,266 eligible participants aged 65 years and older, 2,072 (91.4%) consented to participate and were assessed for dementia by trained mental health professionals. The investigation for ECG changes started when the baseline assessment of SPAH was already underway. To minimize the influence of time elapsed from baseline data collection and ECG recording, individuals in whom an ECG recording was not obtained up to one year after SPAH inclusion were excluded from the analysis. Reasons for exclusion are shown in Figure 1. Cases excluded from the analysis did not significantly differ from those with a valid ECG according to age, sex, or ethnicity.

SPAH protocol

Subjects who agreed to participate were invited to participate in a 90-minute interview carried out at the participant's home, approximately one week after recruitment by eight trained mental health workers. A caregiver was also identified for each participant [10]. Information about age, ethnicity, education, socioeconomic status, medical history, and cognitive and daily-life function was collected using a standardized questionnaire. A nurse assistant performed anthropometric assessments and blood pressure measurements at the participants' homes two to 15 days after the assessment interview. A venous blood sample was obtained after an overnight fast for fasting blood glucose and total and HDL-cholesterol measurement.

Diagnosis of dementia

Dementia diagnosis was based on DSM-IV criteria[12]. The presence of dementia was assessed using a dementia diagnostic tool developed by the 10/66 Dementia Research Group and validated for use in population-based studies of low and middle-income countries[13]. Information regarding cognitive impairment, with a detailed assessment of the onset and course of the dementia syndrome, was collected from both the participants and their caregivers. Diagnostic tools included the *Community Screening Instrument for Dementia* (CSI-D)[14], a modified version of the CERAD ten-word list learning task with delayed recall; the animal naming verbal fluency task from the *Consortium to Establish a Registry for Alzheimer's Disease* (CERAD)[15], a community-directed version of the *Geriatric Mental State,* (GMS) a semi-structured clinical interview for the assessment of mental status[16,17] and a structured neurological assessment to ascertain the presence of lateralizing signs, Parkinsonism, ataxia, apraxia, and primitive reflexes. The interview with caregivers consisted

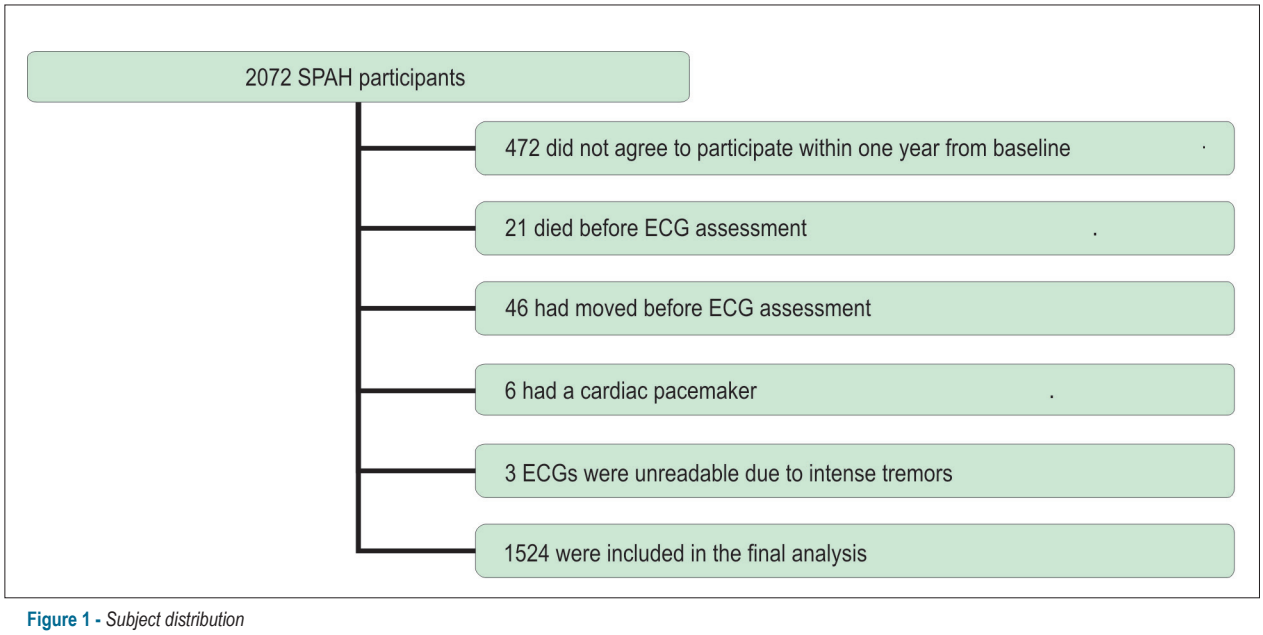

Figure 1 - *Subject distribution*

of inquiries about the participant's functional and cognitive performance according to the CSI-D and a brief history of the participant's functioning and cognitive decline based on the *History and Aetiology Schedule Dementia Diagnosis and Subtype* (HAS-DDS)[18], which was applied when CSI-D pointed towards dysfunction. The HAS-DDS was also used to define probable dementia subtypes such as Alzheimer's disease, vascular dementia, or mixed dementia. The latter was defined as the presence of characteristics from either previous subtypes or a previous history of Parkinsonism.

Diagnosis of atrial fibrillation

The 12-lead resting electrocardiogram recordings were obtained at home. Recordings were independently analyzed by two cardiologists (A.W. and V.S.K.) using the Minnesota code. Agreement on the ECG diagnosis occurred in 92.9% of cases. When a disagreement occurred, a new analysis was done by both cardiologists. A consensus was reached in all cases.

Other variables

Age, education and monthly income were categorized for analysis. High blood pressure was defined as a positive medical history of high blood pressure, current treatment for high blood pressure, or systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg. Diabetes mellitus was defined as a positive medical history of diabetes, current use of insulin or hypoglycemic oral drug treatment, or a fasting blood glucose level ≥126 mg/dl.

Ethical considerations

The study was approved by the Institutional Review Board, and all participants provided signed informed consent. If they were unable to provide consent because of mental or physical incapacities, a signed agreement from the caregiver was obtained. When subjects were illiterate, the information sheet and consent form were read aloud and verbally-witnessed consent was acquired.

Statistical analysis

Data entry was carried out twice using the program EPIDATA 3.0, and a validity check was carried out to identify and correct data entry errors. Data was analyzed using SPSS 16.0. Pearson's Chi-square test and Fisher's exact test were used to compare categorical variables when appropriate. We also performed binary logistic regressions to evaluate the relationship between the presence of AF in ECG recordings and the diagnosis of dementia (all types), Alzheimer's disease, and vascular dementia. We used three models of inclusion for these analyses. In Model 1, all participants with a valid ECG recording were included. In Model 2, we excluded those individuals without AF in the ECG recording, but were using amiodarone and/or warfarin, as this could be evidence of paroxysmal AF. In Model 3, we considered the subgroup of participants receiving amiodarone and/or warfarin as individuals with AF. Data were analyzed as crude ratios and after age-adjustment. Point estimates as well as 95% CIs are shown. *P*-values less than 0.05 were considered statistically significant.

Results

Electrocardiogram recordings were obtained from 1,524 (73.6%) individuals. Table 1 shows the baseline characteristics of the SPAH participants. Individuals with a valid ECG were then stratified by the presence of AF in the recording. AF was found in 37 (2,4%) subjects; 19/603 (3,2%) men and 18/921 (2,0%) women. Individuals with AF were older than those without AF (mean age, 77.7 ± 7.9 years vs. 72.1 ± 6.2 years; $p<0.01$). Of the individuals with AF, 19 (51.4%) received antiplatelet or anticoagulant therapy, 10 (27.0%) received aspirin, 8 (21.6%) received warfarin, and 1 (2.7%) received ticlopidine. Fifteen (40.5%) individuals received rate- and/or rhythm-control medication; 8 (21.6%) received digoxin, 3 (8.1%) received beta-blockers, 2 (5.4%) received amiodarone, 1 (2.7%) received calcium-channel blockers, and 1 (2.7%) received beta-blockers and calcium-channel blockers.

Of the sample with an ECG recording, 66 (4.3%) had a dementia diagnosis, including 44 of 921 women (4.8%) and 22 of 603 men (3.6%). In this ancillary study, 25 (37.9%) individuals had Alzheimer's disease, 25 (37,9%) had vascular dementia, and 16 (24.2%) had mixed dementia. Table 2 shows the odds ratio (crude and age-adjusted) for dementia (all subtypes), Alzheimer's disease, and vascular dementia comparing individuals with and without AF (Model 1). Data are also stratified by sex. Excluding the participants who did not present with AF in the ECG recording, but were receiving amiodarone and/or warfarin (Model 2) at the time of evaluation did not materially alter the results. When we considered participants on amiodarone and/or warfarin treatment as individuals with AF (Model 3), no association reached statistical significance.

Discussion

AF and dementia are chronic disorders associated with high morbidity, mortality, and disability[19,20,21]. In our study, we found an association between AF and dementia in women, but the association vanished after adjustment for age, suggesting that there is no independent correlation between these two conditions. No association was found for men or when analyzing dementia subtypes.

It is difficult to establish direct comparisons among studies that address the relationship between AF and dementia because of methodological differences. One of the main barriers is the fact that instruments used to diagnose dementia and/or cognitive impairment vary widely. In low-income populations, education and cultural differences may also influence the results[22]. In this population-based study, we used a validated algorithm specifically developed for dementia diagnosis in low- and middle-income populations based on DSM-IV criteria that consists of multiple diagnostic tools and is corroborated by earlier studies[13].

As this is a subject of debate in the medical literature and data from previous studies led to conflicting conclusions, it is important to point out reasons that may be responsible for our negative results and the positive results of other authors. First, this is a population-based study. Some authors have found a positive result in samples of individuals with mild cognitive

Table 1 - Baseline characteristics of study participants (n=1.524)

Characteristics	With AF (n=37)	Without AF (n=1.487)	*p*
Age group (years)	n (%)	n (%)	
65 – 69	5 (13.5)	656 (44.1)	< 0.001
70 – 74	10 (27.0)	384 (25.8)	
75 – 79	8 (21.6)	261 (17.6)	
≥80	14 (37.8)	186 (12.5)	
Gender			
Female	18 (48.6)	903 (60.7)	0.14
Ethnicity			
White	22 (59.5)	782 (52.6)	0.77
Mixed	12 (32.4)	447 (30.1)	
Black	3 (8.1)	205 (13.8)	
Asian	0	44 (3.0)	
Native Brazilian	0	1 (0.1)	
Others	0	8 (0.5)	
Educational level			
No formal education	14 (37.8)	488 (32.8)	0.27
1 – 3 years	22 (59.5)	836 (56.2)	
4 or more years	1 (2.7)	163 (11.0)	
Monthly income (US$)			
≤ 85	10 (27.0)	361 (24.3)	0.21
86 –127	11 (29.7)	312 (21.0)	
128 – 246	11 (29.7)	389 (26.2)	
≥ 247	5 (13.5)	425 (28.6)	
High blood pressure	27 (73.0)	1163 (79.7)	0.32
Diabetes	9 (24.3)	333 (23.2)	0.87
Dementia	4 (10.8)	62 (4.2)	0.07

AF: atrial fibrillation. For high blood pressure, diabetes, and dementia definitions, see text

impairment[5,23]. In this type of setting, a higher conversion to dementia is expected, favoring positive results. Moreover, supposing a true association between AF and dementia exists only in a subgroup of individuals, this approach may "select" individuals in whom this process has already started, which also favors a positive result, leading to mistaken conclusions for the whole population.

Our results contrast with the findings of the Rotterdam Study[3], which included younger individuals (inclusion started at age 55 years). Moreover, their results pointed to a stronger association between AF and dementia in younger individuals (aged <75 years). This is a possible explanation for differences observed in their study when compared with ours. As age advances, other mechanisms of disease may become prominent and an association with AF will be weakened. In a low-income sample such as the one in the present study, a survival bias due to premature all-cause[24] and cardiovascular[25] deaths is also expected. This may be at least partially responsible for the smaller rates of AF observed in our study (AF prevalence 2.0% in women and 3.2% in men), compared to the Cardiovascular Health Study (4.8% in women and 6.2% in men)[26] and Rotterdam Study (7.5% in women and 9.7% in men)[27]. This lower prevalence may make it difficult to observe an association between dementia and AF.

Our study has some limitations. The small number of individuals with concomitant AF and dementia impaired the analysis by dementia subtypes. A cross-sectional design is not sufficient to establish a causal relationship between two conditions. However, a lack of association in this kind of study could indicate that a causal relationship may not exist. A single electrocardiogram, utilized for the diagnosis of AF, does not allow the diagnosis of paroxysmal AF and does not identify individuals successfully treated with rhythm control treatment strategies. However, excluding those patients with normal sinus rhythm who were receiving treatment potentially directed to paroxysmal AF (Model 2), as well as considering them as AF

Table 2 - Crude and age-adjusted odds ratio (OR) and 95% confidence interval (95% CI) for the association between atrial fibrillation (AF) and dementia, Alzheimer's disease, and vascular dementia in SPAH (n=1,524)

Condition	Crude OR (95% CI)	Age-adjusted OR (95% CI)
All		
Without dementia (n = 1,458)	1.0 (Reference)	1.0 (Reference)
Dementia (all types) (n = 66)	2.8 (1.0 – 8.1) *p* = 0.06	1.2 (0.4 – 4.0) *p* = 0.73
Alzheimer's disease (n = 25)	3.8 (0.9 – 16.6) *p* = 0.08	1.6 (0.3 – 7.9) *p* = 0.59
Vascular dementia (n = 25)	1.8 (0.2 – 13.7) *p* = 0.57	1.0 (0.1 – 7.8) *p* = 0.98
Women		
Without dementia (n = 877)	1.0 (Reference)	1.0 (Reference)
Dementia (all types) (n = 44)	4.2 (1.2 – 15.1) *p* = 0.03	2.2 (0.6 – 8.9) *p* = 0.26
Alzheimer's disease (n = 20)	3.0 (0.4 – 24.1) *p* = 0.30	1.6 (0.2 – 13.9) *p* = 0.67
Vascular dementia (n = 12)	5.2 (0.6 – 43.1) *p* = 0.13	2.4 (0.3 – 22.9) *p* =0.43
Men		
Without dementia (n = 581)	1.0 (Reference)	1.0 (Reference)
Dementia (all types) (n = 22)	1.5 (0.2 – 11.7) *p* = 0.71	0.5 (0.1 – 5.1) *p* = 0.55
Alzheimer's disease (n = 5)	7.8 (0.8 – 73.5) *p* = 0.07	2.2 (0.1 – 33.9) *p* = 0.57
Vascular dementia (n = 13)	*	*

** None of the 13 men with vascular dementia had concomitant AF*

patients (Model 3) did not significantly alter the results.

Conclusion

Our study did not find an independent association between AF and dementia in a population-based sample living in a low-income area in Brazil. The prevalence of AF may be low in this population owing to premature death, especially by cardiovascular disease.

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Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

This article is part of the thesis of doctoral submitted by Liz

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