European Journal of Internal Medicine xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

European Journal of Internal Medicine

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

Narrative Review

Relationship between atrial fibrillation and cognitive decline in individuals aged 80 and older: A narrative review

Marco Proietti [a,b], Angela Recchia [c], Emma Riva [c], Ugo Lucca [c], Mauro Tettamanti [c], Pier Mannuccio Mannucci [d], Alessandro Nobili [a,*]

[a] Department of Neuroscience, Laboratory of Quality Assessment of Geriatric Therapies and Services, IRCCS – Istituto di Ricerche Farmacologiche "Mario Negri", Milan, Italy
[b] University of Birmingham Institute of Cardiovascular Sciences, Birmingham, United Kingdom
[c] Department of Neuroscience, Laboratory of Geriatric Neuropsychiatry, IRCCS – Istituto di Ricerche Farmacologiche "Mario Negri", Milan, Italy
[d] Scientific Direction, IRCCS Ca' Granda Maggiore Policlinico Hospital Foundation, Milan, Italy

ARTICLE INFO

Article history:
Received 27 June 2017
Received in revised form 25 July 2017
Accepted 8 August 2017
Available online xxxx

Keywords:
Atrial fibrillation
Dementia
Cognitive decline
Oral anticoagulant therapy
Time in therapeutic range

ABSTRACT

Background: Atrial fibrillation (AF) and dementia are largely prevalent and incident in progressively older subjects, suggesting a link between the two conditions. While in the general population there are several findings supporting a causal relationship between AF and dementia, it is unclear whether or not this association is still present in individuals aged 80 and older.
Results: So far, the few studies that analysed this issue did not provide enough evidence supporting the causative role of AF in increasing the risk of cognitive decline or dementia in patients aged 80 and older. Conversely, a relevant role of optimal anticoagulation control in determining a significant reduction in the risk of cognitive decline is suggested, in AF subjects aged 80 years or older.
Conclusions: Further data, coming from population-based studies specifically investigating very old individuals and based upon large samples and comprehensive cognitive assessments, are needed to fully elucidate the relationship between AF and dementia in very old individuals.

1. Introduction

Atrial fibrillation (AF) is one the most commonly diagnosed cardiac arrhythmias in the elderly [1]. In the recent years AF did show a constantly increased incidence and prevalence, particularly in older adults and oldest old subjects [2]. The progressive increase of age represents one of the strongest risk factors for developing AF [2] and older age is one of the strongest predictor of morbidity and mortality [3], also being part of the CHA_2DS_2-VASc score [4].

Similar to AF, cognitive decline and dementia – defined as the development of multiple cognitive deficits that cause significant impairment in social and occupational functioning and represent a significant decline from a previous level of functioning [5] – are largely prevalent and incident in the elderly general population (60 years and older): the estimated prevalence of dementia is 6.8% in Western Europe and 5.7% in United States, while the annual incidence rate in these regions is about 17.5 per 1000 persons [6]. Dementia is a multifactorial disease and many risk factors contribute to its development [7].

With this background, the Rotterdam Study first established 20 years ago the existence of a positive association between AF and dementia, with a >2-fold increased risk for dementia in patients with this arrhythmia [8]. Since then, several publications reported this association, in cross-sectional analysis as well as in prospective studies investigating the role of AF in cognitive decline, showing a strong relationship between the two conditions [9], irrespective of a previous history of stroke [10]. Several possible mechanisms, such as silent brain infarcts, micro-thromboembolism, bleeding, brain hypoperfusion as well as an increased systemic inflammatory state, have been claimed to explain this strong relationship [11,12].

Despite this large evidence of a relationship between AF, cognitive decline and dementia, only limited data in the oldest old patients are available. Aim for this narrative review is to summarise the main evidence available on the association between AF and dementia in very old patients (≥80 years).

2. Methods

We performed a literature search in PubMed for all articles on the relationship between AF and dementia or cognitive decline that reported data or subgroup analyses in oldest old subjects. No inclusion or exclusion criteria were used. Literature search was done by one of us (MP)

* Corresponding author at: Department of Neuroscience, Laboratory of Quality Assessment of Geriatric Therapies and Services, IRCCS – Istituto di Ricerche Farmacologiche "Mario Negri", Via Giuseppe La Masa 19, 20156 Milan, Italy.
E-mail address: alessandro.nobili@marionegri.it (A. Nobili).

http://dx.doi.org/10.1016/j.ejim.2017.08.010
0953-6205/

who selected studies according titles, abstract and full-text analysis. The original search syntax [((dementia) OR cognitive decline) AND atrial fibrillation] retrieved 553 papers. All papers were evaluated if providing data on the oldest old patients. After evaluation, one author (MP) extracted all the relevant data on study characteristics. No statistical tests have been performed.

3. Main findings

Our literature search retrieved only 5 papers specifically reporting data on AF and dementia, or cognitive decline, carried out in subjects ≥80 years old or providing subgroups analyses regarding these subjects [13–17]. Data about the main characteristics of the selected studies are summarised in Table 1, while Table 2 reports some of the pivotal clinical characteristics, the instruments employed for cognitive assessment and the main results reported in the studies. Main association measures and adjusted models are also reported in the table. No specific bias or quality assessment was done.

The Vantaa 85+ study was a prospective, population-based study including all subjects ≥85 years old living in the Vantaa area, Finland [13]. The study, specifically investigated the role of AF in developing dementia in oldest old subjects. After enrolling 553 patients in 1991 they did three follow-up visits in 1994, 1996 and 1999. At baseline, each patient underwent a full assessment of neurological, cognitive and functional status and a full set of measurements. Specifically, all patients underwent the Mini-Mental State Examination (MMSE), the Short Portable Mental Status Questionnaire tests, the Clinical Dementia Rating, Actives of Daily Living and Instrumental Activities of Daily Living scales. The past clinical history was retrieved with the help of a relative. Based on all the elements collected, a diagnosis of dementia was made according to the diagnostic and statistical manual (DSM) III R, based upon the consensus of 2 neurologists. AF was assessed on the basis of the clinical history and ECG recordings on the baseline. All the assessments were repeated at every follow-up time point [13]. At baseline, there was no significant difference in prevalence of dementia between patients with or without AF (41.0% vs. 38.1%). The final multivariate analysis confirmed the lack of association between AF and dementia [13]. Over the follow-up time 100 new dementia cases were diagnosed, but there was no significant difference in the rate of incident dementia between subjects with and without AF (16.4% vs. 18.4%). This notwithstanding, after the multivariate analysis incident stroke was significantly associated with the development of dementia (hazard ratio [HR]: 3.34, 95% confidence interval [CI]: 1.91–5.83; $p < 0.001$) [13].

In 2009, Peters et al. [14] performed a subgroup analysis in the frame of the Hypertension in the Very Elderly Trial (HYVET), regarding AF and cognitive decline. The HYVET was a randomized, double-blind, placebo-controlled trial of indapamide with or without perindopril versus placebo in oldest old subjects (≥80 years). At baseline, all subjects underwent MMSE evaluation and when they scored 24 or less they were then evaluated for the full diagnosis of dementia according to DMS IV. At every 1 year follow-up visit MMSE was repeated and if it had declined to <24 or had decreased of >3 points the subjects were investigated for a full diagnosis of dementia. Out of 3845 patients originally randomized, 3336 had longitudinal MMSE data [14]. At baseline the authors failed to identify a significant association between AF and a diagnosis of dementia. Indeed, AF was not associated with dementia both at the univariate (HR: 1.014, 95% CI: 0.611–1.682) and multivariate (HR: 1.031, 95% CI: 0.619–1.718) analysis [14]. Similarly, cognitive decline was not associated with AF at baseline, as well as with the change in MMSE over the entire follow-up at univariate and multivariate analysis (point estimate: −0.263, 95% CI: −0.659 to 0.132) [14].

In 2010, an analysis coming from the Intermountain Heart Collaborative Study [15], analysed the relationship between AF, incidence of dementia and dementia types (Alzheimer, senile, vascular) in a large cohort of hospitalized patients. They found that AF, after adjustment for potential confounders was significantly associated with all the types considered (odds ratio [OR]: 1.44, 1.06, 1.39 and 1.73 for non-specific, Alzheimer, senile and vascular dementia). When the association was investigated after stratification according to age strata, they documented that while the direct association remained statistically significant for patients up to 79 years old, in patients 80–89 years old only senile dementia was marginally inversely associated with AF (OR: 0.93, $p = 0.004$), with no other type of dementia being significantly associated with AF and no significant association found in patients ≥90 years old [15].

Another analysis from the same cohort did evaluate the relationship between the quality of anticoagulation control and dementia in the cohort of AF patients treated with warfarin [16]. The incidence of dementia was evaluated according to categories of time in therapeutic range (TTR), a well-established measurement of the quality of anticoagulation control [18]. In the overall population, the risk of dementia was progressively higher for those patients in the lowest TTR categories (51–75%, 26–50%, ≤25% compared to >75%) [15]. An age stratified analysis was also carried out in patients <80 and ≥80 years old. In patients ≥80 years old, the main findings were confirmed, showing that continuous TTR was inversely associated with the risk of incident dementia (HR: 0.982, 95% CI: 0.971–0.993; $p < 0.001$). In particular, there was a significant higher risk of dementia in patients with lower TTR (26–50% and 51–75%) compared to those with TTR >75% (HR: 3.56, 95% CI: 1.57–8.10 and HR: 2.04, 95% CI: 1.04–4.01 respectively). However, in patients with TTR ≤25% the association did not reach statistical significance (HR: 3.02, 95% CI: 0.95–9.57; $p = 0.06$). The association between lower TTR and dementia risk seems to be weaker in patients ≥80 years old than in <80 years old ones. Also, the percentage of time in which subjects had an INR >3.0 was significantly associated with incident dementia (HR: 1.022, 95% CI: 1.007–1.038; $p = 0.004$) [16].

Finally, Singh-Manoux and colleagues recently published an analysis coming from the Whitehall II study, a large cohort study enrolling all the subjects employed by the British civil service [17]. The authors analysed all the cases enrolled over the years 1985–1988, who underwent a full cognitive assessment by means of several specific tests examining memory, reasoning and verbal fluency. A global cognitive score was then created from the three aforementioned scores. The relationship between AF and cognitive decline was analysed over a 15-year follow-up observation. In patients who reached the age 60 years, AF was significantly associated with a decline in cognitive function even after adjustment for all baseline covariates, incident stroke or any incident cardiovascular disease. Conversely, when looking at patients who in the long-term follow-up time, have reached the ages of 80 and 85 from the age of 70 years old, the excess of cognitive decline remained

Table 1
Current studies reporting data about atrial fibrillation and dementia in oldest old patients.

Authors	Year	Country	Type of study	Design	N	Age (years)	Follow-up (years, mean)
Rastas et al. [13]	2007	Finland	Population based	Prospective	553	≥85	3.5
Peters et al. [14]	2009	Multinational	RCT	Prospective	3336	≥80	2
Bunch et al. [15]	2010	USA	Hospital registry [ICD codes]	Prospective	NA	≥80	5
Jacobs et al. [16]	2014	USA	Hospital registry [ICD codes]	Prospective	849	≥80	4 (median)
Singh-Manoux et al. [17]	2017	United Kingdom	Cohort study	Prospective	NA	≥80[a]	14.7

Legend: NA = not available; RCT = randomized controlled trial.
[a] Age for this study is intended at follow-up.

Please cite this article as: Proietti M, et al, Relationship between atrial fibrillation and cognitive decline in individuals aged 80 and older: A narrative review, Eur J Intern Med (2017), http://dx.doi.org/10.1016/j.ejim.2017.08.010