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ScienceDirect

Journal of the Chinese Medical Association 79 (2016) 465−467

www.jcma-online.com

Editorial

Atrial fibrillation and dementia: Do risk factors matter?

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia encountered in clinical practice. The prevalence of AF steadily rises with increasing age. Up to 10% of people age ≥ 80 years suffer from this arrhythmia, and it is estimated that the number of elderly patients with AF will triple in the next 20 years.[1] Similar to AF, one of the most prevalent neurological disorders is dementia. Worldwide, ~40 million people have dementia, and this number is expected to increase, owing to an aging population.[2] Although the exact pathophysiological mechanisms of dementia are largely unknown, there is abundant evidence implicating cardiovascular disease and its risk factors.[3] In this regard, common conditions associated with aging and AF, such as diabetes, hypertension, hyperlipidemia, heart failure, obesity, sleep apnea, and smoking may also predispose individuals to developing dementia.

Multiple studies have demonstrated the association between AF and dementia. Ott and colleagues[4] were the first to describe this risk of dementia, in the Rotterdam study. The estimated odds ratio (OR) of dementia in patients with AF was 2.3 [95% confidence interval (CI): 1.2−3.4]. However, the cross-sectional design of this study prevented the authors from making conclusions regarding a causal relationship. Since then, several longitudinal studies[5−9] and systemic reviews[10,11] have confirmed the associations of AF with dementia. In a population-based, longitudinal study, de Bruijn et al[9] found that the presence of AF was associated with an increased risk of dementia in younger (< 67 years) people. Furthermore, the same group also found that the duration of AF was significantly associated with the development of dementia in younger but not in elderly patients. In a semisystematic review, Udompanich et al[11] found that, in cross-sectional studies, patients with AF had a 1.7−3.3 greater risk of cognitive impairment and a 2.3-fold increased risk of dementia, compared with patients in sinus rhythm. Furthermore, AF is significantly associated not only with vascular dementia (VaD), but also with Alzheimer's dementia (AD) and other forms of dementia.[8] In a cohort of 37,025 patients, Bunch et al[8] found that, in an age-based analysis, AF was significantly associated independently with all dementia types during the 5-year follow-up. The highest risk was in the younger group (< 70 years old). In addition, the presence of AF was associated with a markedly increased risk of mortality.

Given these observations, what are the etiology and potential pathogenic mechanisms underlying dementia in patients with AF? As previously noted, common vascular risk factors, such as age, sex, hypertension, diabetes, heart failure, and hyperlipidemia, were prevalent in both patients with AF and those with dementia. Of these, hypertension is the most important risk factor. AF is often the result of hypertensive heart disease. Both hypertension and AF are also important risk factors of stroke and related cerebrovascular disorders. Therefore, one possible explanation of the association of AF and dementia is that both are the end-stage symptoms of the systemic disease process of hypertension that gradually increases vascular stiffness and impairs end-organ microvascular function. The triple insult of stroke, cerebral microbleeding, and non-uniform cerebral blood flow during AF would therefore substantially increase the risk of dementia in this group.[12]

Compared with the general population, patients with AF have a five-fold increased relative risk of stroke. Loss of cortical matter from stroke is likely to result in impairment of memory and cognitive abilities. Elderly patients are more vulnerable to dementia from stroke, due to the lower cortical volume in these patients. Furthermore, there is increasing evidence to show that, in addition to clinically overt stroke, AF patients also have a higher rate of silent stroke than those in sinus rhythm.

How about the association between AF and AD in which prior strokes are excluded? It is possible that the dementia associated with AF is on a spectrum related to repetitive cerebral injuries, ranging from macroevents (i.e., VaD) to microevents (AD with chronic volume loss).[13] The association of cerebral microvascular injury with AD was confirmed by an autopsy study.[13] The authors found that this kind of injury was a common root mechanism that stemmed from cerebral atherosclerosis—silent, previously undetected lacunar infarcts, and microemboli. Small repetitive vascular injuries are believed to be a common cause of white matter lesions that are linked to cognitive impairment in patients with AF.

http://dx.doi.org/10.1016/j.jcma.2016.05.001

In addition to the above-mentioned cerebrovascular diseases, variability in pulse and cerebral perfusion pressure in AF may also play an important role in the development of dementia. Hypoperfusion of the brain in patients with AF has been theorized to be at the core of leukoaraiosis or white matter changes, and the resulting impairment of the ability of flowing blood to remove microemboli from the vessels, which results in embolic infarcts. Therefore, if the variance in R-R interval explains the association between AF and dementia, what about the burden of ectopic heart beats? Frequent variance in R-R intervals and cerebral perfusion pressure may explain, in part, the association between AF and dementia.[13] Normalizing R-R intervals and treatment approaches might impact risk and improve function.

If AF is linked to the development of cognitive impairment and dementia, then, what are the risk factors of dementia, and how can one predict its occurrence among Asian patients with AF? The $CHADS_2$ and CHA_2DS_2VASc scores have recently been increasingly used to guide antithrombotic therapy for stroke prevention in AF patients. In addition to AF, several components of these scores, such as older age, hypertension, heart failure, and diabetes, are also important risk factors for dementia, as mentioned previously. Given this, could these scores predict the occurrence of dementia? In a nationwide, population-based cohort study, Liao et al[14] found that patients with AF possessed a higher risk of dementia, with a hazard ratio (HR) of 1.420. The $CHADS_2$ and CHA_2DS_2VASc scores were significant predictors of dementia, with an adjusted HR of 1.520 and 1.497 per each single increment of the $CHADS_2$ and CHA_2DS_2-VASc scores, respectively. Therefore, could these scores be useful for risk stratification with regard to dementia occurrence among patients with AF?

In this issue of the *Journal of the Chinese Medical Association*, Chou et al[15] reported on the occurrence and risk stratification of dementia in patients with AF. In an analysis of the National Health Insurance Research Database, the authors found that, of the 15,430 patients with AF, there was a mean $CHADS_2$ score of 2.73 ± 1.63 and no dementia initially, and 1135 patients developed dementia (241 VaD and 894 AD) during a mean follow-up period of 3.71 ± 2.78 years. Compared with patients without dementia, patients with AF and dementia were older (77.37 ± 8.01 years vs. 69.54 ± 13.1 years, $p < 0.001$) and had a higher incidence of vascular risk factors, such as hypertension, coronary artery disease, previous history of stroke/transient ischemic attack, and chronic kidney disease. Furthermore, the risk of developing dementia was associated with an increasing $CHADS_2$ score over time, whether patients developed VaD or AD. In multivariate analysis, an increase by one point in the $CHADS_2$ score was independently associated with a 54% increase in the risk of VaD (HR 1.54; 95% confidence interval 1.41−1.69, $p < 0.001$) and a 40% increase in AD (HR 1.40; 95% confidence interval 1.34−1.46, $p < 0.001$). This study demonstrated that the $CHADS_2$ score is a useful predictor for the development of all types of dementia in patients with AF. Further, large prospective studies are needed to confirm the feasibility of the $CHADS_2$ score in the prediction and management of developing dementia in patients with high-risk AF.

Acknowledgments

This work was supported by grants from Taipei Veterans General Hospital, Taipei, Taiwan (V101C-105, V105C-110, and VGHUST101-G7-1-2).

Conflict of interest

The authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

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