The Cognitive Impact of Atrial Fibrillation

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LESSONS LEARNED AT THE INTERFACE OF MEDICINE AND PSYCHIATRY

The Psychiatric Consultation Service at Massachusetts General Hospital sees medical and surgical inpatients with comorbid psychiatric symptoms and conditions. Such consultations require the integration of medical and psychiatric knowledge. During their twice-weekly rounds, Dr Stern and other members of the Consultation Service discuss the diagnosis and management of conditions confronted. These discussions have given rise to rounds reports that will prove useful for clinicians practicing at the interface of medicine and psychiatry.

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Have you ever wondered whether atrial fibrillation (AF) predisposes one to cognitive impairment, and, if it does, by what mechanisms? If you have, then the following review and discussion of the literature should prove useful and assist you when making treatment recommendations for your patients with AF.

WHAT IS ATRIAL FIBRILLATION?

Atrial fibrillation is an irregularly irregular cardiac rhythm that occurs secondary to abnormal electrical signals throughout the atria. These irregular electrical impulses result in a loss of coordinated activity between the atria and ventricles, allowing the atria to contract rapidly and irregularly (ie, to fibrillate), with a subsequent impairment in cardiac output.[1]

During normal cardiac conduction, electrical signaling is initiated in the sinoatrial node within the right atrium. From the sinoatrial node, electrical activity flows throughout the right and left atria, leading to atrial contraction and emptying of blood from the atria into the ventricles. The atrioventricular node, located between the atria and ventricles, then receives electrical current that continues to course throughout the ventricles, causing ventricular contraction. In a patient with AF, the electrical signals are not initiated within the sinoatrial node but rather within other parts of the atria or the pulmonary vein; these impulses then spread through the atria to the atrioventricular node in a rapid and disordered manner. These abnormal electrical signals can lead to rapid and uncoordinated ventricular contractions, at times exceeding more than 100 beats per minute (called AF with a rapid ventricular response), which can adversely impact ventricular filling and cardiac output (especially during exercise) and lead to heart failure.[1]

Atrial fibrillation can be classified on the basis of its duration and frequency of symptoms as follows: first detected (those patients with only 1 episode), paroxysmal (recurrent episodes ending in less than 7 days), persistent (recurrent episodes lasting longer than 7 days), and permanent (continuous episode).[2,3] Other descriptors of AF include lone AF (which refers to AF without associated cardiovascular disease, pulmonary disease, and/or structural heart disease), nonvalvular AF (which refers to patients without cardiac valve disease), and secondary AF (which occurs in the setting of a primary illness, such as a myocardial infarction, pneumonia, pulmonary embolism, or hyperthyroidism).[2,3] Symptoms of AF are often associated with a fast and irregular heart rate that leads to dyspnea, palpitations, and angina, as well as to neurologic symptoms associated with transient ischemic attacks or stroke.[2,3]

WHAT CAUSES ATRIAL FIBRILLATION?

Atrial fibrillation often occurs in the setting of atrial dilation, fibrosis, and subsequent electrophysiologic abnormalities.[3,4] Atrial dilation can be the result of multiple etiologies, including valvular disease, congestive heart failure, congenital heart defects, and hypertension, and can also be a consequence of atrial fibrillation itself.[3,5] In addition, hyperthyroidism, central sleep apnea, pulmonary pathology (including emphysema), and use of stimulants can be associated with AF.[6] However, AF can also be present without coexisting conditions (ie, lone AF). The presence of AF

Clinical Points

- Atrial fibrillation is associated with increased rates of central nervous system complications including cognitive impairment and dementia.
- The mechanism by which atrial fibrillation causes cognitive impairment is unclear; potential mechanisms include microemboli and transient cerebral hypoperfusion secondary to atrial beat-to-beat variability.
- Future studies are needed to better determine whether treatment interventions for atrial fibrillation, including either rate or rhythm control, will lead to improvement in cognitive dysfunction.

leads to more electrical and mechanical changes within the atria, further promoting AF ("AF begets AF")[7] and eventually (if left untreated) leading to irreversible structural and functional abnormalities.[7–9]

HOW COMMON IS ATRIAL FIBRILLATION?

Atrial fibrillation affects approximately 1% of the general population[2]; it is the most common sustained cardiac arrhythmia in clinical practice. Its prevalence increases with age, affecting 0.1% of people under the age of 55 years and more than 9% of those above the age of 80 years.[2,10–12]

WHAT CENTRAL NERVOUS SYSTEM COMPLICATIONS CAN DEVELOP IN ASSOCIATION WITH ATRIAL FIBRILLATION?

Unfortunately, AF is associated with an increased risk of stroke and with poststroke dementia; depending on the location of the stroke, cognitive impairment can be common. However, even having AF without a stroke may place a patient at increased risk for cognitive dysfunction.[13] In fact, AF, along with other cardiovascular diseases (eg, hypertension, hypercholesterolemia, diabetes), is a risk factor for the development of vascular cognitive impairment and for Alzheimer's disease,[14] as vascular risk factors for both vascular dementia (ie, multi-infarct dementia) and Alzheimer's disease are well established.[15]

One of the first studies to assess the association among AF, dementia, and cognitive dysfunction was the Rotterdam Study.[16] The study determined that cognitive dysfunction is almost twice as common in patients with AF as it is in those without AF; the investigators also found a positive link between AF and the development of dementia.[16] The strongest association between AF and development of dementia was for Alzheimer's disease with cerebrovascular disease rather than cerebrovascular disease alone. This finding is consistent with more recent findings that the pathology of cognitive impairment in the elderly is often a mixture of microvascular disease and Alzheimer's disease.[14,17] In the Rotterdam Study, a history of stroke did not account for the associations between AF and increased rates of cognitive impairment and dementia.[16]

Miyasaka and associates[18] found that rates of developing dementia in patients with new-onset AF and without a history of stroke are 2.7% at 1 year and 10.5% at 5 years. This study found that rates of dementia are strongly correlated with age in patients with AF.[18] In addition, Forti and coworkers[19] found that having AF increases the conversion from mild cognitive impairment to dementia in the elderly. Knecht and colleagues[20] studied patients with AF (without stroke or dementia) and compared them to patients without AF; they found that patients with AF performed worse on cognitive testing (including the Mini-Mental State Examination [MMSE] and Trail-Making tests), independent of stroke or other cardiovascular risk factors. The researchers found that stroke-free patients with AF showed impairments in learning, memory, attention, and executive function. In addition, the authors demonstrated that patients with AF had a reduced hippocampal volume on magnetic resonance imaging (MRI), which may explain some of the cognitive dysfunction (including memory impairment).[20] Bellomo and coworkers[21] found that patients with AF were at increased risk of developing cognitive impairment (measured by scores on the MMSE) as well as depression (measured by scores on the Geriatric Depression Scale) even in the absence of stroke.

WHEN IN THE COURSE OF ATRIAL FIBRILLATION DO COMPLICATIONS ARISE?

Atrial fibrillation is associated with increased rates of morbidity and mortality. The Manitoba Follow-Up Study[22] sought to determine the prognosis of patients with AF over a 44-year period and determined that the presence of AF led to increased cardiovascular mortality, total mortality, congestive heart failure, and stroke. In the Framingham Study,[23] the age-adjusted incidence of stroke in patients with AF compared to those without the condition was almost 5-fold higher, and the risk increased with advancing age (1.5% for those aged 50–59 years to 23.5% for those aged 80–89 years). This study also found that the longer AF lasted, the more strokes occurred; however, a specific period of vulnerability during which strokes occurred was not identified.[23]

Multiple prospective cohort studies have demonstrated the relationship between AF and subsequent cognitive dysfunction; however, it is difficult to determine the time course for the development of these symptoms, as these studies have differing follow-up periods. Elias et al[24] used a relatively short follow-up period (8 months after the AF surveillance period) in order to determine the presence of cognitive dysfunction in patients with AF, while several recent studies[25–27] have had follow-up periods of several years.

HOW MIGHT ATRIAL FIBRILLATION LEAD TO COGNITIVE DYSFUNCTION?

The mechanisms by which AF causes cognitive dysfunction in patients without a stroke are not well defined. One hypothesis posits that AF creates a hypercoaguable state and that formation of microemboli leads to cognitive impairment. Another hypothesis relates to AF's atrial beat-to-beat variability and to a difference in stroke

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volume, cardiac output, and blood pressure (that can lead to transient cerebral hypoperfusion). Leukoaraiosis (white matter hyperintensities on T2 MRI), which is common in AF, is thought to be secondary to intermittent cerebral hypoperfusion and is associated with cognitive impairment.[28] In addition, cerebral amyloid angiopathy has been found to be a risk factor for AD as well as for vascular cognitive impairment.[14] Kalaria[29] has argued that ischemic changes can lead to increased deposition of amyloid precursor protein and to lesions associated with AD.

HOW CAN ATRIAL FIBRILLATION BE TREATED?

The treatment of AF includes decreasing circulatory instability (thereby reducing palpitations, cardiac output impairment, and cardiomyopathy), as well as preventing stroke. Anticoagulation for stroke prevention is typically managed with aspirin or warfarin. Rate control for the treatment of AF is typically achieved with β-blockers, calcium-channel blockers, and digoxin. Rhythm control for the treatment of AF is typically achieved with electrical or pharmacologic cardioversion or with ablation. The benefits of cardioversion for the treatment of AF include the restoration of atrial mechanical function, with subsequent improvement in cardiac output and cardiorespiratory symptoms. Cardioversion is recommended for patients with persistent symptoms (despite rate control), for those with an inability to maintain rate control, and for those with a first episode of AF (especially in young patients), as well as those in heart failure and in the elderly (if anticoagulation is contraindicated). Several studies, including the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) Study,[30] have not demonstrated a mortality benefit in patients with rate versus rhythm control; however, a substudy of the Sotalol Amiodarone Atrial Fibrillation Efficacy Trial[31] demonstrated an increased quality of life and exercise performance in those with chronic AF who were converted and maintained in sinus rhythm. The decision of whether to rate control or rhythm control remains controversial, especially as safer antiarrhythmic medications and catheter ablation techniques are more readily available and may make rhythm control more favorable.[32]

Despite multiple studies showing that vascular risk factors (eg, hypertension, hyperlipidemia, AF) contribute to cognitive impairment, most clinical guidelines for the treatment of vascular diseases do not include cognitive impairment as a negative sequela of untreated disease or as a target for intervention.[33] A critical question that has been relatively unanswered is whether the treatment of AF leads to cognitive improvement. Kilander and colleagues[34] performed a cross-sectional study assessing cognitive functioning in patients with AF treated with digoxin versus those who were not treated with digoxin; they found that patients treated with digoxin performed better on cognitive testing than did those not treated with digoxin. In the AFFIRM functional status substudy, however, no difference was found in MMSE scores of patients who were rate controlled as compared to those who were rhythm controlled.[35] To date, no published study has found cognitive improvement in AF patients after elective cardioversion. This critical question remains: Does improving cardiac output and cerebral perfusion after cardioversion improve the patient's cognitive function after the procedure as compared to before the procedure? If a treatment effect can be found, it would most likely impact current treatment strategies for AF.

CONCLUSION

Atrial fibrillation is the most common sustained cardiac arrhythmia, and it is associated with increased rates of morbidity (including an increased risk of stroke, dementia, and cognitive impairment), as well as increased rates of mortality. While the etiology of cognitive impairment associated with AF is not entirely clear, potential mechanisms include microembolic phenomenon and hypoperfusion of the central nervous system. Despite multiple studies that demonstrate that AF contributes to cognitive impairment, most clinical guidelines for the treatment of AF do not include cognitive impairment as a target for treatment most likely because studies have not yet determined whether cognition can be improved with interventions (such as optimizing rate control or converting to sinus rhythm). Future studies need to determine how to improve cognitive impairment secondary to AF, especially as the population ages and the prevalence of AF increases.

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