Cardiovascular Topics

Clinical characteristics and outcome of lone atrial fibrillation at a tertiary referral centre: the Groote Schuur Hospital experience

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Abstract

Introduction: Atrial fibrillation (AF) is a relatively common arrhythmia. When AF represents an electrophysiological phenomenon in structurally normal hearts, it is termed lone AF. This study was a retrospective, case-based analysis of patients attending the Cardiac Clinic at Groote Schuur Hospital (GSH) and describes the clinical characteristics and outcomes of patients classified as having lone atrial fibrillation. To the best of our knowledge there are no such studies reported from Africa.

Methods: This was a retrospective, descriptive study in which 289 medical records of patients with AF at the GSH Cardiac Clinic were reviewed from 1992 to 2006. The clinical data were interrogated to exclude identifiable causes of AF. Information on clinical characteristics and outcomes were entered into a data-entry form. Baseline descriptive statistics were expressed as means and range for continuous variables, and counts with percentages for categorical variables.

Results: Fifteen per cent ($n = 42$) of patients were identified as having lone AF, with a mean follow-up time of 5.8 years. Males comprised 57% ($n = 24$) and females 43% ($n = 18$). Fifty per cent ($n = 21$) of the patients had paroxysmal AF, 29% ($n = 12$) had persistent AF, and 12% ($n = 5$) progressed from paroxysmal to permanent AF. Subsets of lone AF included concomitant atrial flutter (17%) ($n = 7$) and sick sinus syndrome (21%) ($n = 9$). Complications were stroke (10%) ($n = 4$), tachycardia-related cardiomyopathy (17%) ($n = 7$) and bleeding complications on warfarin (11%) ($n = 3$).

Conclusion: Lone AF is not an uncommon arrhythmia, with a preponderance in thin, middle-aged males. The symptoms of lone AF can be debilitating. It has associated morbidity, including tachycardia-related cardiomyopathy and thrombo-embolism. Rate control and appropriate anticoagulation are the cornerstones of patient management.

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Atrial fibrillation (AF) is a common and obstinate arrhythmia that represents a growing epidemic, with significant health consequences. It is often difficult to manage. The classical risk factors for developing AF include hypertension, valvular heart disease, thyroid disease and cardiomyopathies, including those related to ischaemia.[1] In some patients with AF, no underlying cardiovascular pathology is present and the aetiology remains unknown. This is known as lone atrial fibrillation. Lone AF accounts for three to 20% of cases of atrial fibrillation.[2,3]. The concept of lone AF is arbitrary and negative: the absence of detectable structural heart disease.

There is increasing evidence that from a pathophysiological point of view, the underlying mechanism of lone AF is different from that of AF in the setting of underlying structural heart disease. The latter is more substrate related, showing diseased and dilated atria due to stretch and fibrosis. By contrast, lone AF is probably more related to electrophysiological phenomena in apparently structurally normal atria. This explains why patients with lone AF have a normal life expectancy compared with individuals without arrhythmia, a lower risk of heart failure, and why paroxysmal lone AF has a lower risk of progression to persistent or permanent AF.[3-5] By contrast, AF in the setting of underlying cardiac pathology usually progresses from paroxysmal to persistent and/or permanent AF and is associated with an increased incidence of stroke, heart failure and death.

Although lone AF follows a relatively benign course, it adversely affects the quality of life and exercise capacity of affected individuals.[6] Regular follow up of lone AF patients is essential, as in time, risk factors such as hypertension, diabetes and ischaemic heart disease may develop, thereby altering the prognosis.[2,4,6] Recurrent paroxysms of AF in patients with lone AF may also predispose to the formation of an atrial structural substrate, which in time leads to left atrial dilatation.[7-9] This in turn increases the risk of progression to persistent or permanent AF, with its attendant increased risk of stroke and tachycardia-

related cardiomyopathy.[7-9] Recently, in addition to the classical risk factors, there is an increasing body of evidence linking lone AF to several novel genetic, molecular and pathophysiological mechanisms, thereby making it a 'not-so-lone AF'.[10,11]

The autonomic nervous system plays an integral role in the onset and offset of AF. Triggers for AF include adrenergic-mediated states such as the alcohol-associated 'holiday heart',[12,13] caffeine[14] and dehydration.[15] This can be contrasted with vagally-mediated states such as sleep, postprandial and post-exercise situations that tend to be triggers for AF in tall, lean and physically fit middle-aged males involved in endurance sports.[16-19]

On the other hand, the pathophysiology of AF noted in overweight patients has been linked to the inflammatory state associated with the metabolic syndrome.[20,21] There are several subsets of lone AF, including familial AF[22-24] and AF associated with conduction system disorders, such as sick sinus syndrome (SSS) or the bradycardia–tachycardia syndrome.[25] In the near future it is hoped that elucidating the aetiology of lone AF will lead to a more tailored and therapeutic approach to the management of AF.

To the best of our knowledge, there are no studies to describe the clinical characteristics and outcomes of patients with lone AF in Africa and other developing regions of the world. The purpose of this study was to describe the clinical characteristics and outcomes of patients with lone AF attending Groote Schuur Hospital (GSH) in Cape Town.

Methods

This study was a retrospective, descriptive study of the clinical characteristics and outcomes of patients with lone AF who attended GSH from January 1992 to December 2006. All medical records of patients with AF over this 15-year period were reviewed to identify those with lone AF. The patients had presented to GSH Emergency Department, had already been attending the Cardiac Clinic or had been referred to the Cardiac Clinic from day hospitals or private medical institutions. The medical records were reviewed for findings of their clinical examinations, electrocardiograms, echocardiograms, chest X-rays, laboratory results and, if clinically indicated, the 24-hour Holter, exercise stress test and coronary angiograms.

Our inclusion and exclusion criteria were comparable to the Mayo Clinic series,[2,3] the exception being the subset of patients who had AF and concomitant SSS, which we included in the study. Patients with any of the following at the initial diagnosis of AF were excluded from the study: hypertension treated with medication, or systolic blood pressure > 160 mmHg or diastolic blood pressure > 90 mmHg on two or more consecutive occasions; coronary artery disease according to clinical or laboratory data; hyperthyroidism as per laboratory data; left bundle branch block or pre-excitation on electrocardiogram; valvular heart disease; chronic obstructive airway disease; idiopathic dilated cardiomyopathy; and patients who developed atrial fibrillation in the context of an acute medical or surgical condition.

We included patients with systolic blood pressures recorded between 140 and 160 mmHg or diastolic pressures between 80 and 90 mmHg on fewer than two consecutive occasions, as long as there was no evidence of left ventricular hypertrophy on the electrocardiogram or echocardiogram; elderly patients over 60 years, to assess their clinical characteristics and outcomes;

patients with documented AF and concomitant flutter or SSS; and those with documented echocardiograms. More inclusion criteria than those used in previous studies were chosen, to investigate a population without any evidence of organic heart disease at the first presentation, which may reflect what is commonly found in clinical practice.

Although the Mayo Clinic series[2,3] did not include patients with AF/SSS, a subsequent study[25] did include these subjects. Patients who had symptoms and signs of heart failure and/or a dilated left ventricle on echocardiogram in the absence of classical risk factors or metabolic causes and with a normal QRS duration and morphology at the initial diagnosis of AF (normal apart from the AF) were included only if they demonstrated a subsequent improvement of their symptoms and signs of heart failure and left ventricular function on repeat echocardiogram, once their rate was controlled.

The following baseline characteristics were entered into a data-entry form: age at diagnosis, follow-up time, gender and race (white, black or mixed race). The height and weight of patients were noted and a body mass index of < 25 kg/m^2 was considered normal and > 25 kg/m^2 was considered to be overweight. The type of AF (paroxysmal or persistent) and the number of patients who progressed from paroxysmal to permanent AF, and subsets of patients with atrial flutter and conduction system disease were noted. Family history was reviewed. Presenting symptoms, their duration and possible triggering factors were noted. Mortality rate and complications, including tachycardia-related cardiomyopathy and thromboembolism were recorded.

Therapy instituted to control or terminate the AF was reviewed. The indications and therapy chosen for prevention of thromboembolism were reviewed. The number of patients who developed bleeding complications while on anticoagulants was also reviewed.

Baseline descriptive statistics were expressed as means and range for continuous variables. Counts with percentages were used for categorical variables.

Results

Of the 289 patients with AF in the period under review, 42 were identified as having lone AF (15% of all patients with AF). The mean follow-up time of these patients was 5.8 years. Males comprised 57% ($n = 24$), and 43% ($n = 18$) were females. The mean age of the males at diagnosis was 46 years with no males being older than 60 years. The mean age of the females was 62.4 years; 55% ($n = 10$) were less than 65 years of age at the time of diagnosis and they had a mean age of 45 years. The remaining 45% ($n = 8$) were older than 65 years.

The racial composition was 50% ($n = 21$) white, 36% ($n = 15$) mixed race, 7% ($n = 3$) black and 7% ($n = 3$) not having their race specified. Forty three per cent ($n = 18$) of patients were of normal weight, 36% ($n = 15$) were overweight and 21% ($n = 9$) were not specified.

At the time of diagnosis, 50% ($n = 21$) of the patients had paroxysmal AF, 29% ($n = 12$) had persistent AF and 12% ($n = 5$) progressed from paroxysmal to permanent AF over the follow-up period. Subsets of AF included those with concomitant atrial flutter (17%) ($n = 7$) and those with SSS (21%) ($n = 9$). A family history of AF or palpitations was poorly documented in the medical records.

The reasons for seeking medical attention at the time of diagnosis varied. These included palpitations (71%) (*n* = 30), dizziness (64%) (*n* = 27), dyspnoea (45%) (*n* = 19), near blackouts (40%) (*n* = 17), chest pain (21%) (*n* = 9) and fatigue (21%) (*n* = 9). The mean duration of symptoms prior to presentation was 7.7 years.

Triggers included exertion 26% (*n* = 11) and alcohol consumption (17%) (*n* = 7). Other triggers such as stimulant use, caffeine, postprandial states and sleep were not well elucidated on history in the medical records.

Complications of lone AF included stroke (10%) (*n* = 4) and tachycardia-related cardiomyopathy (17%) (*n* = 7). No deaths were recorded.

Therapy instituted included atrioventricular nodal blocking agents, such as beta-blockers (60%) (*n* = 25), digoxin (29%) (*n* = 12) and verapamil (14%) (*n* = 6). Often a combination of beta-blockers and digoxin was used. Twenty one per cent of patients (*n* = 9) required amiodarone. Twelve per cent (*n* = 5) had radiofrequency ablation of the concomitant AF and one patient had radiofrequency ablation of the atrial ectopic foci arising from the pulmonary veins. Ten per cent of patients (*n* = 4) went on to have an atrioventricular nodal ablation and permanent pacemaker insertion because of inadequate rate control with drugs. One patient was put onto flecainide and another onto propafenone. Cardioversion was attempted at least once in 29% (*n* = 12) of the patients.

Eighty per cent of patients (*n* = 34) were on anticoagulant therapy. Sixty-seven per cent (*n* = 28) of our subjects were on warfarin and 26% (*n* = 11) were on aspirin. Eleven per cent (*n* = 3) had bleeding complications while on anticoagulation therapy with warfarin. There was a 12% (*n* = 5) crossover between the anticoagulants. Indications for warfarin included age over 75 years (*n* = 2); age between 60 and 75 years (*n* = 8); tachycardia-related cardiomyopathy (CHADS$_2$ score 1) (*n* = 3); post stroke (CHADS$_2$ score 2) (*n* = 3); possible or probable hypertension that developed during follow up (CHADS$_2$ score 1) (*n* = 6); and myocardial infarction with heart failure (CHADS$_2$ score 1) (*n* = 1) during follow up. Two patients had no clear indication for warfarin.

Indications for aspirin included age over 75 years and patient reluctance to be on warfarin (*n* = 1); tachycardia-related cardiomyopathy (*n* = 1) (could not tolerate warfarin); and possible or probable hypertension that developed over time (*n* = 1). Three patients who had bleeding complications on warfarin were placed on aspirin. Two were placed on aspirin for less-robust indications, such as dilated left atria. Three patients had no clear indications for aspirin

Discussion

Fifteen per cent of the patients with AF presenting to the Cardiac Clinic at GSH over a 15-year period had lone AF. This finding is similar to other studies in which lone AF accounted for three to 20% of cases of AF.[2,3]

As opposed to most studies, our study included patients with lone AF over the age of 60 years at the time of diagnosis, as this is more reflective of what we see in our clinical practice. The male-to-female ratio of 1.3:1 was lower than that reported in most studies. Those studies did not however include patients over 60 years.[2,4,9] If we excluded patients over the age of 60 years, males comprised 70% (*n* = 24) and females 30% (*n* = 10). The higher male-to-female ratio of 2.3:1 in patients under 60 years is in keeping with that found in other studies.[2,4,9]

If we excluded patients over the age of 60 years, the mean age for male patients at diagnosis was 46 years, and 45 years for females. The mean age for all patients under 60 years at diagnosis was 45.5 years, which is comparable to the mean age of 44 years found at the Mayo Clinic.[2]

This study is unique in that it included patients of various racial backgrounds. Fifty per cent (*n* = 21) were white, 36% (*n* = 15) were of mixed race and 7% (*n* = 3) were black. Seven per cent (*n* = 3) did not have their race specified. The differences mirror access to tertiary healthcare afforded to the various racial groups.

Forty-three per cent (*n* = 18) of the patients were of normal weight (body mass index < 25 kg/m²), 36% were overweight (body mass index > 25 kg/m²) and 21% did not have their weight specified. This is of interest as there are epidemiological studies linking atrial fibrillation to obesity.[20-22] Postulated mechanisms include the inflammatory state associated with the metabolic syndrome, neurohormonal activation, autonomic dysfunction associated with sleep apnoea, and increased left atrial size.[10,11,16,20,21] It is intriguing to speculate that weight reduction may lower the risk of atrial fibrillation in this group of patients.

As found in other studies, the majority of patients (50%) (*n* = 21) had paroxysmal AF and 29% (*n* = 12) had permanent AF. Twelve per cent (*n* = 5) progressed from paroxysmal to permanent AF, which is slightly higher than the 7.8% reported in the study by Patton *et al*.[25]

We also report on a subset of patients with lone AF and concomitant atrial flutter. Seventeen per cent of these patients (four males and three females) had one or more episodes of documented atrial flutter at diagnosis or during follow up. This is comparable to the 19.7% reported in the study by Patton *et al*.[25]

There was another subset of patients with structurally normal hearts, AF and associated SSS (SSS/AF) or the bradycardia–tachycardia syndrome. Twenty one per cent (*n* = 9) of our patients had SSS/AF in comparison to the 6% reported in the study by Patton *et al*.[25] Seven of the nine patients had a permanent pacemaker inserted. Five patients were female, of whom three were older than 60 years. Interestingly, all three patients suffered a thromboembolic event. Four patients were males, all younger than 60 years.

Traditionally, the bradycardia–tachycardia syndrome (SSS/AF) is considered to be a degenerative, age-related disorder. Interestingly, it has recently been shown that AF and conduction-system disorders tend to run in families and mutations in both the *lamin A/C* and the *ankyrin 2* genes have been associated with this condition,[26] therefore prioritising these genes to be potential candidates for further investigation into the likely aetiology of this subtype of AF.

Triggers for symptoms of AF in our cohort included exertion (27%) and alcohol consumption (17%). Our figures are lower than that reported in the study by Paton *et al*.[25] where patients reported their episodes to be triggered by adrenergic states such as alcohol consumption (34%) and exercise (36%).

Seventeen per cent (*n* = 7) of patients developed a tachycardia-related cardiomyopathy. This is comparable with the 18% reported in the study by Jahingir *et al*.[4] Four of these patients presented with symptoms and signs of heart failure, rapid AF (otherwise normal ECG), left ventricular dilatation (otherwise normal echo), and normal metabolic screen. Their symptoms and signs resolved

with rate control and there was a marked improvement in left ventricular function. The remaining three started with good left ventricular function that deteriorated due to poor rate control, thereby necessitating more drastic measures to achieve rate control. The mean age of our cohort of patients with heart failure was 45 years (range 28–73 years), which is less than the mean age of 74 years that was reported in the Jahingir *et al*. study.[4]

Ten percent of patients (*n* = 4) developed thromboembolic complications. One patient was a male who had developed hypertension over time. He consequently developed an ischaemic stroke that necessitated anticoagulation therapy with warfarin. This highlights the importance of constant vigilance for thromboembolic risk factors in lone AF patients during follow up.

The remaining three patients with thromboembolic complications were females over the age of 60 years who were part of the subset of patients with AF and SSS or the bradycardia–tachycardia syndrome. They were not on any anticoagulation therapy prior to the stroke. Intriguingly, in the study by Rubenstein *et al*.,[27] there was a high incidence of systemic embolisation in the SSS/AF patients, and they recommended anticoagulation in this group regardless of age or the CHADS$_2$ score. They hypothesised that the fibrillating atria predispose to thrombus formation, and the sudden cessation of fibrillation predisposes to a thromboembolic event. This leaves scope for a study to assess whether young patients with frequent, recurrent episodes of paroxysmal lone AF are at higher risk of thromboembolism compared to the young general population and young patients with persistent/chronic lone AF.

There were no deaths recorded in our series. This could have been due to the relatively short follow-up period of each individual patient (mean follow up of 7.7 years). The study by Kopecky *et al*.[2] recorded a death rate of 20% over a 30-year follow-up period. Seventy per cent of the deaths were due to cardiovascular causes (coronary artery disease, heart failure, stroke and aortic aneurysms). Sixteen per cent of these deaths resulted directly from embolic events.[2]

At the GSH Cardiac Clinic, to improve symptoms, therapy is aimed at achieving rate or rhythm control, which can significantly improve quality of life and prevent complications such as tachycardia-related cardiomyopathy. Timely anticoagulation with aspirin or warfarin is instituted (if bleeding risk is low) to prevent thromboembolic complications.

Cardioversion was attempted at least once in 29% (*n* = 12) of patients in an attempt to achieve rhythm control. Two patients who could afford the drugs were placed on class IC anti-arrhythmics (flecainide/propafenone) in an effort to maintain sinus rhythm because of severe symptoms during AF. These agents may be used in young patients with structurally normal hearts, however due to various constraints in the public health sector, the use of class IC anti-arrhythmic drugs was limited.

For rate control, 60% (*n* = 25) of patients were on beta-blockers, 29% (*n* = 12) were on digoxin and 14% (*n* = 6) on verapamil. Often beta-blockers were used in combination with digoxin. Rate control was considered adequate if the resting ventricular rate was < 80 beats/min.

If patients failed to respond to rate-controlling agents or could not tolerate the side-effect profile of these atrioventricular nodal-blocking agents, they were put on a class III anti-arrhythmic drug, such as amiodarone, in an attempt to maintain sinus rhythm. Twenty-two per cent (*n* = 9) progressed on to amiodarone. Of

these patients, 67% (*n* = 6) developed complications related to the long-term use of amiodarone, including hypothyroidism (*n* = 2), hyperthyroidism (*n* = 2), interstitial pneumonitis (*n* = 1) and chronic inflammatory demyelinating polyneuropathy (*n* = 1). This emphasises the non-benign nature of this agent, and that the decision to place patients on long-term amiodarone should not be taken lightly. Sotalol was avoided due to its potential QT-prolonging effect and subsequent risk of torsades des pointes, which has been documented in patients with structurally normal hearts.[28,29]

Twelve per cent of patients (*n* = 5) had radiofrequency ablation of the concomitant atrial flutter and one patient had radiofrequency ablation of the atrial ectopic foci in the pulmonary veins. This form of AF ablation became available only late in the course of the study period.

Ten percent of patients (*n* = 4) did not respond or developed an adverse side-effect profile on medical therapy and went on to have an atrioventricular nodal ablation and permanent pacemaker insertion. In patients who are refractory to medical management, options include atrioventricular nodal (AVN) ablation and pacemaker insertion, aso known as the 'ablate and pace' strategy. It is considered an extreme form of rate control. There is lifelong pacemaker dependency after this procedure.

A recent meta-analysis by Chatterjee *et al*.[30] compared AVN ablation with pharmacotherapy in patients with drug-refractory AF. Of the five studies included in the efficacy analysis, four were randomised trials, comprising 314 subjects in total. The efficacy analysis demonstrated that AVN ablation improved symptoms and quality of life significantly in patients with medically refractory disease, compared with pharmacotherapy alone.[30]

The GSH Cardiac Clinic policy is to assess the thromboembolic risk using the CHADS$_2$ scoring system in patients who have AF without underlying structural heart disease, and balance this against the bleeding risk so that an anticoagulation strategy can be tailored for each patient. Patients considered to be at high risk for thromboembolism are those with congestive heart failure, hypertension, age above 75 years, diabetes mellitus and previous stroke. A CHADS$_2$ score of 1 is at intermediate thromboembolic risk and aspirin is recommended. A CHADS$_2$ score ≥ 2 is a high thromboembolic risk and warfarin is recommended.

Limitations

Although the subjects in our study were identified retrospectively, the history of events was analysed prospectively from the time of diagnosis. The importance of these observational studies is determined by the paucity of patients with lone AF in randomised studies and their relatively short follow-up time. The sample size was relatively small but this was a consequence of strictly adhering to a clinical definition of lone AF in a geographically defined population. Our follow-up time of each individual patient was relatively short and this may have resulted in underestimation of certain events.

Groote Schuur Hospital is a tertiary referral centre in the public sector and as a result, there may have been a referral bias in our cohort of patients. The number of subjects in some subsets was small and it may be premature to extrapolate the associations observed in this study to the general population with AF and no underlying organic heart disease. Additionally, these subjects were largely symptomatic, and there may be

an under-representation of asymptomatic individuals in this cohort. The medical records were also lacking in information in certain areas, such as family history of lone AF. Despite careful attention to exclusion criteria, it is possible that occult cardiovascular disease may have been present in some patients, therefore overestimating the events.

Conclusions

This is the first study to describe the clinical characteristics and outcomes of patients with lone AF in a racially diverse population in Africa. The clinical characteristics of the patients with lone AF who attended GSH were similar to those described in other studies.

Lone AF occurs in all racial groups. Further phenotypic subsets of lone AF were characterised in the study and included lone AF with concomitant atrial flutter, and lone AF with concomitant SSS, which seems to be a strong risk factor for stroke. Additionally, a few patients who were initially characterised as having lone AF, developed risk factors for stroke with time, therefore emphasising the importance of constantly reviewing the indications for anticoagulation during the follow-up period.

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