Prevalence of Atrial Fibrillation in Patients with Brugada Syndrome in Taiwan

Jyh-Ming Jimmy Juang, Ching-Yu Chen, Yen-Bin Liu, Lian-Yu Lin, Wen-Jone Chen, Ling-Ping Lai, Chia-Ti Tsai and Jiunn-Lee Lin

Purpose: The aim of this study was to assess the prevalence of atrial fibrillation (AF) in patients with Brugada syndrome (BrS) and their clinical characteristics in Taiwan.

Methods: The patient group consisted of 47 symptomatic BrS patients consecutively enrolled from 2000 to 2010. The definition of BrS patients with AF was a BrS patient with at least one episode of AF in a 12-lead electrogram or 24-hour holter (permanent, persistent or paroxysmal) during follow-up, or before diagnosis of BrS.

Results: Six BrS patients were identified with AF, and all of them were male. Two experienced sudden cardiac death (SCD), 2 presented with seizure and 4 with syncope. The mean age at onset of BrS was 47 ± 16 years, similar to those BrS patients without AF (45 ± 14, p = 0.67). Compared to those BrS patients without AF, significantly higher percentages of the BrS patients with AF presented with seizure and documented ventricular tachyarrhythmia (p = 0.02 and 0.03, respectively). Five of them had spontaneous Brugada type I electrogram, similar to those BrS patients without AF (p = 0.9). The SCN5A mutation rate is similar between BrS patients with AF and those without AF (p = 0.69). The prevalence of AF in BrS patients in Taiwan was 12.7% (6/ 47, 95% confidence interval 0.06-0.19) which is not significantly lower than the 20% prevalence found in the Caucasian population (p = 0.16).

Conclusions: BrS patients with AF had distinct clinical features from those patients without AF in Taiwan.

Key Words: Atrial fibrillation • Brugada syndrome • Taiwan

INTRODUCTION

In 1992, Brugada first described patients with a history of sudden death and a distinct electrocardiogram (ECG) pattern (right bundle-branch block with ST-segment elevation in the V1-3 leads).1 It is the most common cause of sudden cardiac death in young adults in South Asia.2,3 The prevalence of Brugada syndrome (BrS) is estimated to be 5 per 10,000 in western countries and higher (12 per 10,000) in Southeast Asia, where BrS is considered to be the major cause of sudden death in young individuals.4,6 In our previous study, the prevalence of Brugada-type ECG in Taiwan was 0.13%.7

BrS is an inherited condition transmitted in an autosomal-dominant model with incomplete penetrance. After two decades, the syndrome is to believed to have a heterogeneous genetic basis.8 The SCN5A gene that encodes the α subunit of the sodium channel has been linked to BrS and is the most common disease-causative gene of BrS (~20-25% of BrS cases).9,10 Several other genes recently have been reported to be linked to the syndrome. For example, mutations in the glycerol-3-phosphate dehydrogenase 1-like gene (GPD1L) cause abnormal trafficking of the cardiac Na+ channel to the cell surface and a reduction of approximately 50% of
the inward Na\(^+\) current.\(^{11}\) Mutations in genes encoding the α1- (CACNA1c) and β2b- (CACNB2b) subunits of the L-type cardiac calcium (Ca\(^{2+}\)) channel lead to a decrease of the calcium current (I\(_{\text{Ca}}\)), and result in a combined BS/short QT syndrome.\(^{12}\) KCNE321 (encoding MiRP2, a protein that decreases the potassium (K\(^+\)) transient outward current (I\(_{\text{to}}\)) by interacting with channel Kv4.3, resulting in an increase of Ito magnitude and density.\(^{13}\) In summary, the development of ventricular arrhythmia in BrS is in part involved with sodium, potassium and calcium channels.

Life-threatening ventricular arrhythmias are the hallmark of BrS. The arrhythmogenic substrate in BrS may not be restricted to the ventricular level. Similar changes occur in the atria and could be the substrate for re-entrant atrial tachyarrhythmias. Atrial arrhythmias are being increasingly recognized in patients with BrS. Incidences of spontaneous atrial arrhythmias of between 6% and 38% have been reported in the literature.\(^{14-17}\) Atrial fibrillation is the most common atrial arrhythmia found in BrS, although a few cases of associated atrioventricular nodal re-entrant and atrioventricular re-entrant tachycardia with accessory pathway have also been noted.\(^{18}\) This is particularly important in terms of medication management in BrS patients with concomitant AF because commonly used sodium channel blockers for AF, such as propafenone, may be contraindicated for BrS.

To date, the prevalence of AF in patients with BrS has been reported to be around 20% in the Caucasian population.\(^{18,19}\) However, the prevalence of AF in BrS patients in the Chinese Han population in Taiwan remains unknown. Herein, we investigated the prevalence of AF in BrS patients and their clinical features in a large referral cohort in Taiwan.

**RESULTS**

**Prevalence of AF in BrS patients in Taiwan**

Six of the 47 BrS patients in our study were identified with AF. The prevalence of AF in BrS patients in Taiwan was therefore 12.7% (6/47, 95% CI 0.06-0.19), that is not significantly lower than 20% reported in Caucasian population (p = 0.16, Figure 2).\(^{18,19}\)

**Clinical characteristics of BrS patients with AF**

The average age at onset of these 6 BrS patients with AF was 47 ± 16 years (ranging from 20 to 69 years) that was similar to those BrS patients without AF (47 ±

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**MATERIALS AND METHODS**

**Participants**

From 2000 to 2010, 47 BrS patients were recruited or referred consecutively from medical centers and hospitals in Taiwan. BrS was definitively diagnosed when a Type 1 (Coved-type) ST-segment elevation (Brugada ECG) was observed in more than one right precordial lead (V1-V3) in the presence or absence of a sodium channel blocking agent and in conjunction with at least one of the following criteria: SCD, documented ventricular fibrillation (Vf), polymorphic ventricular tachycardia (VT), syncope or nocturnal agonal respirations.\(^{20-23}\) Clinical information including age, sex, past history (including syncope or sudden cardiac arrest), circumstances surrounding these events (including sleeping or working) and family history of sudden cardiac death (< 45 years old) and a 12-lead ECG after index event were collected. The subjects were excluded if they had any acute ischemic, metabolic, electrolyte abnormality and underlying structural heart diseases. The definition of BrS patients with atrial fibrillation was a BrS patient with at least one episode of atrial fibrillation in a 12-lead ECG or 24-hour holter (permanent, persistent or paroxysmal) during follow-up clinically or before diagnosis of BrS (Figure 1). The study was approved by the local ethical committee of National Taiwan University Hospital (NTUH), and all study subjects granted informed consent.

**Statistical analysis**

All continuous data were expressed as mean ± standard deviation. Student’s t test was used when appropriate to compare continuous variables among the different groups. A frequency comparison (categorical variables) was performed by using the chi-square or Fisher’s exact test. Confidence intervals (CI) of the binominal distribution were calculated for the prevalence rates (SPSS 16.0 Inc., Chicago, Ill., USA). A 2-tailed p value of < 0.05 was considered significant.
Two of them had a family history of SCD, and a predominance of male patients was also observed. All of the subjects had normal physical examinations and none had significant biochemical abnormalities that could be correlated with electrical events. Cardiac catheterization and echocardiography of these patients did not reveal any coronary artery diseases or obvious structural valvular heart diseases. Two of the patients experienced SCD and the rest presented with syncope or seizure. In these 6 BrS with AF, 5 had spontaneously type I Brugada-type ECG. The presence of spontaneously type I ECG in BrS with AF was not different from that of those BrS patients without AF (p = 0.9). The SCN5A mutation rate is similar between BrS patients with AF and those without AF (p = 0.69). The comparison of clinical characteristics of these 6 BrS patients with AF with those BrS patients without AF is summarized in Table 1. Compared to those BrS patients without AF, significantly higher percentages of the BrS patients with AF presented with seizure and documented ventricular tachyarrhythmia (p = 0.02 and 0.03, respectively).

**DISCUSSION**

The aim of this study was to investigate the prevalence of AF in BrS patients in Taiwan and their clinical characteristics. We found that the prevalence of AF in BrS patients in Taiwan was 12.7%, similar to but slightly lower than those reported in the Caucasian population, and those BrS patients with AF showed distinct clinical features.
Although life-threatening ventricular arrhythmias are the hallmark of BrS, atrial arrhythmias are being increasingly recognized in patients with BrS. Incidences of spontaneous atrial arrhythmias reported were between 6% and 38%. The inducibility of atrial arrhythmias ranged from 3% to 100%.14-17,24-29 It is believed that the disease process is more advanced in BrS patients with atrial arrhythmias.26 A large multicenter study in Europe reported that 22 of the 220 BrS patients receiving an ICD had AF (10% of patients).29 In our study, the prevalence of AF in BrS patients in Taiwan was around 12.7%. In a serial case study in China, 3 of 10 BrS patients had spontaneous or inducible AF.30 However, our study enrolled BrS patients with and without an ICD implantation and all of them were symptomatic when they were enrolled in this study. The difference of Brugada phenotypes between study populations may contribute to the different prevalence of AF in BrS patients.

In 1998, Chen et al. first reported that BrS has a genetic basis that is linked to mutations in SCN5A, the gene that encodes the β-subunit of the sodium channel.9 After two decades, the SCN5A gene is still the most common BrS-causative gene and is responsible for 20-25% of this disease in Caucasian populations.8,31,32 The SCN5A mutations might increase atrial vulnerability observed in subjects with BrS.33-35 In other words, the arrhythmogenic substrate in BrS may not be restricted to the ventricular level and could be the substrate for re-entrant tachyarrhythmias in the atrium. Recently, several minor BrS-susceptibility genes involving calcium channels (CACNA1C, CACNB2B, CACNA2D1) were discovered.30 AF has also been associated with mutations in both the sodium and calcium channels of the heart.12,22 This could explain, in part, the association between AF and BrS. Some studies have reported prolongation of atrio-His and His ventricular (HV) interval; these changes occurred principally in patients with SCN5A mutations and are consistent with a decreased excitability in the conduction system secondary to the loss of function of sodium channel activity.36 Vagal activity is believed to contribute to the ST segment elevation and slower atrioventricular conduction in BrS as well as in the initiation of paroxysmal AF.25 Bordachar et al. noted that patients with an HV interval > 55 ms had significantly more atrial arrhythmias than those with a normal HV interval (66% vs. 8.5%; p < 0.001).26 Unfortunately, not all of our BrS patients received invasive electrophysiological studies, and we did not have the data to correlate longer HV intervals with AF occurrence in our BrS patients.

The gender predominance of BrS is generally 8 to 10 times more prevalent in men than in women.19 It is not clear whether this gender distinction also extends to the prevalence of AF. Studies in which an association of AF with Brugada syndrome has been evaluated have revealed male predominance in Japanese and Korean populations.14,15,18,25 The BrS patients with AF were all male in our study.
CONCLUSIONS

We showed that the prevalence of AF in BrS patients in Taiwan was 12.7%. The prevalence of AF in BrS patients in Taiwan is similar to that in the Caucasian population. However, a large BrS cohort is required to make a definitive conclusion regarding the prevalence of AF in BrS patients in the Chinese Han population. On the other hand, rhythm control therapy by sodium channel blockers is widely adopted for the treatment of paroxysmal AF. For example, pill-in-the-pocket treatment using pilsicainide or propafenone should be applied only after confirming the drug safety to the BrS patients with AF. The drug choice for BrS patients with AF warrants more clinical attention because of the contraindication for a serious of antiarrhythmic drugs.

CONFLICT OF INTEREST STATEMENT

No conflicts of interest to declare.

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